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OCULAR COMPLICATIONS OF HERPES ZOSTER OPHTHALMICUS

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Ronald John Marsh

MB.BS.(hons)(London), FRCS (England), FRCOPHTH

Training Institutions

The Royal London Hospital Medical College

Turner Street

Whitechapel

London E1 2AD

and

Moorfields Eye Hospital

City Rd London EC1V 2PD

Consultant Ophthalmologist

Moorfields Eye Hospital

City Road, London, EC1V 2PD

&

St Mary's Hospital Eye Department

(Western Eye Hospital)

Marylebone Road

London NW1 5YE

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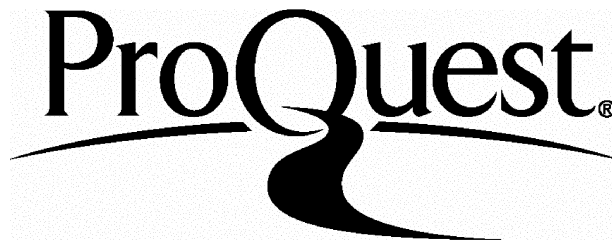
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2 ABSTRACT

Fifty percent of patients with ophthalmic zoster develop ocular complications. These may be mild or severe, and can lead to loss of sight which, by timely and good management can be prevented in most cases. Unfortunately knowledge of the complications and their management is often poor making the design and interpretation of clinical trials difficult. 1356 cases of ophthalmic zoster were collected over fifteen years with at least 6 months follow up. Their details and complications were entered into a database.

There is a generally held impression that patients developing zoster do so because of impaired immunity. Analysis of our findings showed that this was not so.

The database results were analyzed to quantify the incidence of complications and their correlates.

Two common corneal complications that are difficult to manage and lead to visual impairment were studied in detail including:

Mucous plaque keratitis is defined as a distinct entity appearing at an early or late stage and occurred in forty seven cases. Poor management leads to visual impairment from neurotrophic ulceration, megaplaque keratitis and glaucoma.

Lipid keratopathy induces diminished visual acuity and photophobia. It occurred in thirty six cases. Careful and prolonged treatment of chronic stromal keratitis with topical steroid will prevent this occurring, but when it does successful laser occlusion of corneal blood vessels halts the deposition of lipid and may actually disperse it or make the host cornea safer for keratoplasty.

One hundred and seventy six patients were screened orthoptically and the *incidence of extraocular muscle palsies* assessed with regard to distribution and natural history. Possible pathogeneses are discussed. Overall recovery was good.

Lastly *iritis and iris atrophy* were identified in five hundred and twenty patients and twenty three were investigated with anterior segment fluorescein angiography. This showed that they were associated with an ischaemic vasculitis.

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ERRATA & CORRIGENDA

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5 The incidence of clinical impairment in immunity

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6 The incidence of ocular complications in ophthalmic zoster and Supplementary notes on some complications.

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10 Iris angiography of zoster iritis and iris atrophy

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GLOSSARY OF COMMONLY USED ABBREVIATIONS AND TERMS

ACTH	adrenocorticotrophic hormone
ACV	acyclovir
A&E	accident and emergency
AIDS	acquired immune deficiency syndrome
AraA	adenine arabinoside
BV araU	bromovinyl arabinosyl uracil
BVDU	bromovinyl deoxyuridine
CD	cluster differentiation
DNA	desoxyribonucleic acid
ESR	erythrocyte sedimentation rate
Idu	iodoxyuridine
IF	immunofluoresence
Ig	immunoglobulin
HHV	human herpes virus
HIV	human immunodeficiency virus
HSV	herpes simplex virus
HZO	herpes zoster ophthalmicus
LK	lipid keratopathy
MPK	mucous plaque keratitis
NMR	nuclear magnetic resonance
NTK	neurotrophic keratitis
PCR	polymerase chain reaction
PET	positron emission tomography
PHN	postherpetic neuralgia
PMMA	polymethylmethacrylate
PMN	polymorphonuclear leucocytes
PN	polyarteritis nodosa
RNA	ribonucleic acid
SLE	systemic lupus erythematosis
TENS	transcutaneous nerve stimulation
VCR	videocassette recorder
VZV	varicella zoster virus
WBC	white cell count

2 INTRODUCTION

2.1 THE PROBLEM

Herpes zoster of the ophthalmic division of the trigeminal nerve can be a very serious illness, with multiple local and systemic effects, especially in elderly patients. Some of these effects may be very damaging to vision, particularly if not correctly managed.

Despite being well described in the literature since 1864, the circumstances precipitating an attack are still unknown, and the natural history and incidence of ocular complications are not well established.

The varicella/zoster virus is known to be present and proliferating initially in an attack, but the mechanism of chronic ocular disease is poorly understood.

Post mortem and enucleated eyes have shown chronic perineuritis and perivasculitis in the uvea and neurovascular bundles even years after the disease onset. However, as there have been no biopsies carried out there is little information as yet in vivo. These facts have relevance to the short and long term management of the disease for despite the availability of antiviral and anti inflammatory drugs, severe complications continue to occur.

Until now the relatively small series of patients collected in previous studies (the largest being 94) have made randomisation and efficacy of treatment difficult to determine.

This study of 1356 cases of ophthalmic zoster has provided the opportunity of assessing whether there was clinical evidence of impaired immunity associated with the disease and the incidence of ocular complications.

2.2 SCOPE OF THE INQUIRY.

2.21 The incidence of clinical impairments in immunity will be reported.

For many years it has been suggested that patients contracting herpes zoster have compromised immunity (Edgerton, 1945; Walsh & Hoyt, 1969; Wright & Winer, 1961; Sokal & Firat, 1965), and the zoster infection is symptomatic of an underlying immunosuppressive process. However, zoster occurs widely in the community, especially in the elderly, and there is no good evidence for preceding impairment of immunity in the scientific literature. Clearly laboratory tests for impaired immunity were not

particularly wide ranging 15 years ago and it was decided at that time to look for clinical evidence by carrying out a retrospective study on 1000 of the Moorfields patients to see if this impression was correct and to see if the infection and ocular complications were more severe in those patients with underlying disease.

2.22 The incidence and correlations of ocular complications will be assessed.

The database of 1356 patients with ophthalmic zoster offered useful information on the incidence of complications and their correlations.

It was also valuable for designing future clinical trials particularly with regard to randomisation.

2.23 The natural history and management of the following most serious ocular complications will be described:

2.23a Mucous plaque keratitis: Dendriform corneal epithelial disturbances have long been recognised in ophthalmic zoster but only relatively recently described in the literature (Piebenga & Laibson, 1973; Marsh, 1973). The collective term 'pseudodendrite' precludes a satisfactory classification of these disturbances, gives no indication of the nature of the lesion, and is unhelpful in their management. This collection of cases began in 1971 and this entity was defined and classified in a group of 47 cases.

2.23b Corneal vascularisation and lipid keratopathy: Lipid keratopathy is sometimes a feature of late ophthalmic zoster keratitis. Dense lipid deposits in the cornea seriously impair vision and minor degrees give rise to troublesome visual distortion and photophobia. Thirty six cases were studied to determine predisposing causes and possibility of argon laser photocoagulation of the feeding vessels as a treatment modality.

2.24 External oculomotor palsies: The quoted incidence of these palsies in the literature varies from 5.8% to 29% and there has been mention of a contralateral VIth nerve paresis in the literature (Norris et al, 1970). Full ocular motor examination was made of 176 consecutive patients by 2 orthoptists.

2.25 Some features of iritis and iris atrophy: An early series of 520 patients from the database were examined for iritis and iris atrophy over an 18 month period and 23 patients were investigated with fluorescein

angiography of the iris to try to establish if atrophy was the result of a vasculitis or obstruction.

3 HISTORICAL REVIEW OF THE LITERATURE

The disease was well known to the Greeks (erpo = to creep and zoster = a girdle) and in Roman times Pliny is said to be the first to use the term 'zona' for the eruption. von Barensprung was the first to demonstrate its association with a lesion of the posterior root ganglion (von Barensprung, 1861) shortly afterwards confirmed in the trigeminal ganglion by Hutchinson (1867) and Bowman (1867). Wyss (1871) reported a case involving the whole division of the trigeminal nerve, with death occurring 7 days after the start of the rash. Here the ophthalmic vein was thrombosed, the eye muscles contained small abscesses and there was extravasation of blood adjacent to the ganglion and origin of the ophthalmic division.

3.01 VIROLOGY

Varicella-zoster virus (VZV), or as it is now known, human herpes virus 3 (HHV3), is a typical herpes virus containing: DNA, an icosahedral nucleocapsid and a glycoprotein-containing outer membrane. Under the electron microscope it is indistinguishable from the rest of the herpes family of viruses. Until recently, it had not been possible to acquire enough pure virus to characterise its constituents, but now the complete DNA sequence has been elucidated (Danson & Scott, 1986). Using conventional methods there has only been one VZV strain detectable, but with the advent of restriction endonuclease analysis more are definable: this makes possible the tracing of virus in one host or within a population. Some of the genome is homologous with other herpes viruses (Davison and Wilkie, 1983) and in a few cases amino acid sequences have been shown to be very similar to those of HSV-1 (Davison & Scott, 1986). Some gene functions have been elucidated. There are transregulatory genes responsible for virus replication, setting the stage for the production, trimming and assembly of structural proteins into a new infectious progeny virion and others for the production of glycoproteins which reside in the outer coat and appear in the later stages of viral replication. Many VZV proteins are involved in viral replication, including thymidine kinase and thymidylate synthetase enzymes, two virus-specified protein kinases, a range of DNA binding proteins including the viral DNA polymerase and several immediate-early (IE) transcriptional regulators (Kangro & Jeffries, 1995). Comparisons with HSV-1 also suggest evolution

from an ancestral genome, so it is very likely that VZV gene products appear in a similar way to those of HSV, with an early phase (concerned with regulatory function), an intermediate (concerned with DNA synthesis), and a late (concerned with capsid and membrane synthesis).

Laboratory research on VZV has been sketchy because, unlike HSV, it is difficult to obtain cell-free virus and no satisfactory animal model has yet been developed. Both viruses are neuro-and epithelio-tropic, tending to cause direct cell damage in the acute stages: this is especially so for HSV and post mortem examination of the trigeminal ganglion in ophthalmic zoster shows extensive neuronal damage. When they establish latency there is little evidence of cellular disruption but HSV seems to establish latency and reactivate more easily perhaps because it is situated in the neuronal cells as opposed to zoster where the latent virus is thought to reside in the satellite cells of the ganglion (Liesegang, 1991). Both viruses have humans as their only reservoir, HSV being more widespread with an endemic pattern, and VZV being more prevalent in urban societies and showing an epidemic pattern. The presence of antibodies as shown by sero-conversion in adult life approaches 70% for HSV and 95% for VZV (Weller, 1982; Tullo, 1985) implying that virtually the whole population comes into contact with varicella/zoster virus, although not all get clinical manifestations of chicken pox or zoster.

3.02 EPIDEMIOLOGY

The classic paper on epidemiology is that by Hope-Simpson (1965), which describes 192 cases of zoster seen in general practice: he found the annual incidence of new cases in a population of 3534 persons to be 0.074% under 10 years, a plateau of 0.25% from 20-50 years, and over 1% over 80. Cooper looked at the Moorfields Hospital Database (Cooper, 1987) and found a slightly different pattern: there seeming to be a steady exponential rise rather than a dramatic increase in later life. Hope-Simpsons figures came from general practice and referred to zoster in all parts of the body whilst Cooper's mostly from referrals to Accident & Emergency at Moorfields and are all ophthalmic zoster, so they are not strictly comparable. Whether the differences in incidence in the older age groups is related to this difference in distribution is difficult to say. There appears to be no

consistent changes with season, or with sex.

The weekly returns from the Royal College of General Practitioners (Flemming et al, 1991) give countrywide figures on zoster which is not a notifiable disease and are based on about 80 practices (Cooper, 1987). Zoster incidence stays steady at 3-4 per 1000 and does not follow the epidemic pattern of chickenpox, thus making it unlikely that Zoster is an immediate result of contact with VZV. This is contrary to the old theory of aetiology where close exposure to the virus was thought to cause a change in immunity resulting in reactivation of virus and an attack of zoster. It is also significant that at the vesicular phase of zoster close contacts who have not suffered from chickenpox risk acquiring the infection. The higher zoster prevalence rates in the older age groups are the opposite to those in chickenpox, but the age intervals provided by the RCGP are not sufficiently narrow to make any comparison with the Moorfields figures. Females have a slightly lower incidence for chickenpox and a higher one for zoster than males. AIDS, Hodgkins disease, and other conditions causing impaired cell mediated immunity are associated with a higher incidence and severity of the clinical disease. Varicella in the first year of life leads to a high incidence of a mild variety of zoster within the next year (Guess et al, 1985; Baba et al, 1986). Second attacks of herpes zoster are rare (Lightman et al, 1981, Liesegang, 1985) and two areas of the body can be affected simultaneously.

3.03 IMMUNOLOGY

It is often stated that the development of zoster is associated with a temporary depression of immunity and so there have been many studies on the subject.

3.03a Humoral immunity: It has been known for many years that there is an anamnestic rise in the level of varicella neutralizing antibody during an attack of herpes zoster, demonstrating that the virus had been encountered previously (Miller and Brunell 1970). There is typically a rise in IgG and IgA within 2 days of rash onset, reaching a peak in 2-3 weeks, and declining to very low levels at a year (Cradock-Watson et al, 1979, Ceretini et al, 1983). There is an elevation of IgM reported in some series which would usually suggest a primary infection, but the kinetics of the responses would suggest a secondary IgM response due to waning immunity. Although the antibody

pattern of response to zoster has components similar to varicella there are some additional ones which make it distinct despite both diseases being caused by the same virus (Weigle & Grose, 1984). Circulating antigen-antibody complexes have been demonstrated in serum from 50% of a group of otherwise healthy subjects with localized zoster (Nielsen et al, 1980). This observation suggests the possibility of tissue damage resulting from immune-complex deposition in the pathogenesis of severe infection (Weller, 1982). Nevertheless the outcome of varicella, either as zoster or chickenpox, does not seem to be adversely affected by the absence of serum antibodies (Gershon & Steinberg, 1981), conversely those with Hodgkins disease, who have normal antibody levels may have severe disease. The consensus is that other, presumed cellular, factors are more important.

3.03b Cellular immunity: Cellular responses to VZV have also been examined extensively and reveal a consistent depression of cell-mediated immunity in the first 5 days of the zoster rash as assessed by blastogenesis of peripheral blood cells and reduced delayed type sensitivity response as measured by skin testing (Weller, 1982). It is possible that this is either a true depression of cell mediated immunity or is due to recruitment of immunologically competent cells into affected tissues so they are not available in the circulatory pool. A reversal of the ratio of CD4/CD8 subsets in the peripheral blood has been noted (Neumeyer and Hirsch, 1986) and this may be either due to reduced circulating number of CD4 + T cells or to increased numbers of circulating CD8 + T cells.

Cytotoxic CD8 + T cells are important in destroying virally infected cells and are probably the host defenders against reactivation of VZV. These CD8 + cells can become activated when their receptor recognises viral antigens (VZV glycoproteins, gpl-V and the immediate early tegument protein) binding with class I HLA antigens on the infected cell surface. Activation of CD8 + cytotoxic T cells results in target cell death by membrane cell lysis after secretion of substances such as perforin by the activated T cells. CD4 + cells are necessary for the maturation of cytotoxic CD8 + T cells and for the production of specific neutralizing antibody by B cells maturing into plasma cells, which occurs as a result of lymphokine

secretion.

3.04 AETIOLOGY

The current theory of aetiology is that, after an initial attack of chickenpox with its attendant viraemia, virus is retained in the posterior root ganglion in a latent form that later on reactivates under the influence of unknown trigger factors, replicates, and migrates chiefly centrifugally down the sensory nerves (Garland, 1943, Hope-Simpson 1965). The virus eventually reaches the skin where it produces the familiar herpes zoster vesicles and, in some cases of ophthalmic zoster, the eye. It can be isolated from both sites (Weller and Coons, 1954; Pavan-Langston and McCulley, 1973). It causes a perineuritis and perivasculitis in the affected dermatome and underlying areas leading to varying amounts of direct and indirect tissue damage.

3.05 GENERAL PATHOGENESIS

Herpes zoster is a reactivation of latent VZV, in a similar way that cold sores are of HSV.

3.05a Latency: HSV and VZV are thought to become latent in the primary attack, HSV having been found to be transported from the epithelial vesicles along the sensory axons to the neural cell body (Claoue et al, 1987, Claoue et al, 1988). This has been demonstrated in animal models for HSV, and has been measured by the amount of neutralising antibody required to prevent a peripheral rash (Blyth et al, 1984; Simmons and Nash, 1984). A similar process has been inferred for VZV (Pavan Langston and Dunkel, 1989), because the frequency of dermatome involvement in zoster parallels that of rash density in chickenpox, being most common on the trunk and head. Latency occurs in only a small fraction of neurones, and involves the incorporation of virus into the host genome. This appears to be in the satellite cells of the dorsal root ganglion (Croen KD et al, 1988) but with HSV it is as extrachromosomal DNA in a circular episome of the neurone. VZV RNA and DNA have been demonstrated in virtually every cadaver trigeminal ganglia of individuals who were seropositive for VZV (Mahalingham et al 1990), and at a rate of 1:1000 neurones (Hyman et al 1983). To date the same strain of virus has been shown to appear in separate sites during zoster, (Pichinir et al, 1983) and probably at the

primary and recurrent stages (Straus et al, 1984).

3.05b Reactivation. The mechanisms of reactivation in HSV and VZV are likely to be similar and relate to the symbiosis of the virus and host: a disturbance of this causes clinical and possibly sub-clinical disease. Many factors may cause HSV to break out of latency, and it has a much greater inherent potential for doing this than VZV: this might be related to the location of the latent virus, quantity of viral genome, proliferative potential or loss of immunological control (Marsh & Cooper, 1993). Traditional hypotheses of reactivation involve alterations in the immune system with time, trauma and neural degeneration.

3.05b1 *Reduced immunity*. Hope-Simpson (1965) suggested that when the titres of antibody or reactive cells fall below a certain level, the virus somehow escapes control and causes clinical damage. There is no good evidence for this in humans for either virus. After the primary infection with VZV, circulating antibody levels fall over a year and become barely detectable (Weller, 1982). Titres do not consistently decrease with age, as is required if this is to be the main determinant of disease, and there is an anamnestic response in the majority of individuals who have zoster, implying that circulating immunity has not faded. Moreover, those who have suffered zoster early in life are not more likely to have a second attack after a lesser interval than others who get their first attack in middle age (as might be expected if the fall in titres was host-dependant). Cell-mediated responses also decrease with age but there does not appear to be any research which has demonstrated this for VZV in particular, and the predominantly lymphocytic infiltration into trigeminal ganglia during the acute phase indicates that cells may certainly be induced to respond specifically and with effect.

3.05b2 *Trauma*. It seems that damage to part of the neurone or iontophoresis of adrenaline reliably lead to reactivation of HSV (Tullo, 1985) and recovery of virus from tissue is difficult unless there has been a certain amount of damage, such as in inoculation of tissues (Claoue et al 1990). It is interesting that mild and transient attacks of herpes zoster can follow retrobulbar or trigeminal ganglion injections and neurosurgical incisions - so-called symptomatic zoster-(Juel-Jensen and MacCullum, 1972). Equally

exposure to ultra violet light, nerve section and irradiation are well known to reactivate HSV. Neuronal metabolism in the adult is mostly concerned with maintenance of the cell and there is virtually no proliferative activity: most of the DNA is inactive. If the cell is damaged in some way, such as sectioning the axon, repair mechanisms start and it is feasible that the viral DNA may be involved in this process, leading to viral proliferation which may or may not overwhelm the cell and lead to viral shedding. The likelihood of this happening with VZV is small because of the very low frequency of neurone colonisation and its potential for reactivation is also low, but over a lifetime the chances of viral shedding could well be significant. What is difficult to explain is why in typical zoster, unlike in Herpes Simplex, the neurones are completely destroyed and therefore there is no potential for recurrence of zoster. It is perhaps at this stage that the immune system is important: the frequent recurrences of HSV shedding keep the immune response active and control local spread very quickly, but as VZV recurrence is very infrequent, the response is probably delayed allowing more viral spread in the ganglion and a more vigorous tissue response when it eventually occurs (Straus, 1992).

3.05b3 *Other Factors* Neurones may be damaged by other factors, for instance HIV infection; clinically HSV is often reactivated by colds, influenza and pneumonia which may have a direct effect on neuronal metabolism rather than indirectly by a specific immune response (Liesegang, 1992). So far there is no evidence that other acute infections precipitate zoster.

3.05b4 *Aging* Most episodes of zoster cannot be related to a specific precipitating event and occur chiefly in older age-groups. It is possible that a latently-infected cell is involved directly or indirectly by the normal neuronal death rate which is relatively high and possibly due to a fall off of neurotrophic factors (Tuszynski & Gage, 1994) and so sets off the process of reactivation: an intellectually satisfying idea for which there is as yet no evidence. Also there is a progressive loss of the regulatory control of T lymphocytes with aging, and lymphocytes from people 65 years and over are much less responsive in culture to varicella antigen than lymphocytes from young people (Weksler, 1992). Against the theory of aging is the fact that zoster can present at any time of life. Cooper's analysis of the

Moorfields clinic incidences, showed a form of exponential rise with age which is comparable to a mortality statistical model (Cooper, 1987).

3.06 Pathogenesis of eye disease: There is undoubted viral replication in the eye in the acute phase of the disease, as confirmed by the culture of virus from material scraped from corneal epithelial lesions (Pavan-Langston & McCulley, 1973) and there may or may not be in the stroma, endothelium, iris and retina. Once virus reaches the tissues, acute and chronic inflammatory processes attempt to clear virus and viral antigens; the dose and strain of virus, efficacy of immune response, tissue involved and treatment are some of the governing factors (Marsh & Cooper, 1993). Inability to clear the viral antigenic stimulus and the establishment of a type of chronic, low-grade inflammation is probably the main cause of the long-term problems (apart from acute damage such as denervation). There has been failure to grow the virus in chronic keratitis from either corneal epithelial scrapings or scarred corneal discs removed in keratoplasty and submitted to maceration (Marsh & Cooper, 1993). Admittedly these techniques were rather insensitive and have recently been superseded by immunofluorescence cytology and DNA PCR (viral DNA has been found in post-mortem eyes within the neurovascular bundles and corneal buttons (Yu et al,1993)). There may be an alteration of the viral DNA stimulating an exaggerated local immune response or an alteration in the local immune response by the host engendered by unidentified external factors (either way there is no demonstrable viral replication). In this way it differs from HSV.

3.07 HISTOPATHOLOGY

There is relatively little in the literature on the histopathology of zoster. Perhaps the earliest paper is by Head and Campbell (1900) describing inflammation, haemorrhage and necrosis of ganglion cells in the dorsal root ganglion followed by scarring. They stressed the marked variation in the severity of the lesions paralleling their clinical experience. There appears to be a very short phase of viral replication in the nerves and closely related tissues at the very onset of the disease (Hedges et al,1982). This is followed shortly afterwards by infiltration with inflammatory cells and then by variable necrosis of cells - principally neurones. There may then be resolution or continuing chronic and relapsing inflammation persisting for

many years with continuing damage to the tissues and scarring. The trigeminal ganglion, brain, peripheral nerves, orbit and globe have been examined.

Trigeminal ganglion. Virus has been isolated in the very early stages; (Esiri and Tomlinson, 1972) within two weeks there is infiltration with polymorphonuclear granulocytes, plasma cells and predominantly lymphocytes (Rejke-Nielsen et al, 1986). The presence of the latter suggests that there is already a coordinated cell-mediated response rather than a purely inflammatory one (Oxman, 1987). The adjacent dural sheath and carotid arterial radicals are involved in the inflammatory process. Early on there is a varying amount of neuronal necrosis, indeed, in some patients practically all the neural cells may be destroyed (Head & Campbell, 1900).

Brain. The mesencephalic nucleus of the trigeminal nerve may show large nodular collections of microglia with later effacement of structure. There may be a lymphocytic leptomeningitis and lastly lymphocytic infiltration of both the cranial nerves and their nuclei bilaterally may occur (Hedges et al, 1982).

Peripheral nerves: At the onset there is a perineuritis with an adjacent perivasculitis. About 10 days after the onset there is secondary loss of axones and myelin sheathes followed by fibrosis (Zacks et al, 1964).

Orbit: There can be extensive vasculitis, haemorrhage, perineuritis and inflammatory cell infiltration of other orbital contents including the extraocular muscles.

Globe: Most histopathological reports are in the later stages of the disease when the eye had been enucleated (Naumann et al, 1968). The commonest findings are perineuritis and perivasculitis in the scleral channels, in the long and short ciliary nerves and arteries. Presumably the virus reaches the eye via the ciliary nerves. The connection between this and subsequent chronic inflammatory reactions has not been clarified (Naumann et al, 1968). Although viral replication has not been demonstrated in late phases of the disease viral DNA has been found (Yu et al, 1992). It is interesting that, at times, lesions of different tissues develop in the same sector of the eye (Redslob, 1923; Bonnet, 1939) confirming the neurological distribution of the disease in the globe.

3.1 General Clinical features

3.10 Onset: There is a prodromal 'flu-like illness of varying duration, with headache, pyrexia, malaise, depression, and sometimes neck stiffness, which may last up to a week before the rash appears. This is shortly followed by localised pain over the distribution of the ophthalmic nerve, lymph node swelling in the corresponding drainage areas, and, occasionally, a red eye. The localised pain is well known to precede the rash by several days in some cases (Duke-Elder and Perkins, 1966, Liesegang, 1985). Little is known about the pathology of this phase but these early features probably represent the replication and migration phases of the virus and are possibly accompanied by a limited viraemia (Marsh & Cooper, 1993).

3.11 Age and Sex distribution: Most series quote an equal incidence for males and females (Burgoon et al, 1957; Liesegang, 1985) and a steady increase with age (Edgerton, 1945).

3.12 Rash: This varies enormously in distribution, density, and severity. It commences as macules which rapidly progress to papules, vesicles (whence VZV can be cultured) and pustules (Walsh and Hoyt, 1969 , Liesegang, 1985). Crusts start to form from about 6 days onwards. All, or just one, of the cutaneous branches of the ophthalmic nerve are affected. The lesions are described as: small, discrete, scattered, and superficial to large, confluent, and deep with haemorrhagic bullae. It has been suggested that the latter are due to a vasculitis in the dermal papillae which leads to severe tissue ischaemia (Burgoon et al, 1957). Oedema is a variable complication, developing after the first 2 or 3 days. It may be so pronounced as to completely close the lids of the affected eye and spread across the midline to involve the other lids giving the erroneous impression that it is a bilateral disease (Marsh, 1976). Furthermore it is probable that oedema is not due to secondary bacterial infection in the majority of cases, since it rapidly resolves without any antibiotic therapy (Marsh, 1990).

Differential Diagnosis

The rash can be mimicked by zosteriform herpes simplex which takes on a dermatome distribution (Slavin and Ferguson, 1950). Herpes simplex vesicles are smaller and frequently recurrent; they do not form the large distinct crusts or the typical punched-out scarring of herpes zoster and are

not as painful. The two infections may be differentiated by culturing vesicle fluid and assessing fluorescent antibody membrane antigen FAMA (Walpita et al, 1986). Differentiation from impetigo is usually straightforward because of the lack of dermatome distribution in the latter (Edgerton, 1945).

3.13 Systemic Involvement: The vast majority of patients seen by ophthalmologists are otherwise healthy, however, patients seen from centres specialising in tumours and immunosuppressive diseases are a highly selected group with atypical disease (Lightman et al, 1981; Liesegang, 1991). A small number of patients attending eye clinics develop a systemic vesicular rash and severe illness 1-2 weeks after the disease onset. Most of these patients have reticuloses, other malignant tumours (Stevens and Merigan, 1972), diseases causing immunosuppression such as AIDS or are iatrogenically immunosuppressed (symptomatic zoster). Furthermore herpes zoster is more frequent and severe in patients with these diseases. Recently an increased incidence of ophthalmic zoster has been described in Pre-AIDS patients in New York and Africa (Sandor et al, 1986, Kestelyn et al, 1987).

3.14 Investigation: It is advised that all patients with an accompanying generalised rash should be screened by a clinical immunologist or oncologist for malignant disease and immunosuppression (Stevens and Merigan, 1972). However, it has been stated that it is unnecessary to investigate uncomplicated cases of ophthalmic zoster (Lightman et al, 1981). There has been a tradition that all young children with zoster should be investigated for systemic disease (Guess and Broughton, 1985). However, there is little in the literature to substantiate this and certainly not a large series of patients. On the other hand it has been advised that young patients from an AIDS endemic community should be screened (Marsh, 1987).

3.2 OCULAR AND NEUROLOGICAL FEATURES

Ocular involvement: Complications fall primarily into those associated with inflammatory changes, those resulting from nerve damage, and those subsequent to tissue scarring (Head & Campbell, 1900). Inflammatory changes may be in the form of dendritic, nummular, and disciform keratitis or a vasculitis in episcleritis/scleritis, iritis, ischaemic papillitis and orbital vasculitis. Those resulting from nerve damage include neurotrophic (neuromyolytic) keratitis, some ocular motor palsies and neuralgia. Those

subsequent to tissue scarring are lid deformities, neuralgia and lipid keratopathy (Edgerton, 1945). The course of the ocular disease falls into 3 phases:- acute, chronic and relapsing (Marsh 1976). Acute lesions of the globe and orbit develop within 3 weeks of the rash. They may rapidly and completely resolve but can lead to a chronic course, especially if untreated, and linger for years. Alternatively, acute lesions may appear to clear but then relapse years after the disease onset. Recurrence is a particularly distinctive feature of the disease. Hutchinson's rule that cutaneous involvement of the nasociliary nerve heralds ocular complications has been confirmed by others (Edgerton, 1945; Head & Campbell, 1900). However, severe ocular complications have been described with a very mild insignificant rash anywhere on the forehead (Edgerton, 1945).

3..20 Acute Ocular lesions

Eyelids: The lid margin is often involved by the rash. Ptosis is common and is usually due to mechanical factors such as inflammation and oedema (Marsh & Cooper, 1994). Less frequently it is neurological. Haemorrhagic bullae here are a bad sign, heralding severe scarring with all its consequences and postherpetic neuralgia (Marsh, 1976).

Conjunctivitis: Catarrhal conjunctivitis is described as one of the commonest manifestations of herpes zoster (Duke Elder, 1965). It is generally transitory, resolving in a week, rarely becomes chronic and is nearly always associated with vesicles on the lid margin (Edgerton, 1945, Marsh, 1976).

Episcleritis and scleritis: Episcleritis has been described as rare (Duke-Elder, 1965) but later authors found sectoral or diffuse inflammation relatively common (Scheie, 1969; Marsh,1976; Harding et al 1987; Womack & Liesegang 1983). Less commonly, scleritis occurs usually at the end of the first week. It may be adjacent to the limbus with accompanying corneal stromal infiltrate and swelling, producing sclerokeratitis (Edgerton, 1945). Nodular episcleritis has been described in a minority of patients, usually starting in the second week of the disease and is more indolent. Fluorescein angiography in these cases demonstrates ischaemia in the centre of the lesions with surrounding dilated leaking episcleral vessels (Watson and Bovey, 1985) suggesting a vasculitis. However, the mild cases of episcleritis may just be a lymphocytic response. Areas of increased scleral

translucency may develop following scleritis and nodular episcleritis (Marsh, 1976).

Corneal lesions:

Acute epithelial keratitis may occur concurrently with acute conjunctivitis. It is characterised by small fine multiple dendritic or stellate lesions which are quite common but difficult to see because of the difficulty of corneal examination with swollen lids and the transitory nature of the lesions. The slit-lamp appearance is of slightly raised and intra-epithelial lesions. They are located generally in the peripheral part of the cornea and occasionally small plaques of opaque desquamated epithelium and mucus overlie them (Liesegang, 1985, Pavan-Langston & McCulley, 1973, Marsh, 1973). These epithelial lesions stain moderately well with Rose Bengal and fluorescein but only minimally with Alcian blue. They are self-limiting appearing within a few days of the rash onset resolving 4 to 6 days later and are always associated with catarrhal conjunctivitis (Marsh, 1981; Liesegang, 1985). Some authors think they are followed by underlying superficial stromal infiltrate (Liesegang, 1985). Varicella/zoster virus has been cultured from them (Piebenga and Laibson, 1973). A transitory filamentary keratitis has been described (Edgerton, 1945). No topical treatment is required for them. Acute Nummular keratitis is the commonest corneal lesion (Edgerton, 1945, Duke Elder, 1965) and is characterised by multiple fine granular deposits in the stroma just beneath Bowmans membrane surrounded by haloes of stromal haze (Duke Elder, 1966; Marsh, 1973; Leisgang, 1985). They appear 10 days or so after the onset of the disease and are at first white but later become brown. They sometimes underlie preceding epithelial lesions, but more often they are seen in close proximity to thickened corneal nerves (Marsh, 1976). They fade with topical steroid administration.

Chronic Nummular keratitis The infiltrates can behave like those associated with adenovirus type 8 infection in that they fluctuate in density, become chronically active and can diminish visual acuity (Duke Elder, 1965, Marsh, 1973). They both respond well to low doses of topical steroid. Peripheral infiltrates may consolidate over the years, if untreated, and form facets which show primary lipid deposition and can later become vascularised with secondary lipid deposition (Cogan, 1960, Marsh, 1973, Liesegang, 1985).

They may rarely extend into the central region of the cornea profoundly reducing vision and necessitating corneal grafting (Marsh & Cooper 1993). Acute Disciform keratitis Early cases present 3 - 4 weeks after the disease onset and less often after 3 months. It is generally situated centrally, but can be eccentric and varies in the degree of stromal oedema and infiltrate (Edgerton, 1945). It seems to follow preceding nummular keratitis with new infiltrate appearing in the stroma underlying the corneal granules and occasionally is surrounded by infiltrate in the shape of one or several immune rings. Commonly there is an associated iritis with fine keratic precipitates underlying the swollen stroma. When the disciform keratitis is eccentric it often merges into a sclerokeratitis (Edgerton, 1945; Marsh, 1976; Liesegang, 1985). When the endothelium has been examined with the specular microscope it showed sporadic loss of endothelial cells and blebs (Reijo et al, 1983, Sundmacher & Miller, 1982). It is very sensitive to topical steroid.

Chronic Disciform keratitis if untreated with topical steroid, nearly always becomes chronic with progressive accumulation of infiltrate in its centre and immune rings. This is followed by lipid deposition and vascularization with very dense nebula formation often adversely affecting vision (Edgerton, 1945; Cogan, 1966; Marsh, 1973, Liesegang, 1985). Here, too, corneal grafting has proved very successful because the corneal sensation is usually preserved.

Diffuse Corneal Oedema may develop as a presenting feature in patients. It would appear to be due to diffuse damage to the endothelium, because, later, after the oedema has resolved, endothelial microscopy shows more severe changes than disciform keratitis (Reijo et al, 1983, Sundmacher & Miller, 1982). Very fine deposits are be visible with the slit lamp on the endothelial surface and there is often raised intraocular pressure with minimal signs of iritis. Like iritis, and disciform keratitis it is sensitive to topical steroid especially early on (Liesegang, 1985).

Acute Neurotrophic keratitis: Total loss of corneal sensation may occur at the onset of the disease and in some of these cases an immediate neurotrophic keratitis with corneal ulceration ensues (Edgerton, 1945). It may occur as early as 7 days after the first signs of cutaneous zoster or as

late as 2 years after rash onset following late loss of corneal sensation or in a previously quiet anaesthetic cornea. In many cases it is difficult to manage and preserve useful vision (Marsh,1981). It is characterized by generalized corneal epithelial bedewing, punctate epithelial erosions with or without frank interpalpebral epithelial ulceration and infiltration of the underlying stroma (Kenyon, 1985). The epithelium stains moderately well in a punctate fashion with fluorescein and rose bengal. The ulcers tend to be oval in shape with opaque water-logged epithelial edges, and the base stains brilliantly with fluorescein and moderately well with rose bengal, but alcian blue should not be used because of the risk of long-term stromal staining (Marsh, 1981). Neglected ulcers grow rapidly with excavation and tendency to perforate or there may be secondary bacterial infection. The underlying stroma may become rapidly calcified (dependent on the state of the collagen, glycoaminoglycans, tear calcium and phosphate). Histology of the ulcers shows degenerative changes in the epithelium and extensive necrosis in the stroma (Kenyon, 1985).

Its pathogenesis is poorly understood and there is little published. It has been suggested that it is a disease of abnormal cell turnover (Mackie, 1994). It is thought that trophic factors pass centrifugally down functioning sensory neurones. Likely mediators include acetylcholine, proteins, amino acids, cyclic nucleotides and perhaps substances akin to epidermal growth factor (Hallerman,1952). After nerve section in animals respiratory and glycolytic activity are markedly reduced in corneal epithelial cells and the amounts of acetylcholine here are reduced (Simone,1958). It also has an adverse effect on normal epithelial mitosis rates (Mishima,1957). The stromal ulceration results from proteoglycan and collagen degradation from proteolytic and collagenolytic enzymes which may be elaborated by damaged corneal epithelial cells, conjunctival cells, corneal fibroblasts and by inflammatory cells (Berman et al, 1983; Wint-Johnson, 1980). Loss of corneal sensation alone does not lead to this type of keratitis. Other factors are required, such as chronic conjunctivitis, lid margin deformities and loss of lid margin and bulbar conjunctival sensation (Mackie,1978; Turss, 1980; Waring et al, 1981; Marsh,1981).

Sclerokeratitis is unusual and may be accompanied by marginal guttering,

sometimes called serpiginous keratitis (Liesegang, 1985). It responds well to topical steroid but tends to be indolent. Neglected sclerokeratitis runs a very chronic course with progressive deposition of infiltrate, vascularization, and lipid in the cornea which may remain either confined to the periphery to form a faceted type of scarring or may migrate across the cornea causing severe visual embarrassment (Marsh, 1973, Hedges & Albert, 1982; Liesegang, 1985).

Acute Iritis: Iritis is a common complication of herpes zoster ophthalmicus; Edgerton (1945) reported an incidence of 20%. Duke-Elder (1940) divided the iritis into two types: diffusely exudative and locally eruptive. However, these observations were made prior to the introduction of therapeutic corticosteroid, the administration of which markedly altered the course of iritis. It appears within 2 weeks of the rash (Marsh et al, 1974). It is characterized by very fine deposits on the corneal endothelium, the aqueous flare is generally minimal and is associated with only a small quantity of cells. Posterior synechiae are unusual. Often there is complicating ocular hypertension and overlying corneal stromal oedema (Marsh 1976). All these features respond rapidly to topical steroid.

Iritis often becomes chronic and in the pre-steroid era frequently led to posterior synechiae formation (Rollet, 1928). It may also progress in its ischaemic manifestations to massive iris atrophy (Schoeppe, 1923).

Glaucoma has been well described in the acute phase of herpes zoster, is due to hypertensive iritis and is exquisitely sensitive to topical steroid (Marsh 1976). It is most likely caused by a trabeculitis associated with the iritis and endotheliitis (Marsh, 1976; Liesegang, 1985). Unfortunately, confusion can occur during the management of this condition when steroid induced glaucoma also develops (Marsh, 1976; Marsh, 1990).

Choroiditis and choroidal detachments have been described (Meller, 1976; Lincoff et al, 1957). The latter is confined to 3 case reports, 2 of which are massive exudative detachments associated with severe uveitis which spontaneously recovered with steroid treatment and the other was rhegmatogenous.

Retinal vasculitis has been described in both the living (Collier, 1959) and post mortem eye (Naumann et al, 1968). Again the clinical description is in

the form of a case report and may, in fact, be referring to what is now called acute retinal necrosis.

Retinal pigment epithelial lesions have been described where there is minimal embarrassment of vision and small pale lesions scattered around the macula (Amono et al, 1986).

Acute retinal necrosis has been well described with both ophthalmic zoster and zoster at other sites (Yeo et al, 1986). There seems to be a defined pattern of retinal involvement in AIDS and this consists of a multifocal progressive chorioretinitis (Lowder et al, 1990; Forster, 1990) which rapidly leads to profound visual loss. The only treatment available is systemic acyclovir which has a variable influence on the course of the disease (Johnston et al, 1993). Its pathogenesis is either due to a direct viral cytopathic effect on the tissues or an indirect effect via an ischaemic vasculitis or a combination of both (Rummelt, et al, 1992).

3.3 ACUTE NEUROLOGICAL LESIONS: Cranial involvement takes many forms:

A meningoencephalitis may develop (Schiff and Brain, 1930; Krumholz and Luihan, 1945; Worster-Drought and Sargent, 1949; Appelbaum et al, 1964; Norris et al, 1970) mainly in severe cases of herpes zoster with systemic spread of virus and a defective reticuloendothelial system: it is often fatal.

Contralateral hemiplegia occurs rarely, either in an isolated form (Baudouin and Lantvejoul, 1919; Rollet and Colrat, 1926; Biggart and Fisher, 1938; Marsh et al, 1977; Cope and Jones, 1954; Minton, 1956; Hunt, 1909; Acers, 1964), or accompanied by hemianopia (Franceschetti et al, 1955), aphasia and agraphia (Gordon and Tucker, 1945; Leonardi, 1949; Worster-Drought, 1923). It appears at about 7 weeks but usually recovers well (Laws, 1960; Acers, 1964). Other cranial nerves may be implicated simultaneously.

Pathogenesis: Recent reports have suggested a virus induced granulomatous angiitis is responsible producing thrombosis of small intracerebral vessels (Victor and Green, 1986; Hilt et al, 1983; MacKenzie et al, 1987). Other have reported intravascular thrombosis of the large proximal vessels leading off the circle of Willis such as the middle cerebral artery (Eidelberg et al, 1986). There is minimal infiltration in the media of these vessels

demonstrated at postmortem. Angiography demonstrates irregularity of the vessels walls with aneurysm formation and obstructions (Kolodny et al, 1968).

Optic neuritis has been well described (Duke-Elder, 1940; Edgerton, 1945; Pemberton, 1964; Harrison, 1965; Ramsell, 1967).

Ipsilateral External ocular muscle palsies are well described (Edgerton 1945; Goldsmith, 1968) including the third which is the most common, then the fourth and sixth (Edgerton 1945) but a contralateral VIth nerve paresis has been described in 1 case (Norris et al, 1970). Rarely a total exophthalmoplegia develops (Carmody, 1937; Edgerton, 1945; Lister, 1948; Pincus, 1949; Von Siegert, 1964). The majority of palsies recover subjectively within 3 months but a defect of function remains (Hughes, 1951). The subject is discussed in a later section (Chapter 9).

The VIIth nerve may be involved (Siegert, 1964; Edgerton, 1945; Ramsell, 1967) but it is very rare. It is uncertain if it is due to an extension of the virus infection to the VIIth nerve nucleus or a separately induced motor neuritis.

3.36 Acute Neuralgia: This occurs in most patients during the rash phase, sometimes preceding it by up to a week and tends to remit at the end of the first week. The pain in the trigeminal dermatome is reported as more severe than elsewhere in the body (Demorgas and Kierland, 1957). It has been described as a continuous aching, itching or burning often with superimposed lancinating pain. The latter is precipitated by touching or moving the involved area. The region becomes hyperaesthetic and there is frequently exquisitely tenderness around the vesicles which can worsen as ulceration and secondary infection occur. It is often followed by a reactive depression possibly of the post viral infection type (Marsh, 1976) and especially so when the pain cannot be ameliorated (Portenoy et al, 1986). Its severity is directly related to age but is not related to the severity of the rash or sex (Demorgas & Kierland, 1957). It is localized to the dermatome distribution of the rash and tends to be more severe in older patients (Demorgas & Kierland, 1957; Burgoon et al, 1957).

The pathogenesis is thought to be due to activation of nociceptor primary afferents by direct viral attack and the secondary inflammatory changes in

the skin, dorsal root ganglion, nerve roots and leptomeninges (Portenoy et al, 1986).

3.4 LONG-TERM CONSEQUENCES

Skin: Varying degrees of scarring are described, ranging from undetectable lesions to extensive areas of deep scarring resembling that seen after full thickness burns, and cicatrix production. Generally, the typical punched-out geographical scars appear early with differing amounts of pigmentation or depigmentation, loss of hair, and some acne formation. These lesions frequently fade with time.

Eyelids: Persistent ptosis is common and nearly always of mechanical aetiology due to chronic inflammation, oedema, and scarring (Marsh, 1976). Chronic blepharitis secondary to scarring of the lid margin is less commonly seen (Edgerton, 1945, Burgoon et al, 1957, Marsh & Cooper, 1993). Severe scarring of the lids may lead to trichiasis, loss of lashes, abnormal tear film distribution, ectropion, entropion occlusion of lacrimal puncta and notch defects (Marsh & Cooper 1989). Very rarely full thickness lid loss occurs.

Conjunctiva: Mucus-producing conjunctivitis is a common chronic lesion and may be associated with lid scarring. The mucus is abnormal in quality and adversely affects the tear film, making it greasy and unstable. Less often, large lipid-filled granulomas appear under the subtarsal conjunctiva and severe submucosal scarring similar to that of old trachoma can develop (Marsh, 1976).

Episcleritis and scleritis: Scleritis and nodular episcleritis are particularly chronic and frequently leave patches of increased scleral translucency and scleral atrophy (Edgerton, 1945; Duke Elder, 1966).

Corneal lesions: Chronic inflammation following acute keratitis has been described above but late onset keratitis also occurs.

3.4a Mucous plaque keratitis A strange form of keratitis has been described in a minority of patients which is characterised by the sudden appearance of dendriform white-grey plaques deposited on diffusely swollen epithelium accompanied by a mild ciliary injection, interstitial keratitis and keratitic precipitates (Piebenga and Laibson, 1973; Marsh, 1973). The white-grey plaque has sharply demarcated margins, and may be linear or branched

(dendriform). There are usually several, which vary in size, shape, position, and number day by day, with no preferential corneal site. They stain sparingly with alcian blue, moderately with fluorescein, and brilliantly with rose bengal (Marsh et al, 1976). Application of acetylcysteine drops usually dissolves them and debridement of the plaque leaves an intact but abnormal epithelium. Frequently rapid formation of corneal dry spots is seen and quite often they take on a dendriform shape. Slit-lamp examination with retroillumination shows faint superficial stromal haze over most of the cornea. The mucous plaque deposition tends to continue for several months, but usually the tear film and epithelium eventually stabilize leaving a faint stromal haze which may reduce vision by one or two lines on the Snellen chart.

Mucous plaque keratitis is ushered in by ciliary injection, mild iritis and a profuse deposition of fine keratitic precipitates. Interestingly, the results of the Schirmer test are usually within normal limits but corneal sensation is always impaired. They are usually preceded by an episcleritis, disciform keratitis, or iritis (Marsh et al, 1976). Complications ensuing include neurotrophic keratitis and ulceration, glaucoma, cataract and corneal stromal scarring.

Mucous plaques also occur with filamentary keratitis, keratoconjunctivitis sicca, superior limbic keratitis, varicella keratitis, (Nesburn et al, 1974) and rarely with herpes simplex (Roussel et al, 1984).

3.4b Diffuse epitheliopathy Under this heading comes an ill-defined group of patients who show generalised corneal epithelial bedewing which often advances to grossly oedematous areas of epithelium with the formation of white ridges horizontally in the interpalpebral area (Marsh, 1973). This may or may not be associated with lid deformities (Duke Elder, 1965, Liesegang 1985). Rose bengal and fluorescein drops reveal diffuse punctate staining with moderate linear staining along the ridges. There is generally accompanying hyperaemia of tarsal and bulbar conjunctivae and always an extremely unstable tear film. The Schirmers test and tear production appear to be normal but plugs of mucus are often seen in the tear film. Strangely, the corneal sensation is only partially lost initially (Marsh, 1981). Abnormalities of the lids are unusual and the lid margins may or may not be

healthy. There is usually good blinking (Liesegang, 1985). The onset is usually just after the start of the rash but can be delayed. It runs a protracted course where topical viscous agents are only partially effective. Some chronic cases may go on to develop a neurotrophic keratitis and permanent superficial stromal haze formation (Marsh, 1981; Liesegang, 1985). Attempts can be made to stabilise the epithelium in this condition by intermittently taping the eye closed and lid hygiene but artificial tears and simple ointments do not appear to help.

Lipid Keratopathy. This has been described complicating severe cases of nummular, disciform, and sclerokeratitis (Cogan, 1951, Marsh, 1973; Liesegang, 1985). It may take many years to evolve and is nearly always associated with vascularisation (Cogan, 1951). It may cause severe visual loss and photophobia. It is usually related to inadequate treatment of the primary inflammatory lesion and will be discussed later.

Cataract: Posterior subcapsular lens opacities and nuclear sclerosis have been described in severe and chronic cases of iritis (Burgoon et al, 1957; Marsh, 1976).

3.5 CHRONIC NEUROLOGICAL LESIONS

Optic atrophy follows optic neuritis with a profound loss of vision: 6/60 and less (Edgerton, 1945, Liesegang, 1991).

Postherpetic Neuralgia (PHN): The definition is variable. Simply put it is the persistence of pain after resolution of the rash, but also described as starting at 4 weeks, 6 weeks, 2 months and 6 months (Portenoy et al, 1986). It is different in nature from the acute neuralgia and poor differentiation leads to anomalous results in clinical treatment trials of PHN. It is reported as occurring in from 12-20% of patients (Portenoy et al, 1986) and to be present in from 16.5-25% at 1 year (Rogers et al, 1971; Ragozzino et al, 1982). It is more common with increasing age (Demorgas & Kierland, 1957). It may take on different forms and has been described as: a chronic constant pain or ache, an intermittent severe stabbing pain (closely resembling tic douloureux), an intermittent very unpleasant paraesthesia or a sensation of crawling under the skin (Marsh, 1976). Allodynia, hyperaesthesia and fasciculation have also been described (Portenoy et al, 1986). The pain is often aggravated by touch, heat, cold winds and is worse

at night. The majority of patients improve slowly over one year; a small proportion do not and usually suffer depression which proceeds to severe exhaustion and even suicide (Edgerton, 1945, Marsh, 1976, Liesegang, 1991; Portenoy et al, 1986).

Pathogenesis: There is some doubt if this neuralgia is of peripheral or central origin (Portenoy et al, 1986). The peripheral theory is that as there is a preferential loss of large nerve fibres and an increases transmission of pain through unopposed smaller fibres - an impairment of segmental modulating systems (Noordenbos, 1968). It is sometimes known as the gate control theory of pain (Melzack & Wall, 1965).

The lancinating pain may be related to the activation of primary pain fibres investing the nerve trunk. On the other hand the central theory suggests it is a form of deafferentation pain (Peet, 1929, Rogers & Tindall, 1971) due ultimately to changes in central pathways induced by peripheral nerve or nerve root injury (Liesegang, 1991). In some cases it is undoubtedly associated with severe scarring of the peripheral nerves and skin (Burgoon et al, 1957).

3.6 RECURRENT OCULAR DISEASE

Perhaps the most puzzling aspect of ophthalmic herpes zoster is the recurrent nature of the ocular complications which although common in clinical experience is rarely mentioned in the literature. Complications can reappear as late as 10 years after the onset of the disease, seem to be unrelated to the severity of the initial disease but are often precipitated on suddenly stopping or reducing the topical steroid treatment (Marsh, 1976; Liesegang, 1985).

It should be borne in mind that all these recurrent lesions may be separated by some time from a previous attack of herpes zoster and, indeed, the original attack may have been forgotten or so mild as to have passed unnoticed (Marsh, 1976) or there may be even have been no rash at all (zoster sine eruptio). It is advised that the diagnosis of herpes zoster should be considered when any of the lesions described above are seen in a patient for the first time especially when old stigmata of zoster are apparent. These include the typical geographic skin scarring, areas of increased scleral translucency and patchy iris atrophy (Marsh, 1976).

3.7 TREATMENT

3.70 SYSTEMIC THERAPY

Short-term Admission: (5 days) Physicians recommend this on rare occasions for those with severe disease, the aged, the immunosuppressed, and poor social circumstances (Marsh, 1976).

Steroidal Anti-inflammatory drugs: The routine use of systemic steroids or ACTH in patients with ophthalmic herpes zoster is controversial. Although some physicians used systemic steroids routinely, claiming lessening of zoster complications in particular PHN (Appelman, 1955; Frank and Lysiate, 1953; Elliot, 1964; Pearse, 1973) there is only one properly controlled trial using systemic triamcinolone that supports this (Eaglstein et al, 1970). Others could not confirm benefit and stress the increased risk of systemic spread of the disease with high doses (Rado et al, 1965, Merselis et al, 1964). A recent double blind, controlled trial compared a combination of acyclovir 800 mg 5 times a day and prednisolone 575 mg total for 7 days against acyclovir alone and found the steroid helped in the acute neuralgia only (Esmann et al, 1987). Another double blind study comparing systemic acyclovir alone or in combination with systemic steroid showed a slight benefit for PHN with the combination (Wood et al, 1994). Corticosteroids have been advocated for the following complications of ophthalmic zoster: ischaemic optic neuritis, haemorrhagic skin bullae, orbital apex syndrome and contralateral hemiplegia starting with 80 mgm of prednisolone rapidly reduced over the following week (Marsh, 1990; Liesegang, 1991).

Non steroidal anti-inflammatory drugs: Very little has been published on this group of compounds in zoster but oral Flurbiprophen (Froben) 50 mgm tds is claimed to be useful in cases of episcleritis, scleritis and sclerokeratitis (Watson, 1982).

Systemic Antiviral drugs: A variety of systemic antiviral drugs have been used in zoster, three of which (Adenine Arabinoside, Acyclovir and interferon) interfere with viral replication.

Iodoxyuridine is far too toxic for systemic use and *cytosine arabinoside* proved less effective than the control in one clinical trial (Stevens et al, 1973).

Vidarabine (ARA A) or adenine arabinoside inhibits viral deoxyribonucleic

acid polymerase and proved useful controlling ophthalmic complications in immunosuppressed patients (Whitely et al, 1982). It is however insoluble so introduction intravenously in an effective dose risks fluid overloading (Marsh et al, 1981).

Interferon. Both interferon alpha and beta have been used in very limited trials with equivocal results in diminishing the healing time, pain and dissemination of the rash (Emodie et al, 1975; Merigan et al, 1978). Complications with systemic administration include: fever, neurasthenia and bone marrow depression.

Acyclovir (ACV) inhibits viral replication by its selective phosphorylation of the virus encoded thymidine kinase and by its selective inhibition of the triphosphate of viral deoxyribonucleic acid polymerase. Although the concentration of ACV to inhibit varicella-zoster virus is a hundred times higher than that needed to inhibit herpes simplex virus, serum concentrations exceeding this level can be achieved intravenously and with maximal oral therapy (Liesegang, 1991). All immunosuppressed patients should be treated with systemic ACV; preferably starting as soon as possible after the prodromal phase and initially by the intravenous route at 10 mgm/kg over 1 hour, repeated every 8 hours for 7 days (Balfour et al, 1983). Oral ACV may then be substituted at a dose of 800mgm 5 times a day for a further 7 days. This improves the virological, cutaneous and acute pain parameters (Balfour et al, 1983). The results of oral and intravenous courses of treatment in immunocompetent patients are controversial; although acute neuralgia and rash healing times are marginally improved (Peterslund, 1981; Bean et al, 1982; McGill et al, 1983; McKendrick et al, 1984) reports of its effects on incidence and duration of postherpetic neuralgia are conflicting (McKendrick et al, 1989; Whitely & Straus, 1993; Crooks et al, 1991). There is one large randomised, blind, controlled multicentre trial of 71 patients which shows a reduction in ocular complications in those treated within 72 hours of developing the rash but all those with significant ocular complications at presentation were excluded (Cobo et al, 1985; Cobo et al, 1986). A retrospective trial failed to demonstrate its efficacy in preventing ocular complications (Aylward et al, 1994). Overall there are few complications with the drug: gastrointestinal

upset is uncommon but intravenously it can cause renal toxicity by crystallisation within the collecting tubules.

Valaciclovir is an ACV prodrug which is better absorbed than ACV but rapidly converted to ACV after absorption with 3-5 times the bioavailability of ACV. One preliminary trial showed favourable results for postherpetic neuralgia (Smiley, 1993).

Famciclovir is a prodrug of penciclovir and a preliminary report of a clinical trial also seemed favourable for acute and postherpetic neuralgia (Tyring et al, 1993).

Bromovinyl deoxyuridine BVDU would appear to be promising because the virus is very sensitive to the drug (Liesegang, 1991) but unfortunately has toxicity problems.

Bromovinyl Arabinosyl Uracil Bv-araU, Soriviridine) is perhaps the most interesting antiviral agent. It is extremely active against VZV in vitro more than 20 times more potent than ACV inhibiting viral DNA polymerase. A small trial with oral administration once a day showed it to be effective (Niimira et al, 1990).

Amantadine Despite optimistic claims for Amantadine's efficacy (Galbraith, 1973) there have been no further adequate controlled studies on its effectiveness.

Antibiotics: Although they are widely used for treating the acute rash there appears to be no good scientific evidence that the oedema and crusting are due to bacterial secondary infection and that they are beneficial.

Analgesics:

Acute neuralgia There is good evidence that systemic antivirals, in particular ACV, reduces the duration and severity of acute neuralgia (McKendrick et al, 1986; Liesegang, 1991). There is evidence that good pain control during shingles may reduce the magnitude of the immediate phase of nociceptor evoked hyperexcitability and lessen the probability that subsequent factors will be able to maintain abnormal central processing (Bennett, 1992). The normal range of analgesics, such as aspirin, paracetamol by itself or in combination with dextropropoxyphene hydrochloride (Distalgesic), dihydrocodeine or coproxamol should be used as required; keeping stronger drugs such as buprenorphine (Temgesic) in reserve (Marsh, 1991).

Unfortunately they are often ineffective because the pain is neuropathic in origin and narcotics are the least effective method of reducing it.

Postherpetic neuralgia It is generally admitted that PHN is extremely difficult to treat and like acute neuralgia is more of a problem in older patients. The list of remedies recommended in the literature is legion, (many anecdotal and rather dubious): ranging from posterior pituitary extract to snake venom (Edgerton, 1945); clearly demonstrating the overall failure of treatments for this condition.

Standard analgesics as mentioned above are advised; increasing the strength until the pain is controlled.

Anticonvulsants have been advocated for the lancinating type of pain. A double-blind study found carbamazepine effective (Killain & Fromm, 1968) although others have not been able to confirm this (Portenoy et al, 1986, Marsh, 1990).

Psychotropic drugs have proved effective particularly tricyclic antidepressants when there is depression accompanying the pain. A controlled trial with amitriptyline 50 mgm twice a day has shown significant improvement in pain especially when administered early on (Watson et al, 1982; Portenoy et al, 1986).

Tranquillisers Diphenhydramine (Piriton) 4 mgm 3 times a day and chlorpromazine 25 mgm thrice daily have proved useful with severe irritating paraesthesia (Marsh, 1990).

Antidepressives: Post-viral depression often begins during the acute phase of zoster and may also be an important component of chronic postherpetic neuralgia (Marsh, 1976; Watson et al, 1982). Prompt recognition and treatment with tricyclic antidepressants such as amitriptyline (50 mgm twice a day) have been advocated (Watson et al, 1982).

Supportive: Counselling has been recommended for those with severe chronic PHN not responding to treatment in an attempt to help them live with the pain (Portenoy et al, 1986).

Prophylaxis: *Chickenpox vaccine:* Two attenuated strains of varicella are undergoing clinical trials for vaccination (Weller, 1982, Weibel et al, 1984). The main advantage in using a vaccine would be to decrease the complications of varicella in children and adults, and already it has proved

particularly effective in children who are immuno-suppressed (Kangro, 1990). At best, they prevent or ameliorate the development of zoster but it would be virtually impossible to do a trial to decide this, because of the numbers and time course involved (Plotkin et al, 1985).

3.8 SPECIFIC TREATMENT

3.80 SKIN TREATMENT:

Topical Antivirals: These are advocated in the early vesicular stage of the disease when there is marked virus activity. Idoxyuridine although insoluble in water is highly soluble in dimethyl sulphoxide; preparations are available in 5-40% solutions (Iduridin or Herpid). These are applied as a paint by the patient or as presoaked dressings changed daily for the first 4 days by a nurse and have been claimed to speed the onset of crusting, prevent secondary cropping and reduce acute and postherpetic neuralgia, (Dawber, 1974; Juel-Jensen and MacCallum, 1972; Marsh, 1977) although there were no randomised controlled trials.

Acyclovir 5% ointment applied 3 times a day has also had similar claims of efficacy (Levin et al, 1985).

Topical Anti-inflammatories: Steroid creams and ointment application have been advocated when the vesicular phase has passed - usually 10 days after onset; claiming that there is quicker clearing of crusts and perhaps less scar formation (Marsh, 1990).

3.80c: Topical Management of Postherpetic Neuralgia

Topical Anaesthesia may be administered as somatic blocks *subcutaneously* around the peripheral nerve with or without steroids such as triamcinolone. Reports are uncontrolled and the results mixed (Miller et al, 1980, Riopelle et al, 1984).

Topical anaesthetics may be given as a sympathetic block into the *stellate ganglion*. Success has been claimed when administered within 2 weeks of rash onset; pain relief being achieved in 90% and after 2 weeks in only 40% (Colding, 1964, Harding, 1987). Unfortunately the trials were uncontrolled. The method of action is unknown but may be related to blockade of type C nerve fibres, improvement in blood flow or simply breaking the pain cycle (Portenoy et al, 1986).

Neuroaugmentative approaches consist of afferent stimulation in attempt to

activate endogenous pain modulating systems and include counterirritation, TENS, acupuncture, dorsal nerve stimulation.

Counter irritation: Energetic massage of the affected skin area using a vehicle of lanolin or vaseline has proved effective for neuralgia after crust separation and possibly also reduces scarring (Marsh, 1990). It is based on the gate theory of sensory neural conduction: stimulation of the large afferent nerves with massage inhibits the smaller pain fibre transmissions. It is reputed to be best in the stabbing, intermittent type of pain.

More recently *Capsaicin*, the first of a class of neuropeptide active agents for PHN has been reported to reduce both acute pain and PHN but the results are anecdotal (Bernstein et al, 1987; Bucci et al, 1988). It is thought to act by having a specificity for nociceptive or pain transmitters, type C nerve fibres without affecting the sensations of touch, pressure or vibration. Topical application causes a burst of neuropeptide substance P from the C fibres, causing an initial burning sensation (Liesegang, 1991). The benefit comes only after several weeks of use, after substance P can no longer be replenished. It should be noted it is very irritant if it contacts the eye.

Transcutaneous electrical nerve stimulation (TENS) can be effective, as can short wave diathermy and ultrasound (Loeser et al, 1975; Long et al, 1973).

Neurosurgery includes the following procedures: undermining or resectioning scarred skin, neurectomy, rhizotomy and sympathectomy, centrally cordotomy, trigeminal tractotomy, mesecephalotomy and thalamotomy. All have proved very disappointing because not only may they be unsuccessful but may introduce other problems such as neurotrophic corneal ulcer formation (Portenoy et al, 1986).

3.81 LID TREATMENT: The same topical agents as described for the skin have been advocated. If there is severe scarring of the lids it may be necessary to epilate and electrolyse the trichiasis or to correct lid deformities by plastic surgery (Marsh & Cooper, 1989). It is advised that chronic blepharitis should be treated by lid toilet and the application of antibiotic ointment to the lid margins twice a day.

3.82 OCULAR THERAPY:

Topical Antivirals: Despite early reports that ACV ointment controlled and prevented later ocular complications (Mcgill, 1981) others have been unable

to confirm this (Marsh & Cooper, 1984; Marsh & Cooper, 1991). A recent double blind trial reported ACV alone was inferior to steroid for controlling inflammation but when combined with steroid led to less rebound inflammation on withdrawal of treatment (Marsh & Cooper, 1991).

Topical Antibiotics: Drops such as chloramphenicol are customarily used to prevent secondary infection during the acute stage when lid vesicles are discharging and forming crusts or a mucopurulent conjunctivitis is present. Tetracycline ointment has proven very effective for kerato-conjunctivitis when applied twice daily to chronically scarred or inflamed lid margins (personal communication Peter Wright 1976).

Topical Anti-inflammatory agents: Since the introduction of steroids in the early 1950s they have proved the mainstay of therapy for the ocular complications of herpes zoster especially for scleritis, sclerokeratitis, disciform and mucous plaque keratitis, diffuse corneal oedema, significant degrees of iritis and hypertensive iritis (Marsh, 1976). Prompt treatment at the start of inflammation appears to cut down the ischaemic and fibrotic scarring that usually develops (Marsh, 1976). At the first evidence of these complications it is advocated that 0.1% dexamethasone drops should be instilled every 4 hours and once control is achieved, the potency and frequency of administration can be reduced and the dose of topical steroids titrated against the degree of disease activity in the eye (Marsh, 1990). It has been suggested that as well as reducing the frequency of administration of the drug, serial logarithmic dilutions or a change to another weaker steroid may be made (eg from dexamethasone to betamethasone to prednisolone) and reduction to as little as 0.03% prednisolone daily to maintain control (Marsh, 1976).

Precautions with topical steroids. Patients on topical steroids may develop glaucoma, cataract, secondary infections, mydriasis and ptosis (Becker, 1964). It is therefore advocated that patients receiving long term administration be regularly examined ophthalmically. They also tend to develop a type of 'dependency' on them (Liesegang, 1991) that is that their withdrawal may be difficult without causing a recurrence of ocular inflammation (McGill and Chapman, 1983; Liesegang, 1991). To avoid inducing lens opacities potent doses of steroid should be reduced as soon

as possible (Frandsen, 1966). It is noteworthy that mydriasis and ptosis can occur in zoster in the absence of steroid therapy (Edgerton, 1945). They must be used with great caution in patients with neurotrophic keratitis because of the risk of secondary infections (Marsh, 1990; Liesegang, 1991). **Artificial Tears, wetting agents and mucolytics** are used where there is an unstable corneal epithelium in an attempt to stabilise the surface and prevent mucous deposition. Artificial tears are divided into non-viscous types containing polyvinyl alcohol or adsorptive polymers. Long term drops administration can lead to toxic changes to the epithelium from the preservatives contained and preservative free drops have provided a major advance. Bland lubricants such as lacrilube may be used at night (Roy and Fraunfelder, 1994). 10% and 20% acetylcysteine has been advocated for dissolving mucous deposits and preventing further deposition, particularly in MPK (Marsh, 1976). Simply taping the eyelids closed with Blenderm has been advised for rapidly establishing a stable epithelium (personal communication P Wright, 1982).

3.83 Management of neuropathic keratitis

Attempts are usually made to stabilize the precorneal tear film with artificial tears and protective spectacles. It is advised that any co-existing ulcerative blepharitis should be treated first with lid toilet and antibiotic ointment. Abnormal plugs of mucus in the tear film may be dispersed by mucolytics such as acetylcysteine 10% (Fraundfelder et al, 1977). Topical corticosteroids are strictly contraindicated in the absence of a tarsorrhaphy or lid drop as they tend to encourage rapid excavation and growth of the ulcer; similarly bandage lenses have proved unsatisfactory because of the risks of corneal abscess and hypopyon formation (Marsh, 1981). It is generally recommended that severe indolent ulceration of the cornea is treated by a large lateral half tarsorrhaphy at an early stage, although taping of the lids has been advised as a temporary measure. Recovery after tarsorrhaphy is remarkable, with stabilization of the tear film and rapid healing of ulceration. The lateral third tarsorrhaphy clearly gives better potential for sight and is more acceptable cosmetically but in some cases is ineffective in protecting the corneal epithelium and must be converted to a central tarsorrhaphy (Marsh & Cooper, 1989). A year or two after suturing

it may be possible to open the tarsorrhaphy in cautious small stages (Marsh, 1990). Botulinus toxin induced ptosis, more recently, has been very successful in achieving rapid healing and gives a more acceptable cosmetic appearance; often maintaining stabilisation of the epithelium when the lid elevates after a few months (Adams et al, 1987; Marsh & Cooper, 1993). Corneal grafting should be avoided, but if a neurotrophic ulcer perforates and has to be grafted an accompanying generous one third temporal tarsorrhaphy should be carried out at the same time (Marsh & Cooper, 1989).

3.84 SURGERY.

Very little has been written about ocular surgery in ophthalmic zoster.

Lids: Lid margin deformities arising from scarring (eg. ectropion and trichiasis) are best treated with corrective lid surgery (Liesegang, 1985; Marsh & Cooper, 1989). The lateral half tarsorrhaphy has already been discussed.

Intraocular surgery:

Cataract extraction: The extracapsular technique with posterior chamber implant has proved straight forward when undertaken in a quiescent phase. The main problem observed is postoperative inflammation which may persist for more than a year but always seems to be controllable with a low dose of topical steroid (Marsh & Cooper, 1989).

Glaucoma surgery: Trabeculectomy appears to be trouble free; only postoperative inflammation being a real problem. A high incidence of cataract formation has been described later on (Marsh & Cooper, 1989).

Combined cataract and glaucoma surgery has been undertaken and proved most successful with the same proviso of covering postoperative inflammation (Marsh & Cooper, 1989).

Corneal surgery: Neglected disciform keratitis or sclerokeratitis frequently give rise to dense scarring and lipid deposits in the central cornea. These patients tend to do well with perforating corneal grafts provided that the corneal sensation is preserved and there is not too much vascularisation or the vessels have been closed by argon laser treatment (Marsh, 1988; Marsh & Cooper, 1989). However, those with neurotrophic ulceration do notoriously badly as considerable difficulty may be encountered in

establishing a stable corneal epithelium over the graft and consequently many corneal surgeons carry out a tarsorrhaphy at the same time ((Marsh & Cooper, 1989).

3.85 Summary

It can be seen that many facets of ophthalmic zoster are poorly understood, in particular latency and reactivation of the virus and the pathogenesis of most of the lesions. The major research problems are that there is no satisfactory animal model and there is a dearth of pathological material; compounding this there is also a lack of large accurately observed series of patients. This necessarily leads to poor understanding of the natural history and makes adequate randomised clinical trials very rare. Trials on new systemic antivirals are particularly difficult because of problems using placebos in place of older antivirals and recruiting adequate numbers of patients.

It is to be hoped that recent advances in virology such as PCR will facilitate identification of the virus in tissues and a new generation of systemic antivirals will be more effective in controlling replication of virus.



4 PATIENTS AND METHODS

4.1 Clinical Setting: A Herpes zoster clinic was started in 1968 by Professor Barrie Jones at Moorfields as part of the External Disease Clinic. I assumed responsibility for the clinic in 1972 and have since run 2 clinics a week. All patients were seen by me helped by a constantly changing series of assistants.

4.2 Patient Selection: Patients were, in the main, referred by their GPs directly to casualty at Moorfields. They were drawn from the surrounding area of London and were for the most part fit prior to developing the disease. In the main they were referred promptly to the Zoster clinic. It is probable that a large number of patients with ophthalmic zoster as opposed to zoster elsewhere on the body is referred directly to hospital by GPs because of their fear of the ocular complications.

4.3 History and Examination: A standard ocular history was taken and a basic ocular examination was carried out

4.4 Additional history and examination. Table 4.1 lists these.

Special History	Pain	Degree & quality
Past History	Chickenpox & Zoster	with a note on location
Special Examination	Skin rash	Extent, depth & stage Involvement of lid margin? or dermatome of NC nerve?
	Corneal sensation	Measured in 5 sectors
	Iris & pupil	Transpupillary transillumination
Where appropriate	Referral to	Physician & Neurologist
		Orthoptic examination
		Corneal & iris angiography

Table 4.1 Special history and examinations

Special Investigations: From 1971 until 1982 all patients had the following

routine investigations: a full blood count, differential white cell count, blood film, ESR, liver function tests, electrophoretic strip, blood sugar and chest X ray. Subsequent to the study of clinical immunity in 1982 and influenced by our findings these routine investigations were stopped and only carried out if specifically indicated.

4.41. Corneal sensation was measured with the aesthiometer of Luneau and Coffignon (Clement Clarke). It was assessed in 5 zones: central, top left, top right, bottom left and bottom right quadrants. The minimal stimulation of the cornea was with a 6cm length of fine nylon bristle and the maximum with a 1cm bristle. A cumulative score was reached by adding all sectors together. If no corneal sensation was evoked the bulbar conjunctiva and lid margins stimulated with a 1 cm bristle and the results recorded.

4.42. Transpupillary examination: A bright slit lamp beam was projected into the pupil with the width and height adjusted such that it just fits within the pupil and the beam as coaxial as possible. The areas of pigment epithelial loss of the iris were observed and drawn.

4.43. Fluorescein Angiography:

General technique of anterior segment angiography: A Zeiss photoslit lamp was used and set at X10 magnification. Colour photographs were taken first using a diffuser filter in front of a broad slit. Then angiography modifying the technique described by Easty and Bron (1970). 5ccs of 20% fluorescein was injected rapidly into an antecubital vein. An exciter filter was put in front of the slit objective and a barrier filter put in front of the camera backs and one of the slit lamp eye pieces. Exposures were made every 1.5 seconds and the results were recorded on Ilford FP4 film. The processed films were examined on a dokumator microfilm reader.

4.5 General Recording of information

Notes were kept by me on all patients from 1971 and in 1973 all of those with a 1 year history of follow-up or more had their salient details duplicated on large charts. Later on in 1980 when computer databases became freely available the details were transcribed to this, initially in Dbase 2 (Ashton Tate), tailoring the design of chart to fit the maximum available number of fields and records; later on this was upgraded to DBase 3+ (Ashton Tate).

Appendix 1a shows the recording form for the computer. It can be seen that

a scoring scheme was adopted for most of the complications which was very simple and largely based on 3 degrees of severity. The top half was completed from details recorded in the first 3 months and the lower half recorded complications remaining at 1 year.

4.6 Selection of patients for the different studies.

As time went by the database was added to and for the purposes of this MD ended in 1986 with 1356 patients. However, the different studies were carried out at different time periods. Thus the earliest study was carried out on iris angiography in ophthalmic zoster between 1972 and 1974. Five hundred and twenty cases were sampled in this period of whom 140 were old patients and 140 were new. The next study was on ocular palsies which was a combination of a retrospective study from patients seen from 1972 to 1976 and a prospective study for a period of 8 months in 1977. The third study was a retrospective study of 1000 patients from all the notes in the database from 1972 to 1981 to try to establish if there was impaired clinical immunity. The patients mentioned in the Mucous plaque keratitis were drawn from 1212 patients seen between 1972 and 1985. Those mentioned in the chapter on laser treatment of lipid keratopathy were gathered from a 16 year period from 1978 to 1992 and included those in the general zoster database and a separate lipid keratopathy database. Lastly the chapter on incidence of ocular complications was drawn from the complete database of 1356 over the full period from 1972 to 1986.

5 THE PREVALENCE OF CLINICAL IMPAIRMENT IN IMMUNITY

5.1 Introduction: For many years it has been suggested that patients contracting herpes zoster have compromised immunity (Edgerton, 1945, Walsh & Hoyt, 1969, Wright & Winer, 1961, Sokhal & Firat, 1965). However, zoster occurs widely in the community, especially in the elderly. Our clinical impression was that most of our patients with ophthalmic zoster had no associated systemic disease prior to and following the infection. This had not been described in the literature. A retrospective study on patients seen in the Zoster clinic up to 1981 was conducted to determine whether or not this impression was correct and to test if the infection and ocular complications were more severe in those patients with underlying disease. At the time laboratory tests for impaired immunity then were not particularly refined and so clinical evidence had to be used.

5.2 Patients and methods: One thousand consecutive patients, with a minimum review of 3 months, attending between 1972-1981 were included. Particular emphasis was made on the medical history and previous attacks of zoster. The notes of these consecutive patients were retrieved. All patients had a chest X ray, and the following blood tests carried out at their first visit: a full blood count, differential white cell count, blood film. ESR, liver function tests, electrophoretic strip and blood sugar. The patients were also asked about previous zoster infections and whether they were on systemic steroids. Those patients whose blood tests were abnormal (abnormal being taken as anything outside the normal range in biochemistry, and differing from a normal differential white blood count) were examined in detail and multivariate analysis was undertaken with age, sex, haematological results, biochemical results, and type of eye problem as variants. The incidence of ocular complications occurring in this group were then compared with those having normal blood and was calculated by means of the Fisher exact probability test. Those falling outside normal were referred to the Physicians Clinic.

5.3 Results: Previous systemic disease and the occurrence of systemic rash are summarised in Table 5.1

Table 5.1 The Prevalence of preceding systemic disease in 1000 patients with Ophthalmic Zoster

Previous zoster	Previous systemic disease	Previous malignancy	Systemic rash	Preceding systemic steroid
36	12	12	3	5

Of the thousand patients 72 had no ocular involvement - the infection being confined to the skin. Thirty-six patients reported previous zoster infections which had usually been thoracic or lumbar, but 1 patient had suffered ophthalmic zoster on the other side 18 years previously and had visible pitting and depigmentation in the skin on that side. Three patients developed a disseminated rash with more than 5 spots in places other than those which could have been produced by auto-inoculation. None of these 3 patients had malignant disease or developed it during the period of review.

Five patients were on steroids for unrelated problems including chronic chest disease, eczema, and nephrotic syndrome. Associated diseases included 4 with diabetes, 3 postgastrectomy patients (benign gastric ulcers), 1 patient with discoid lupus erythematosus, 1 with sarcoid, and 3 with ulcerative colitis. None of these were on steroids or had been for at least 4 months. Two patients developed transient hemiplegias on the opposite side to their zoster ophthalmicus 7 weeks after the onset of the rash. One episode was 6 weeks after the onset of the zoster and the other 5 months.

No previously undiagnosed malignancies were found or developed during the period of review. Six patients had carcinoma of the breast, diagnosed between one and 21 years previously. Three had carcinoma of the colon; 1 patient was on chemotherapy and the other 2 had been diagnosed 2 and 6 years previously. There was 1 patient with Hodgkin's disease on chemotherapy, 1 with carcinoma of the lung diagnosed 10 years before, and 1 with a 'brain tumour' diagnosed in 1952.

Three hundred and sixty four patients had abnormal blood results of any sort of which 176 were male and 188 were female. One hundred and thirty nine of these had abnormal differential white cell counts (Table 5.2).

Table 5.2 Abnormal differential white cell counts occurring in 139 patients)

<i>Result</i>	<i>No. of patients</i>
Lymphocytosis	64
Neutrophilia	19
Monocytosis	19
Leucopenia	14
Lymphopenia	13
Eosinophilia	10

(Many of these abnormalities were combined in the same patient)

The commonest age range was 50-70 years, with the youngest being 18 years and the oldest 91. The average period of follow-up was 2 years with the range being less than 1 year to 8 years. Most patients were followed up until their eye was stable and they were discharged, with only 5 defaulting after 3 months.

The commonest eye problems which developed in the 1000 patients were iritis/iris atrophy, episcleritis, and superficial stromal scarring. The age and sex of the patient were unrelated to the type of eye problem which developed, and there were no correlations with abnormal biochemical results. There were no prognostic indicators in the blood results. The outcome of the ocular disease was not affected by the presence or absence of a lymphocytosis, raised gamma globulins or any other blood factors. There was a significant association between the presence of an abnormal haematological result (as opposed to a normal result) and mucus plaque keratitis ($p < 0.0005$), but when the abnormal results were looked at no specific abnormality was more common.

5.4 Comment: Only 12 of the patients, who were from a general rather than a hospital population, had malignant disease, and no new malignancies were discovered on screening or developed during the follow-up period. This confirmed the clinical impression that a predominantly healthy population

was being dealt with. Dissemination of the rash occurred in only 3 patients, and none of these had malignant disease. A previous study of 175 patients with herpes zoster described 17 patients developing widespread vesicular lesions during the course of typical localised herpes zoster and 11 of these 17 patients had serious underlying diseases (Merselis et al, 1964). The difference in results probably reflects the selection of patients, the Moorfields group coming from a general population and not from a hospital population.

Second attacks of zoster were thought to be rare. Head and Campbell (1900) found 4 patients in a survey of 400 (1%) with herpes zoster affecting all parts of the body, whereas 36 of the patients here had suffered previous attacks (3.6%). None of these patients had underlying disease nor a history suggestive of reinfection, so it is difficult to explain how and why they developed the disease.

This study has shown that the great majority of patients contracting herpes zoster ophthalmicus are healthy and therefore do not have diminished immunity. The trigger factors for this disease remain a puzzle and require further investigation. {Subsequent to this study AIDS appeared adding a significant new cause of cell-mediated-immunosuppression which predisposes to infections such as herpes zoster and simplex. As stated earlier in Chapter 3 this is a relatively common problem in the African subcontinent but in the Western world it is rarely associated with Ophthalmic Zoster.}

6 THE INCIDENCE OF OCULAR COMPLICATIONS IN OPHTHALMIC ZOSTER, THEIR CORRELATIONS AND SUPPLEMENTARY NOTES ON SOME COMPLICATIONS

6.1 Introduction: This large single series of patients with ophthalmic zoster offers useful information on the incidence of complications and their correlations. Past series tended to be small and the results very variable.

6.2 Methods: The collection and recording of the database of 1356 patients has been described earlier. This database was closed in 1986 and upgraded to the DB 3+ programme. In 1994 this was used to count the number of complications and the number of combinations of complications. Correlations were then sought.

6.3 Results: Analysis of the database gave the following figures on incidence:

Age and sex: Figure 6.1 shows the age and sex distribution with 595 (44%) males and 761 (53%) females. (The 1981 census for Greater London consisted of 48% males and 52% females.)

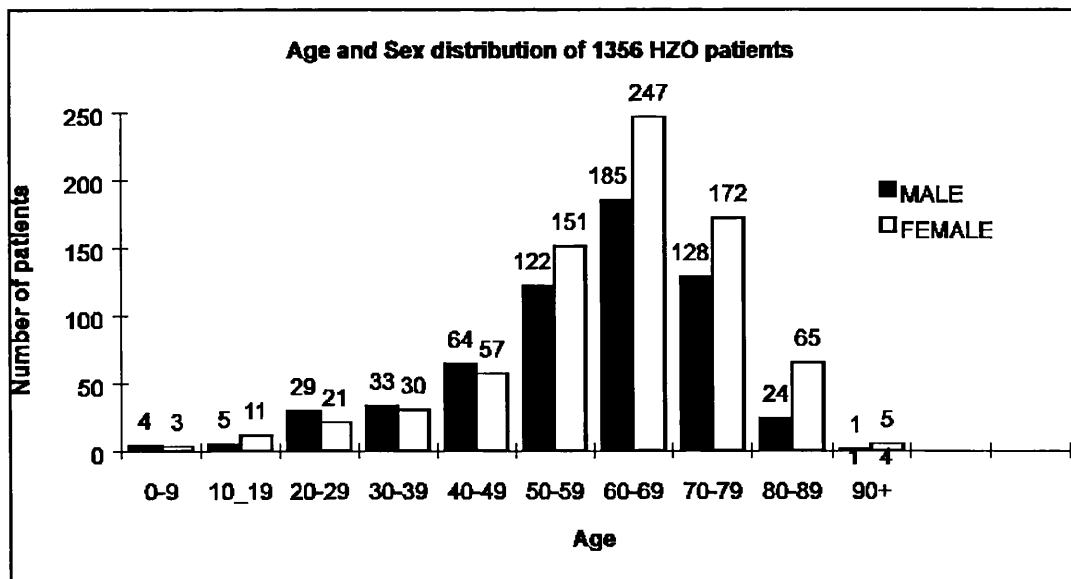


Figure 6.1 Age and sex distribution of ophthalmic zoster

Systemic disease: As seen in the previous chapter only 12 in a continuous series of a 1000 cases had malignant disease (Lightman et al, 1981). The 17 patients under 16 years of age in this series did not suffer or develop serious systemic illness over a minimum period of 3 years.

Rash: 430 patients had a mild rash, 743 moderate and 131 severe (52 were not recorded or minimal). The average ages for the different degrees of severity of rash were: 64 for severe, 61 for moderate and 56 for a mild rash. There were 604 patients with *nasociliary nerve involvement* 6 of whom had no ocular involvement at all. There was a close correlation between the severity of the rash and acute and post herpetic neuralgia as shown in figure 6.2.

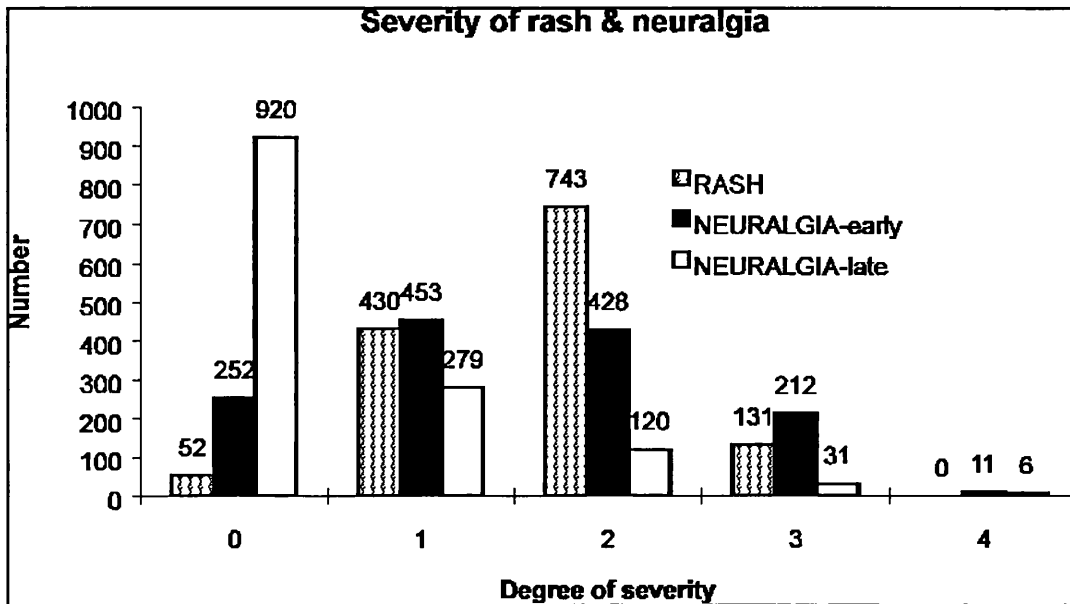


Figure 6.2 *The incidence and severity of the rash, acute and chronic neuralgia in ophthalmic zoster.*

6.34 Ocular Complications: Table 6.1 shows the number of different complications seen in 1356 patients:

Table 6.1

TISSUE	COMPLICATION	TOTAL	PERCENT	mild	mod	sev
Ocular	Conjunctivitis	1015	75			
	Episcleritis	753	55	545	208	
	Nodular Episcleritis	70	5			
	Scleritis	37	3			
(Keratitis)	Microdendritic	253	19			
"	Nummular	411	30			
"	Disciform	112	8			
"	Corneal oedema	72	6			
"	Sclerokeratitis	43	3			
"	Mucous Plaque	53	4			
"	Neurotrophic	43	3			
"	Diffuse epitheliopathy	33	2			
"	Megaplaque	6	0.4			
"	Lipid	60	4			
	Iritis	728	53	551	157	20
	Iris Atrophy	335	25			
	Glaucoma	194	14			
	Steroid Glaucoma	42	3			
Neurological	Optic neuritis	6	0.4			
Palsy	extraocular	133	10			
	facial	7	0.4			
	Encephalitis	2	0.1			
	Hemiplegia	7	0.4			

(Please note the total number of keratitis cases is larger than the global number of patients. This is because 42 patients had a combination of different keratitides. Symptomatic extraocular palsies only are recorded here.)

Table 6.1 continued

MODALITY	None	Mild	Mod	Sev	V Sev
Acute neuralgia	453	252	428	212	11
Chronic neuralgia PHN	920	274	120	31	6

Figure 6.3 shows the incidence and severity of episcleritis/scleritis and iritis. A total of 335 cases of iris atrophy was seen of which 51 were just in the basal region, 278 had combined sphincter damage and 6 massive iris atrophy.

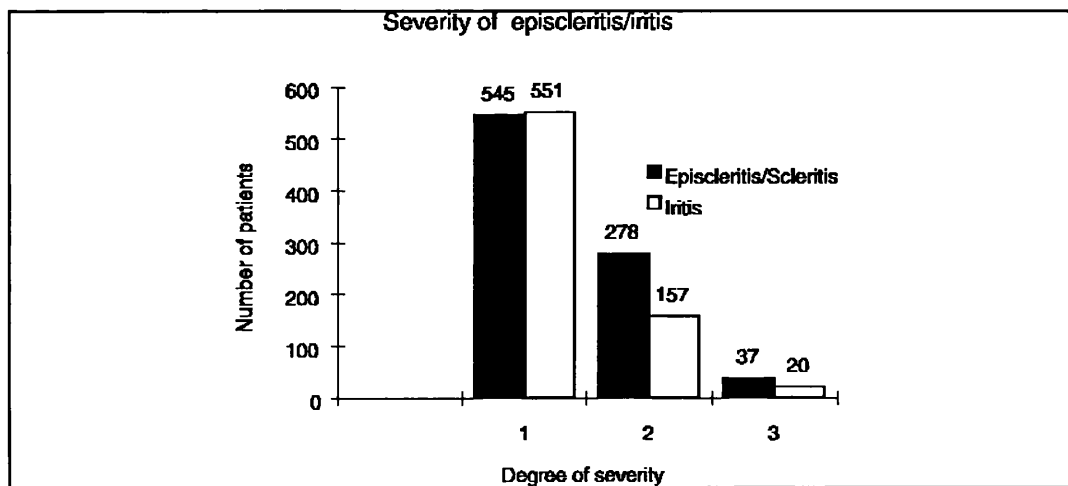


Figure 6.3 Incidence and severity of episcleritis/scleritis and iritis

CONJUNCTIVITIS: This was reported as occurring in 1015 cases and was often a very mild and transitory phenomenon lasting only 2 to 3 days, unassociated with any later eye complication.

6.34a CORNEAL COMPLICATIONS: Figure 6.4 shows the incidence of the different types of keratitis. Please note again that some patients had combinations of early and late keratitis which increases the numbers to 1379 from a total of 1356 patients.

Supplementary notes on some particular types of keratitis:

Five types of keratitis posed particular problems in behaviour, management and loss of vision, 3 are described below including: Neurotrophic, Diffuse epitheliopathy and 'Megaplaque' keratitis, the fourth, mucous plaque keratitis is presented in chapter 7 and the fifth, lipid keratopathy, in chapter 8. In view of the relatively large number of cases collected it seemed to be appropriate to present our findings.

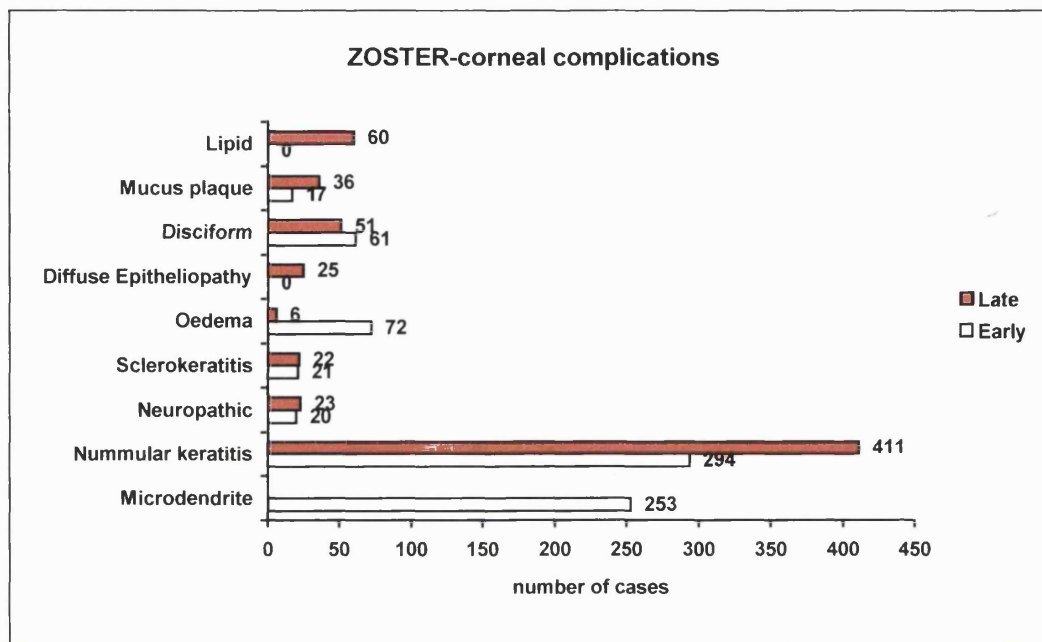


Figure 6.4 Incidence of different types of keratitis

6.34a1 Neurotrophic keratitis (NTK):

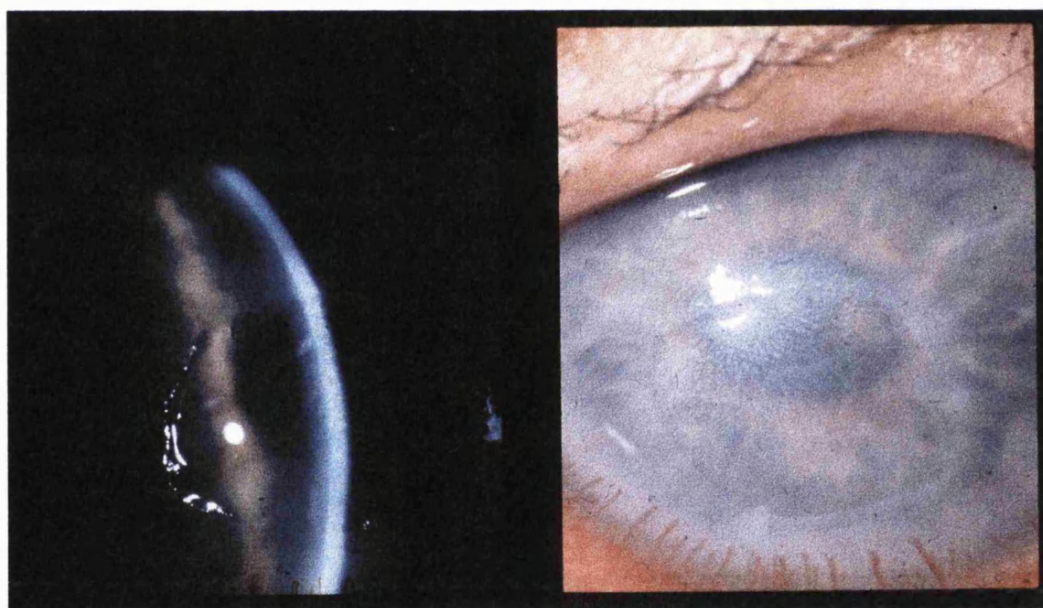


Figure 6.5 Neurotrophic ulcer

Introduction: This is a relatively rare complication and there is sparse literature describing the management of this condition and the management strategies described here were developed during the course of this study.

Methods: In addition to the routine history and examination described earlier sensation of the conjunctiva and lid margins was assessed as described previously at each visit. The

incidence of ulceration and its treatment, complications and associations were recorded. The tarsorrhaphies that were carried out were tabulated as follows:-early or late, central or temporal, the number carried out or expanded on an individual case, time for epithelial healing, late complications and if reopening was successful.

Results: Of a total of 89 patients who lost their corneal sensation at the onset of the disease early ulceration occurred in 20 and late onset ulcers in 23 patients (where there was later loss of corneal sensation or decompensation of a previously quiet anaesthetic cornea). All showed a loss of conjunctival and lid margin sensation confirming Mackie's findings (1978). Six patients had preceding mucous plaques keratitis and the ulceration developed after an average period of 9 months. Two cases perforated. Four developed severe stromal scarring with a subepithelial formation of a dense inspissated mucous deposit (megaplaque keratitis). Four patients developed a corneal abscess and hypopyon following fitting with a soft contact lens.

Thirty five patients with ulceration received tarsorrhaphies of which 30 had an adequate follow up of 2 years. Ten of these 30 were carried out early and 20 late. Thirteen patients had two or more procedures due to disintegration, premature opening and insufficiency of the tarsorrhaphy (six of these were temporals extended centrally). Accurate data on epithelial healing time were available in 29 cases of which 13 recovered within a week, ten within one to two weeks and six were over two weeks. Reopening of the tarsorrhaphy was successful as far as no further ulceration developed in five of 12 cases. One of the 2 patients with a perforated cornea had a successful corneal graft combined with a lateral tarsorrhaphy and the other a conjunctival flap. Eight of the remaining patients with ulceration were treated with Botulinus toxin injection into the Levator palpebrae (with immediate lid drop achieved in 6), two patients required repeat injections to achieve this. In all but one the corneal ulcer healed rapidly.

Correlations: A severe rash usually precedes neurotrophic keratitis as shown in Table 6.3

Discussion: The pathogenesis of neurotrophic keratitis is poorly understood

but it is known that there is considerable destruction of the neurones in the ophthalmic nerve with zoster (Head & Campbell, 1900). Why tarsorrhaphy and drug induced ptosis are so successful in the management of this condition is difficult to construe but may be due to continuous intimate contact between the very vascular upper subtarsal conjunctiva and the cornea which possibly allows diffusion of important trophic factors. It was clear that urgent treatment was required to establish rapid reepithelialisation of the cornea in order to prevent stromal melting and scarring. The ulceration was clearly made worse by bandage contact lenses with the development of corneal abscess and hypopyon possibly due to the facility of soft contact lenses to adsorb bacteria and the impaired metabolism of the cornea. Both cases that perforated had been on topical steroids for several months. When a corneal graft or topical steroids were necessary a tarsorrhaphy or Botulinus-induced ptosis was carried out.

6.34a2 Diffuse epitheliopathy:

Introduction: Under this heading comes an ill-defined group of patients who show generalised corneal epithelial swelling which often advances to grossly oedematous areas of epithelium with the formation of white ridges horizontally in the interpalpebral area (Marsh, 1973). This condition is also associated with lid abnormalities (exposure keratitis) where there is insufficient lid closure and protection of the precorneal tear film and epithelium. A number of cases with zoster were identified, the associated changes identified and management is briefly discussed.

Methods: During examination of these patients particular note was made of the integrity and health of the lid margins.

Results: 25 cases were found and contrary to the diffuse epitheliopathy of other aetiologies abnormalities of the lids were unusual, the corneal sensation was lost in only 3 of the 25 cases and there was usually good blinking. The onset appeared to be just after the start of the rash but could be delayed. It ran a protracted course where topical viscous agents were only partially effective. Five chronic cases went on to develop poor vision 2 due to the development of large central white surface deposits and calcification ('megaplaque' keratitis), and 3 neurotrophic keratitis with permanent superficial stromal haze formation. Attempts can be made to

stabilise the epithelium by intermittently taping the eye closed and lid hygiene but artificial tears and simple ointments did not appear to help. Tarsorrhaphy appeared to stabilize the epithelium in the 2 cases that it was used.

6.34a3 'Megaplaque' keratitis:

In 6 cases a strange form of chronic keratitis was observed which was characterised by the formation of large white plaques deposits on the corneal surface. These were disc-or ring-shaped (Figure 6.6) and were attached to the underlying stroma by a narrow neck. They profoundly interfere with vision and often have epithelial defects around their base where secondary infections gain a portal of entry. They followed NTK in 4 patients and exposure keratitis in 2. Standard artificial tears and mucolytic treatment was unsatisfactory. Surgical removal by superficial keratectomy was carried out successfully in one case and Excimer laser superficial keratectomy was carried out in 2 cases. The latter had a good early response but there was slow recurrence of plaque over a period of 2 years and the procedure had to be repeated in both.

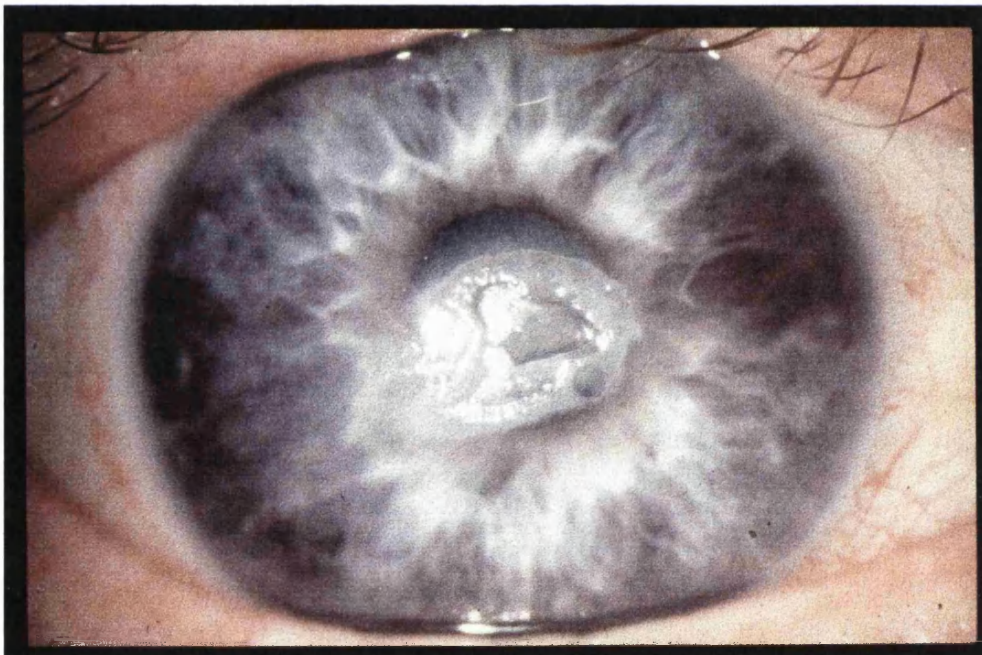


Figure 6.6 *'Megaplaque' keratitis*

6.34b Retinal pigment epithelial degeneration: The 1 case was apparently directly associated with zoster. It presented at 2 weeks with slight diminution of central vision and small areas of pigment epithelial swelling around the macula area. There was no vitreous activity and shortly afterwards subtle areas of pigment migration replaced the acute lesions. Fluorescein angiography showed early multiple small areas of choroidal windowing around the macula with no pronounced late leakage of dye. It was interesting that although the scarring appeared quite substantial and was centred around the macula there was very little diminution of vision.

6.35 NEUROLOGICAL COMPLICATIONS

Optic neuritis resulted in vision of less than 6/60 in all 6 cases and in 4 of the **external ocular muscle palsies** there was a total third, fourth and sixth nerve palsy accompanied by proptosis, scleritis, and iritis. All but one of the **Contralateral hemiplegias** made a good recovery.

Neuralgia: There was a very close correlation between the degree of early neuralgia and rash severity/late neuralgia $X^2 = p < 0.01$ (figure 6.2). There was also a close correlation between neuralgia and loss of corneal sensation (figure 6.7). When measured at 6 months post herpetic neuralgia occurred mildly in 279 patients, moderately in 120, severely in 31, very severely in 6 and was absent in 920. It is correlated with severity of rash, ocular involvement, loss of corneal sensation and the degree of early neuralgia, but surprisingly not age (by chi square $p < 0.01$).

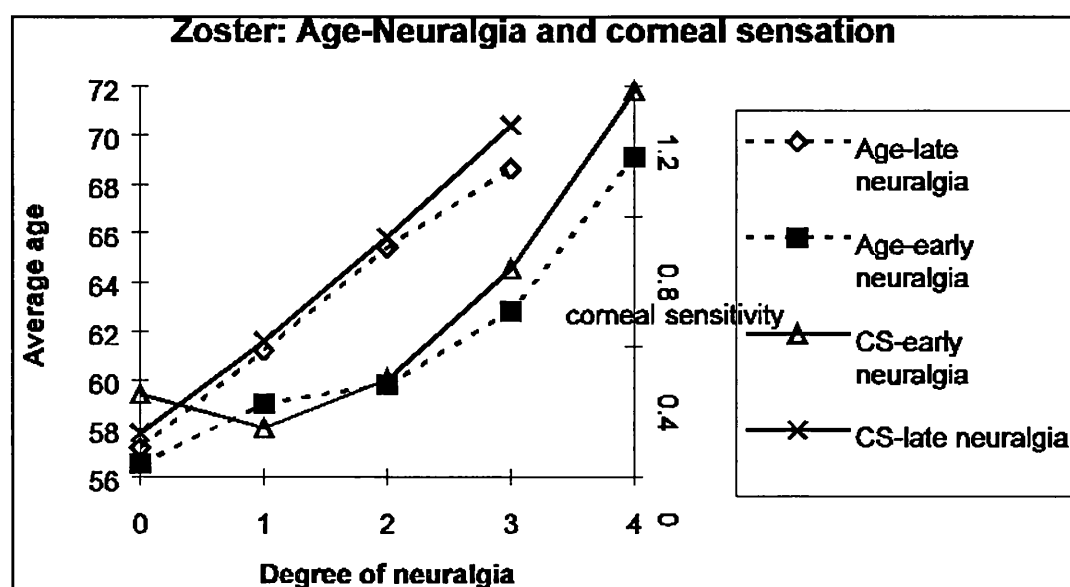


Figure 6.7 The relations between early and late neuralgia corneal sensation

and age. (The average age for the different degrees of neuralgia is plotted on one side along with the average degree of loss of corneal sensation and neuralgia on the other side with corneal sensation scored as 0=normal, 1 = diminished, 2 = lost)

6.36 Correlations:

There were significant associations (using X^2) in the following:-

1. Involvement of the nasociliary nerve and ocular complications $p < 0.001$
(only 6 out of the 604 affected patients had no ocular complication)
 2. Lid margin involvement and ocular complications $p < 0.0006$
 3. Iritis and the severity of the rash (Table 6.2) $p < 0.002$
 4. Severity of the rash and neurotrophic keratitis (Table 6.3) $p < 0.002$
 5. Diminution of corneal sensation and MPK (Table 6.4) $p < 0.0003$
 6. Microdendritic keratitis and nummular keratitis $p < 0.0006$
- (There were 266 cases of microdendritic keratitis and 157 were associated with nummular keratitis.)

Table 6.2 Correlations between iritis and severity of rash

	Severity of rash			
	0	1	2	3
Gross No of cases	56	428	742	130
With minimal iritis (0)	15	209	277	36
mild iritis (1)	16	147	324	61
moderate iritis (2)	9	34	90	18
severe iritis (3)	2	3	12	5

Table 6.3 Correlations between severity of rash and neurotrophic keratitis

	Severity of rash			
	0	1	2	3
Gross No of cases	56	428	742	130
No of cases of early NTK	1	0	11	7
No of cases of late NTK	3	5	13	14

Table 6.4 Correlations between diminished corneal sensation and MPK

Corneal sensation	Total No of cases	MPK
Present (0)	838	13
Diminished (1)	431	34
Lost (2)	90	10

6.37 No Correlations

1. Disciform keratitis and MPK
2. The severity of PHN and MPK
- 3 The severity of the rash and MPK
4. The severity of oedema and the rash
5. Disciform keratitis and the rash

Table 6.5.
Comparisons of the incidence of ocular complications of
Ophthalmic Zoster in different series.

	Marsh & Cooper (1993)	Burgoon et al. (1957)	Womack & Liesegang (1983)	Harding et al. (1987)	Scheie (1970)
Numbers	1356	36	94	71	93
conjunctivitis	75%	7%			
Episcleritis	55%				
N episcleritis	5%				
Scleritis	5%				
Keratitis	49%	8%	61%	22%	28%
Microdendrites	19%		51%		
Nummular	30%		41%		
Disciform	8%		10%	13%	
Oedema	6%				
MPK	4%				
Neurotrophic	3%	4%	25%		
Diffuse Epitheliopathy	2%		11%		
Sclerokeratitis	4%		1%		
Serpiginous	.04%		7%		
Iritis	53%	3%	34%	3%	26%
Glaucoma	14%		3%	12%	
Muscle palsy	10%	3%		3%	2%
Optic atrophy	0.04%			1%	
<u>Neuralgia</u>					
Acute	76%	18%			
Chronic	12%	12%		21.4%	

(The only other large published series of patients was that of Edgerton but this was a collection of patients from many different physicians and centres prior to 1945 and therefore are not included in the table above.)

6.4 Discussion: The difference of incidence between the sexes was statistically insignificant. The peak age incidence was 60-69 and then tapered off. This does not contradict the increased incidence with increasing age because proportionately less patients survive for other reasons after 75.

Hutchinson's rule that involvement of the nasociliary nerve heralded ocular complications was confirmed. This is really not surprising because this nerve provides innervation to the globe. Involvement of the lid margin too usually precedes ocular complications, not only do they have similar innervation but the vesicular lesions release copious quantity of virus directly on the surface of the eye.

Conjunctivitis was the commonest complication but was frequently short-lived, trivial and not requiring treatment. Episcleritis also was often mild and recovered without treatment.

Nummular keratitis was far and away the commonest corneal complication and its precedence by acute microdendritic keratitis suggested either a neural distribution of virus into the corneal epithelium and stroma with later appearance of lesions in the stroma or virus sinking into the underlying stroma from the epithelial microdendrites.

Disciform keratitis was central or eccentric and if inadequately treated with topical steroid was prolonged and often gave rise to permanent corneal scarring. The mechanism was assumed to be an antigen-antibody reaction but it was not possible to demonstrate the presence of replicating virus. Similarly the mechanism of acute corneal oedema was assumed to be due to transient damage to corneal endothelium which also responded well to prompt administration of topical steroid.

The association between mucous plaque keratitis and loss of corneal sensation was not easy to explain but probably reflects the degree of neural damage occurring.

The 3 types of keratitis have been separately described that have distinct natural histories, appreciable ocular morbidity (particularly visual loss) and pose difficult management problems. It was found by early identification and appropriate management morbidity could be minimised. *Neurotrophic keratitis* reflects extensive damage to the ophthalmic branch of the trigeminal nerve and therefore would be expected to occur more often with

severe rash and neuralgia. *Diffuse epitheliopathy* was poorly understood and resembled exposure keratitis but without the lid abnormality. *Megaplaque keratitis* was an end stage of the previous two types of keratitis but only in a minority of cases. The mechanism of calcium deposition was not understood but clearly was related to a disturbed relationship between the corneal epithelium and tear film where both were abnormal.

The incidence and severity of iritis is closely related to episcleritis/scleritis and the zones of iris atrophy and episcleritis are often in the same sectors. This seems logical as both are due to a vasculitis and neurovascular bundles tend to be in a radial distribution in the eye. The incidence of iritis also correlates to the severity of the rash which again suggests a relationship with the degree of vasculitis. It was no surprise that there was a close relationship between the degree of acute neuralgia and severity of the rash because both reflect the degree of viral invasion, inflammation and destruction of the sensory nerves.

6.41 Comparison with other series. Harding's series gives a low incidence for iritis and keratitis which is difficult to explain. Burgoon's was a very small series and it is unlikely that most cases were not examined with the slit lamp. This would possibly explain the low incidence of keratitis. Womack and Liesegang's series is more comparable to this series and was derived from a retrospective survey of notes from the Mayo clinic. The squint figures here are higher than theirs probably because we were examining for this more intensely. Their figures on serpiginous ulcer, NTK and exposure keratitis are higher but there is no clear explanation. The acute neuralgia figures are much greater than the only other series where this is measured. This is probably a difference in interpretation as was the higher incidence of postherpetic neuralgia affecting the ophthalmic nerve in Harding's series and in 2 series including other dermatomes 47.5% (Demoragas & Kierland, 1957) and 46.9% (Rogers & Tindall, 1971).

7 CORNEAL MUCOUS PLAQUE KERATITIS

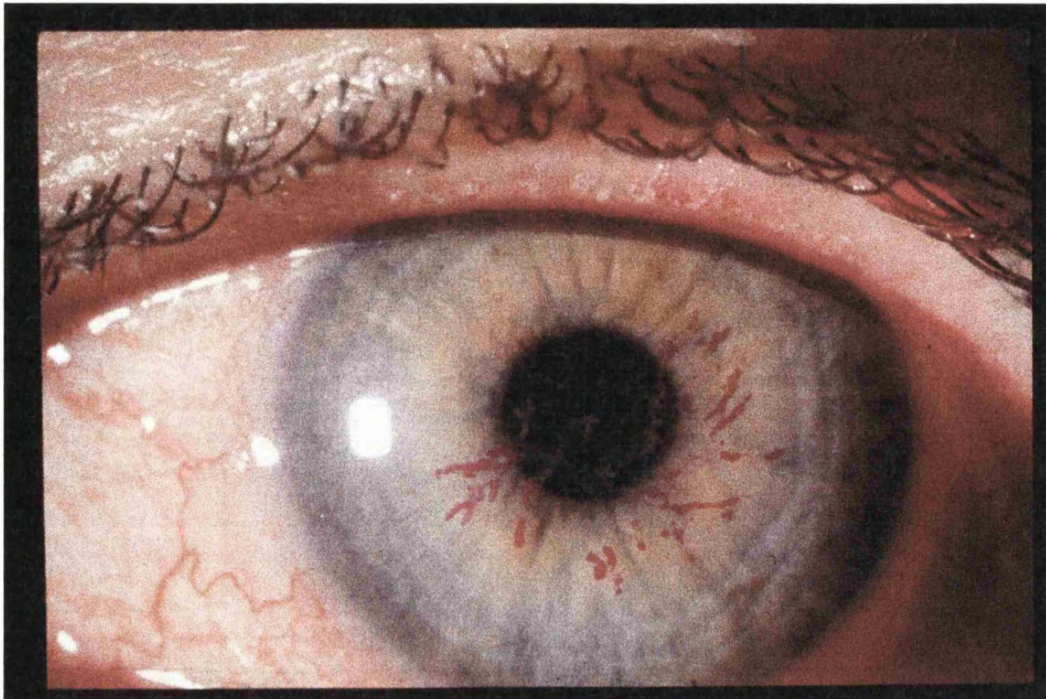


Figure 7.1 *Mucous plaque keratitis stained with Rose Bengal*

7.1 Introduction: Mucous plaque keratitis is an indolent keratitis involving epithelium, stroma and endothelium characterised by brightly staining dendritic figures deposited on the epithelium.

Dendriform corneal epithelial disturbances have long been recognised in ophthalmic zoster but only relatively recently described in the literature (Marsh, 1973, Piebenga & Laibson, 1973). The collective term 'pseudodendrite' precludes a satisfactory classification of these disturbances, gives no indication of the nature of the lesion, and is unhelpful in their management.

There are two distinct entities with dendriform figures in zoster. The first, acute epithelial microdendritic keratitis, occurs a few days after the rash and resolves rapidly without complications. Viable virus is recoverable from the lesions (Pavan Langston & McCulley, 1973). The second, MPK, by contrast

has no clear temporal relationship to the rash and is a chronic disorder which is commonly associated with severe ocular sequelae such as glaucoma, cataract and neurotrophic ulcers. Viable virus cannot be identified in these lesions (Piebenga & Laibson, 1973).

The aim of this study is to define the clinical behaviour of zoster mucous plaque keratitis, to emphasise its difference from herpes simplex keratitis in order to plan appropriate management and to report that the complicating glaucoma, cataract, and neuroparalytic ulcers may be successfully treated surgically.

7.2 Patients and methods: The data were derived from consecutive patients in the database over a continuous 10 year period from 1972 to 1985 which amounted to 1212 patients. One thousand and thirty (85%) of these had follow-up visits at least three monthly over two years, and these form the study group (as opposed to the final global data base of 1356). Examination at each visit concentrated on the corneal epithelial appearance, in particular: the slit profile of the dendritic figures, their staining characteristics with rose bengal, fluorescein and alcian blue, the effect of debridement, 3 had cytology of scrapings from the lesions and culturing for virus. The corneal sensation was checked at each visit and the extent of stromal involvement was recorded. All patients with active inflammation were treated with topical steroids and the principle of therapy was to match the dosage to the degree of inflammation. Dexamethasone drops four-hourly were used initially, and, as the condition ameliorated, the frequency was reduced over months to twice daily. If control was achieved, the drop was changed to betamethasone, any recurrence necessitated returning to dexamethasone immediately. Over the next six months substitution by prednisolone 0.3% drops twice daily was attempted. An unstable corneal surface was treated with mucolytics and artificial tears. Glaucoma was managed with topical antiglaucoma agents. Complicating neurotrophic ulceration was treated by temporal tarsorrhaphy or botulinus-induced ptosis. We compared the accompanying features of MPK with those of all ophthalmic zoster patients (with similar follow-up).

7.3 Results: Forty-seven (4%) cases of mucous plaque keratitis were found in this series of 1030 patients, of whom 39 had regular review data for two

to 13 years (mean six years). When compared with the whole clinic population the patients with MPK were of similar age distribution (Figure 7.2).

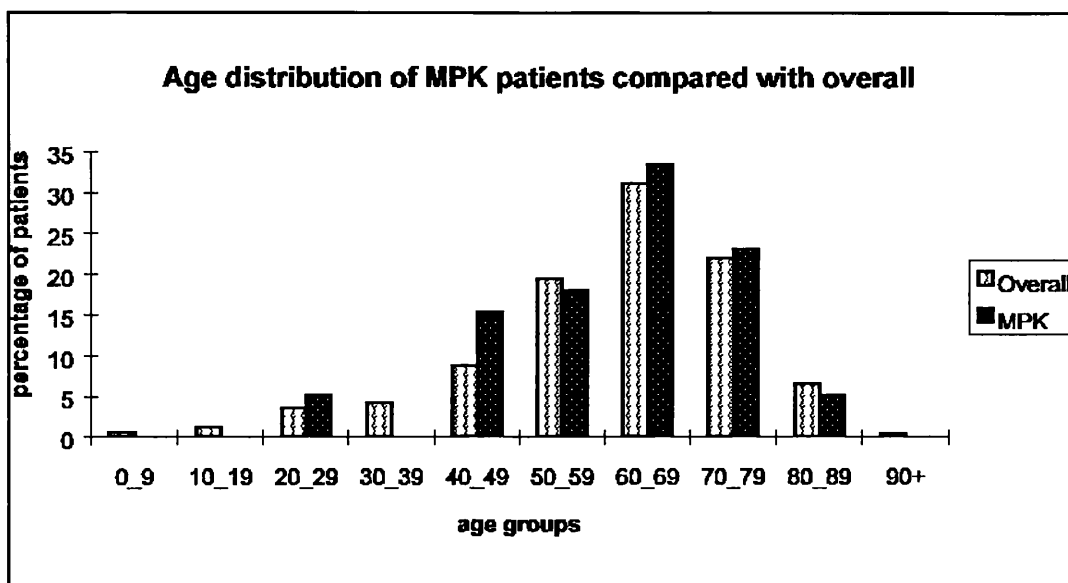


Figure 7.2 Age distribution of 1030 patients and those with MPK

The white-grey plaque which characterises the keratitis is adherent to the surface epithelium, has sharply demarcated margins, and may be linear or branched. There are usually several, which vary in size, shape, position, and number day by day, with no preferential corneal site. They stain sparingly with alcian blue, moderately with fluorescein, and brilliantly with rose bengal (Figure.7.1). They are deposited on a diffusely thickened and abnormal epithelium. Their onset varies from one week to two years after the rash. Debridement of the plaque leaves an intact but abnormal epithelium. Cytology of 3 corneal mucous plaques showed no viable cells but strong positive staining for mucus (Alcian blue and Southgate mucicarmine). Scrapings of the underlying epithelium demonstrate large, multinucleated cells similar to the others with swollen and degenerated surrounding epithelium (Marsh et al, 1976). No Varicella/zoster virus was cultured from 6 of these corneas.

Figure 7.3 shows the time of plaque onset in relation to the rash, the majority occurring within the first three or between six and seven months.

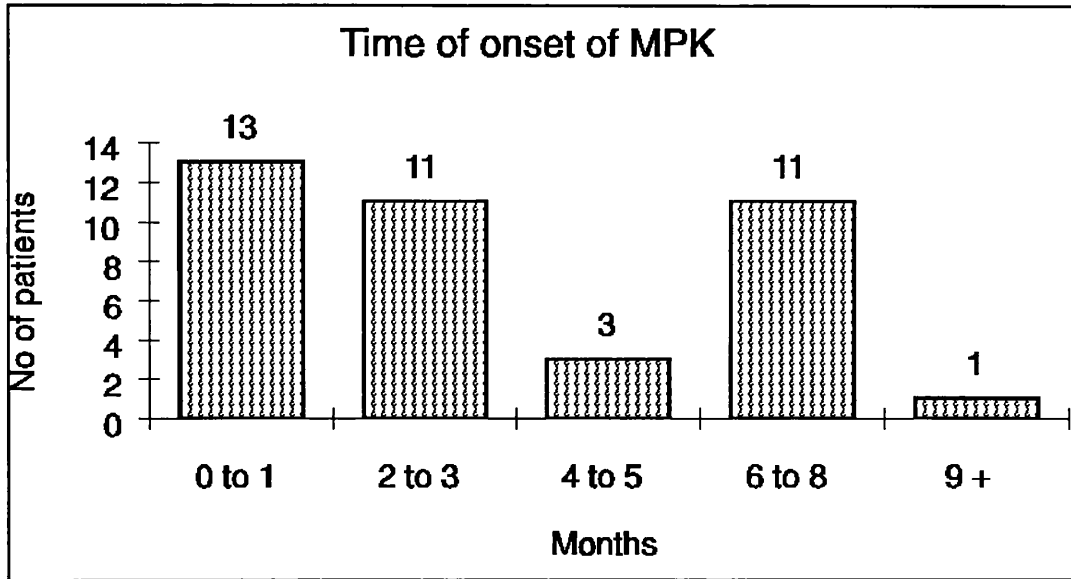


Figure 7.3 The variation in time of onset of 39 cases of MPK.

Figure 7.4 shows the duration of the plaque, which was usually less than five months.

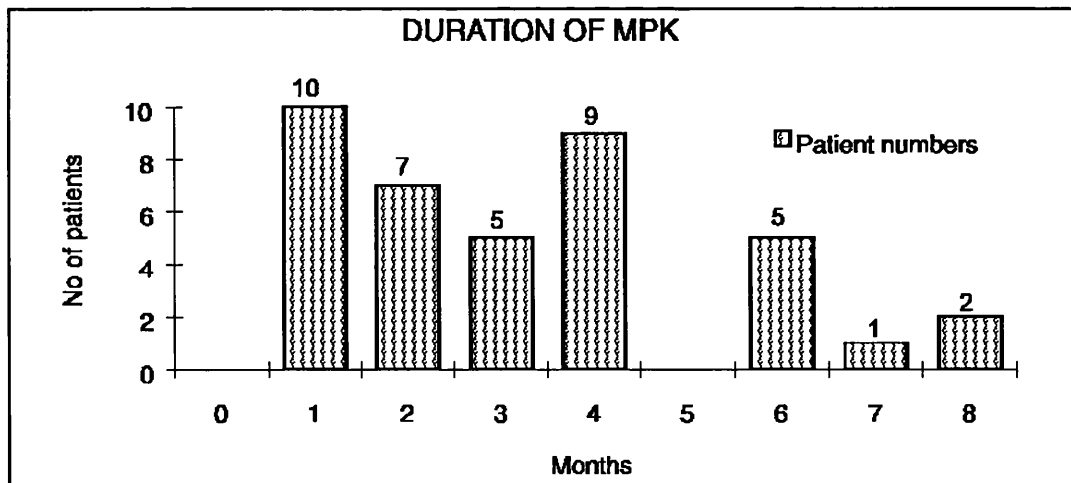


Figure 7.4 Duration of 39 cases of Mucous Plaque Keratitis.

7.30 Associated clinical features may be considered under the following headings: those preceding the onset of the plaque, those associated with it, and those subsequent to it. There were no preceding feature in 28%, but a complication distinguishing them from the rest of the clinic population was an increase in hypertensive iritis as shown in Table 1 ($p < 0.05$ by X^2 test).

Table 7.1. Incidence of associated clinical features occurring before and simultaneously with 39 cases of MPK (out of a total of 1030 patients).

<i>Category</i>	<i>Previous involvement</i>	<i>Coincident involvement</i>	<i>Overall clinic incidence</i>	<i>Significance</i>
Iritis	22 (56%)	20 (51%)	53%	p<0.05
Raised IOP	16 (41%)	9 (23%)	14%	p<0.05
Episcleritis	12 (31%)	22 (56%)	60%	ns
Diminished corneal reflex	14 (36%)	14 (36%)	33%	ns
Microdendrites	9 (28%)	0	19%	ns
Nummular keratitis	13 (33%)	15 (38%)	52%	ns
Disciform keratitis	7 (18%)	4 (10%)	8%	ns
Corneal oedema	7 (18%)	unknown	6%	ns

(The incidence of these features in the clinic as a whole is shown in the last column and the overall clinic incidence excludes all those with MPK. Only 9 patients had MPK without other combined different types of keratitis)

MPK is associated with a combination of episcleritis (usually perilimbal), iritis, superficial corneal stromal infiltration, and a decrease in corneal sensation, though none of these taken individually is more common in mucous plaque keratitis than in the clinic population as a whole.

The sequelae can be split into two groups: one with plaque onset within the first three months of rash onset and the other after this time. Table 7.2 shows a generally more severe outcome in plaques of later onset except with respect to lipid keratopathy, disciform reactions, and uveitis. (p<0.05 by X² test). Only one case had a coincident herpes simplex infection.

Table 7.2. Incidence of clinical features following MPK (in 1030 cases)

<i>Category</i>	<i>Early plaque</i>	<i>Late plaque</i>	<i>Overall clinic</i>	
<i>Significance</i>	<i>< 3 months</i>	<i>> 3 months</i>	<i>incidence</i>	
Corneal stromal haze	16 (67%)	15 (100%)	unknown	
Corneal ulcers	2 (8%)	4 (27%)	4%	p = <0.05
Diminished sensation	6 (25%)	9 (60%)	33%	
Disciform keratitis	6 (25%)	5 (33%)	12%	
Lipid keratopathy	4 (17%)	2 (13%)	5%	
Lens opacities	10 (42%)	2 (80%)	12%	
Refractory glaucoma	1 (4%)	5 (33%)	3%	
Recurrence	6 (25%)	5 (33%)	4%	

(There were many combinations of different corneal lesions)

Two patients rapidly developed large interpalpebral ring-shaped subepithelial plaques with underlying stromal thinning which we called 'megaplaque' keratitis (ch 5). These complications often led to visual loss (Table 7.3).

Table 7.3. Numbers of patients with decreased visual acuity

<i>Snellen Lines lost</i>	<i>No of patients (total = 39)</i>
0	11
1	5
2	7
3	3
4	3
5	10

Most of the visual loss was due to a combination of cataract and corneal

scarring.

We failed to culture virus in 6 consecutive cases in 1976; the plaques were scraped and then put in 2SP virus transport medium and finally inoculated on to human embryo lung fibroblasts.

In view of the possibility that MPK was associated with the prior use of topical steroids we checked patients' drug records and found 11 of the early onset and 21 of the late onset patients had received them (Marsh & Cooper, 1987).

7.31 Differentiating features from dendriform epithelial lesions of herpes simplex and acute zoster microdendrites are:

The dendrites of simplex are finer, more lacy, may or may not have end bulbs but are longer and more central than those of acute zoster dendrites and mucous plaque keratitis.

Unlike MPK rose bengal stains the margins of herpes simplex dendritic ulcers, but only moderately well the acute dendritic zoster lesions. Fluorescein stains the ulcer bed of herpes simplex ulcers intensely, but the zoster lesions are only moderately well stained. Alcian blue stains the corneal mucous plaque well, but the lesions of acute zoster and simplex poorly.

The dendritic lesions of simplex and acute zoster can be removed only if corneal epithelium is detached unlike MPK. Since the corneal mucous plaques are on the surface of the epithelium they can be removed easily by gentle scraping with minimal damage to the underlying epithelium.

Topical corticosteroids, although they alleviate the inflammatory complications, do not have a notable effect on corneal mucous plaques since they vary in size, number, appearance and frequency regardless of whether this medication is used. However, they can and often do appreciably increase the width of individual branches as well as the overall size of dendritic lesions of epithelial herpes simplex.

Scrapings from the margins of herpes simplex and the acute zoster lesions show degenerating and large multinucleated cells with moulding of nuclei and margination of chromatin. The cytology of the corneal mucous plaques shows no viable cells but strong positive staining for mucus (alcian blue and

Southgate mucicarmine (Marsh et al,1976). Herpes simplex virus can be readily isolated from the edges of its ulcer but varicella/zoster virus cannot be obtained from the zoster mucous plaques (Piebenga & Laibson, 1973; Marsh et al, 1976). **Table 7.4** depicts the number of cases requiring surgery. Two patients developed combined cataract and glaucoma which required surgical treatment. Neurotrophic ulcers developed from one month to three years after MPK onset and were always treated with a lateral third tarsorrhaphy. All 4 cases requiring glaucoma surgery were successfully controlled without glaucoma therapy, and the acuities of those patients who also had intraocular lens implants were excellent. All cases required a booster dose of topical steroid over three months postoperatively because of relapsing keratitis and iritis. The tarsorrhaphies were followed by healing of corneal epithelial ulcers within three days.

Table 7.4. Cases requiring surgery

<i>Operation</i>	<i>No</i>
Combined trabeculectomy + extraction + implant	2
Trabeculectomy	1
Laser trabeculoplasty	1
Lateral third tarsorrhaphy	5

7.4 Discussion: These results indicate that mucous plaque keratitis associated with herpes zoster ophthalmicus has a distinct clinical appearance and evolution. MPK is not difficult to diagnose if an adequate history is obtained. Although the appearance is superficially similar to that of herpes simplex, detailed examination of the morphology and of the staining characteristics will distinguish them. It is very rare to have coincident zoster and simplex. Although there have been several cases of epithelial lesions occurring in the course of zoster attributed to herpes simplex superinfection described in the literature (Acers & Vaille, 1967;

Giles, 1969; Sugar, 1971) a review of the cases here showed only one case of ophthalmic zoster with true complicating herpes simplex corneal epithelial disease. It seems, therefore, that coincident corneal epithelial infection with the two viruses is an extremely rare event and that epithelial keratitis with typical ophthalmic zoster rash on the involved side is caused by zoster until proved otherwise.

Most cases of MPK will eventually become quiescent, but, while the inflammation may soon settle, the epithelium may take much longer to recover, especially if there is loss of corneal sensation or a degree of exposure. The patients with MPK fell into two groups: one with early onset keratitis (within the first three months of the rash) and the other with late onset. The latter group of patients have the more severe problems, such as cataract, raised intraocular pressure, and corneal ulceration. The high risk of recurrence may necessitate repeated observations and prolonged topical steroids. A maintenance dose for long term use is recommended because there was a pronounced tendency to relapse even after two years, especially on reducing or stopping treatment. Even prednisolone 0.3% drops on alternate days was enough to control inflammation. Posterior subcapsular lens opacities can arise from both chronic iritis and long-term topical steroid, but steroid is not recognised as giving rise to nuclear sclerosis. Raised intraocular pressure may be due to the necessarily intense and prolonged topical steroid treatment or a trabeculitis accompanying the iritis. An acute hypertensive uveitis will usually settle within a few days on thorough treatment with topical steroids, but if there is steroid-induced glaucoma the steroid drops are replaced by fluoromethalone and timolol eye drops. With severe refractory glaucoma drainage surgery may be necessary. Corticosteroids must be used with great caution where there is continuing denervation of the cornea and conjunctiva leading to neurotrophic keratitis and ulceration. Then an early tarsorrhaphy or botulinus-induced ptosis must be considered. The circinate plaque deposits are distinct from those described in corneal infections (Samples et al, 1986).

Despite traditional reservations about intraocular surgery in patients with complicated ophthalmic zoster and the relatively small number of cases the results were good in this series. A booster dose of topical steroid was

required postoperatively after all intraocular surgery for at least three months because of the tendency to recurrent uveitis and keratitis. Neurotrophic ulcers were completely healed within a few days of tarsorrhaphy. Usually a temporal third was sufficient but occasionally a middle third was essential, and it was important to maintain a low dose of topical steroid to keep the inflammation under control.

7.41 Pathogenesis: The aetiology is obscure; at least two factors are likely to lead to MPK: altered corneal epithelium and disturbance of tear film mucus. Normal epithelium has mucous receptors primarily involved in the maintenance of the tear film (Roussel et al, 1984). Alteration of these could reasonably lead to an accumulation of mucus, especially if the mucus derived from goblet cells is less soluble than usual. The entire corneal epithelium appears abnormal on the slit lamp, as probably is the conjunctival epithelium. This may be due to infection, exposure, inflammatory mediators, and denervation with loss of 'trophic factors', all of which may lead to alterations in cell surface properties. The changing shape, size, and distribution would support the concept of a generalised abnormality that is quite different from the local lesions of acute herpes simplex keratitis, but more akin to those seen in keratoconjunctivitis sicca (although morphologically distinct). There is only one reported patient with fluorescent antibody staining of cells underlying a plaque suggesting a viral infection (Hayashi et al, 1973). The stromal changes are difficult to explain but appear to be associated at the onset with inflammation and infiltration with cells, later on there appears to be permanent stromal scarring. The only significant correlation of associated ocular lesions was hypertensive iritis (chi square $p < 0.05$). Although there does appear to be a connection with the prior use of topical steroids (McGill & Chapman, 1983) many cases of MPK were preceded by inflammatory lesions that required treatment with steroid and when considering their widespread use in ophthalmic zoster the 4% incidence is low.

8 LASER TREATMENT OF LIPID KERATOPATHY IN ZOSTER

8.1 Introduction: The term lipid keratopathy was first coined by Cogan (1960) for the clinical picture resulting from the appearance of fat in an area of previous corneal vascularization.

Lipid may be deposited as a result of an excess of lipids in the blood, failure in fat metabolism, and a defect in cell processing of lipid within the cornea. Cogan suggested that fat is not usually deposited because the substrates in the blood are usually in a bound form and therefore not available to the corneal cells, but if the blood is overloaded with lipids, free fatty acids may become available for lipogenesis (Cogan & Kuwabara, 1955). Like other cells in the body, keratocytes and corneal epithelial cells have the ability to form fat when exposed to specific substrates, an enzymic process requiring the presence of serum and suitable fatty acids (Cogan & Kuwabara, 1958). The presence of fat in the cornea results in further vascularization stimulated by a foreign body type of reaction. It is probable that fat is initially intracellular, the majority being in invading monocytes but when necrosis occurs it becomes extracellular (Baume, 1969).

The main accumulations of fat are in the middle layers of the stroma where the lamellae show necrotic changes and vacuolation with rich deposits of fatty droplets and needle-like crystals in between them (Davidson, 1947). There is also an infiltration of large mononuclear histiocytes undergoing foamy degeneration, the cytoplasm being packed with fatty granules. Although neutral fat is present, the greater parts of the deposits are cholesterol and phospholipids. The older the lesion the more prominent are the crystalline elements and the fewer the histiocytic cells. In the oldest cases degeneration becomes more complete with the appearance of fibrous tissue and calcification (Cogan et al, 1955). Although lipid keratopathy may occur in the absence of demonstrable blood vessels dense deposits are always vascularised. The vessels may stem from the limbus at a narrow origin of a single artery and vein or from multiple stems all around the limbus. In the vascularized area, white or creamy plaque appears, the nature of which varies with the degree of vascularization and the state of the cornea. Thus, when the vascularization is confined to a localized area in a compact cornea, the deposition tends to adopt a disc-like shape; when the

cornea is swollen the deposition takes on a fan-like shape radiating from the ends of the vessels, and in the presence of widespread vascularization the fatty changes are likewise diffuse.

Clearly it would seem logical in the treatment of vascularized lipid keratopathy to attempt to control any increase in blood lipids, the corneal disease precipitating it, to close the feeder vessels and, in cases of severe central deposits, corneal grafting. The first approach has proved disappointing, for despite the possible relationship with fatty change in hypercholesterolaemia there has been no evidence of diet improving the condition. The second approach has been more rewarding with the careful treatment of keratitis with topical steroids. The third approach has been tried by various techniques, including peritomy, severing or cautery of the vessels at the limbus, B-radiation (Lederman, 1952; Michaelson and Schreiber, 1955; Mandras, 1956, Fraser & Naughton, 1961, Ainslie et al, 1962), thiotepa (Langham, 1960, Lavergne & Colment, 1964), and cryotherapy (Mayer, 1967). Of all these B-radiation, thiotepa and topical steroids proved the most effective (Ey et al, 1968). Fourthly, corneal grafting, although initially successful, is often complicated by rejection because of the vascular nature of the scars.

More recently the laser presented itself as a very accurate instrument for occluding these vessels and some encouraging reports have been made for improving or halting the deposition in the short term (Cherry et al, 1973; Read et al, 1975; Cherry and Garner, 1979). Some attempts have been made to improve uptake of laser by the vessels by injecting intravenously complimentary dyes in experimentally induced vascular scars in animals (Mendelsohn et al, 1987; Chamian et al, 1995; Goto et al, 1995) and then in humans (Hennessey et al, 1994; Sheppard et al, 1994). The technique was quite effective particularly with very small vessels.

It seemed by modifying the laser techniques used for closure of small vessels in diabetic retinopathy it might be possible to prevent further deposition of lipid or even allow existing lipids to be absorbed by macrophages and make corneas safer for grafting. Preliminary experience with lipid keratopathies of various aetiologies was good (Marsh and Marshall, 1982; Marsh, 1982; Marsh, 1988). It was appropriate therefore to

analyze separately all the cases of zoster lipid keratopathy treated with laser, sometimes repeatedly, with a follow-up of at least 1 year with particular reference to assessment, treatment and results.

8.2 Patients and Methods: Patients were drawn from 2 sources for the treatment sample:-

a. those in the zoster database

b. those from a lipid keratopathy database

Over the past 15 years from 1980-1995 patients with lipid keratopathy were referred for assessment and treatment from all over England (but chiefly Moorfields and the Western Ophthalmic Hospitals). The aetiologies were variable but only those due to zoster were included in this study.

Examination: Firstly the history was taken including: the suspected aetiology of the keratitis, its duration, therapy and any known systemic lipid abnormalities. The corrected and uncorrected visual acuities were measured. Slit-lamp examination was carried out concentrating not only on the extent, density, and vascularity of the lipid deposit but also on the iris and lens appearance. The shape and position of the deposits were noted:-whether they were central or eccentric disciform, marginal, diffuse interstitial, or deep, and an accurate drawing was made.

Colour photographs of the whole cornea (with a dilated pupil) were taken under standardised photographic conditions. A careful grading was made on the density and extent of the lipid by examining the films on a Dokumator, Carl Zeiss, Jena, the transparency was projected on the built-in screen which was covered by a transparent sheet on which was drawn a circle just large enough to encompass the whole cornea and this area was divided into 100 squares. The extent of the lipid was calculated from the number of squares involved (including those that were more than half filled) and expressed as a percentage of the whole cornea. Density was classified into four categories based on the degree of masking of underlying iris structure: 0 = transparent, 1 = slight blurring of iris crypts, 2; = iris colour only appreciated, 3 = pupil vaguely discerned with full illumination, and 4 = total opalescence with dense creamy yellow lipid.

Corneal angiography: The photoslitlamp was modified with:

1. a 50:50 beam splitter

2. a motorised 35mm camera with black and white film was placed on one arm
3. a monochrome TV camera was placed on the other arm and connected to a Umatic VCR and monitor
4. An accessory halogen light source (Zeiss)
5. Matched filters (Spectrotech, New York) were placed in front of both light sources, each camera and one eyepiece (Marsh & Ford, 1978).

After injection of dye a continuous video recording was taken. The video was rerun and the vessel filling patterns studied. The 35 mm film was also examined and the vascularity scored as slight (1), moderate (2), and profuse (3), whilst the vascular stems at the limbus were defined as single and narrow or multiple and diffuse. A diagram was drawn of these vessels. An example of a disciform shaped keratopathy and early angiogram is shown in (figures 8.1 and 8.2)

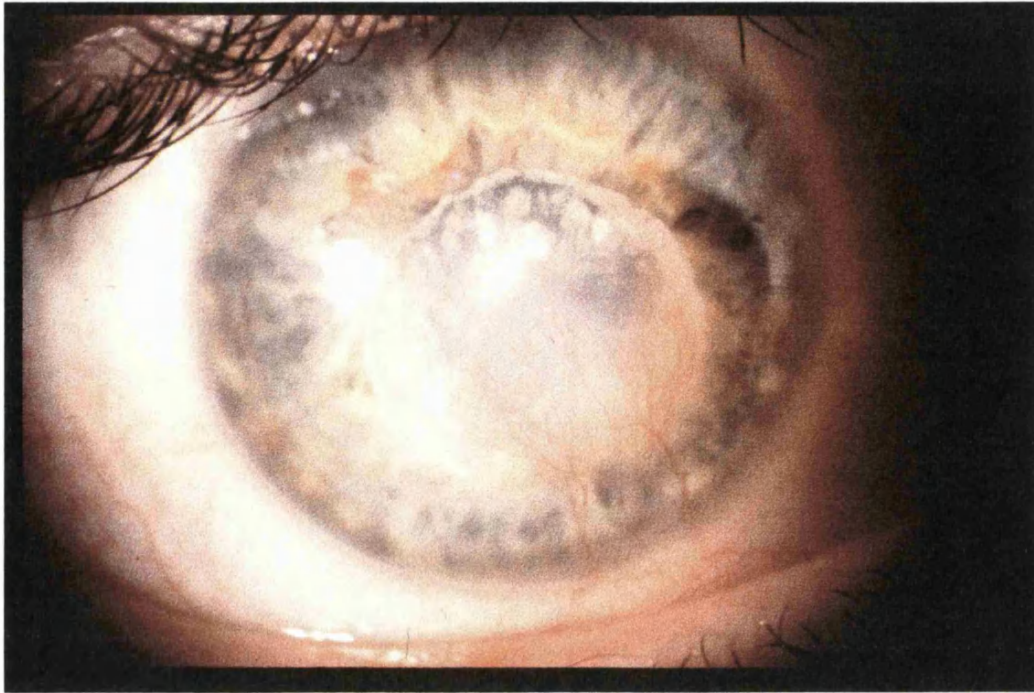


Figure 8.1 *Eccentric type of lipid keratopathy.*

Figure 8.2 *Fluorescein angiography of cornea above.*

Technique of laser treatment: Before treatment with the laser, 1 per cent Amethocaine drops were instilled and large pupils were constricted with 2% pilocarpine drops. An Abraham contact lens (Ocular Instruments inc.) was inserted onto the eye which steadied it and converged the laser beam more precisely on the corneal vessels. The patient was cautioned to be very still and to stare constantly at a fixation light. The laser originally used was an Argon blue/green (Coherent Radiation 900 series) with single firing later on this replaced by the Nova Coherent Argon green with rapid repeat firing. The aperture setting was 50 microns, although it was important to have the focusing of the laser checked at regular intervals so that the beam was properly focused. 0.1 sec. exposures were the slowest speed possible consistent with comfort and when rapid repeat was available 3.3 shots a second. The illumination of the slit was kept as low as possible and the delivery system angled so that the beam was directed away from the pupil to the periphery of the iris. The intensity necessary to occlude the blood column varied from 0.2 to 0.8 watts and again depended upon the state of repair of the machine. Treatment was commenced by sealing the vessels on the scleral side of the limbus firstly with the veins and then any large arteries that were seen. This tended to distend the corneal vessels and slow the blood flow through them. Next the main veins were occluded just corneal to the limbus. These darkened, temporarily expanded and showed fragmentation of the blood column. They were then progressively closed or blackened towards the centre of the cornea. After this the arterial flow had slowed considerably and the arteries were more accessible to closure with the laser. Treatment was continued until flow stopped altogether. Lastly any remaining small vessels were tackled and best treated at crossover points followed by the intermediate sections. Treatment was not carried out where vessels overlay the pupil or where there was a danger of the laser beam causing retinal damage. With new cases it was found best to arrange three treatment sessions in a day because of the tendency of anastomotic channels to open up shortly after laser therapy. Treatment was usually started in the early morning, then mid-day, and lastly in mid-afternoon. Immediately after treatment prednisolone 0.3% drops were administered twice a day until the next visit.

Follow up: In most cases it was possible to achieve closure of vessels in one treatment session, but in cases with dense vascularisation it was best to treat three times in one day and to re-examine a few days later with a view to further lasering. The next routine follow-up visit was at one month and then three or six monthly depending on the success of vessel closure. Any remaining patent vessels were treated by the laser. Where there was profuse vascularization patients were brought back for treatment every 2 weeks, but as successful closure was achieved they returned every 3 months for assessment and if any vessels remained with doubtful blood flow a repeat angiography was carried out. At each follow-up examination the visual acuity, activity of keratitis and vascularity were reassessed and treated accordingly. Colour photographs and applanation tonometry were repeated every 6 months.

Precautions: An attempt was made to withdraw the prednisolone drops, entirely but cautiously, over one year, but they had to be increased after each lasering and if there was any sign of active keratitis. The intraocular pressures were regularly checked while the patients were taking steroids, and in case of raised intraocular pressure fluoromethalone drops were substituted. Where lipid deposits were very dense and central the patients received grafts 3-4 days after intensive lasering.

Recording: All relevant details were recorded on the proforma (**Appendix B**) at first visit and at least 6 monthly. A scoring system was used for recording density, extent and vascularity. Laser treatments were carefully annotated at each visit. Efficacy of treatment was judged by improvement in visual acuity, reduction in density and extent of the lipid, disappearance of vascularization, and improvement in photophobia.

8.3 Results: Thirty six patients were reviewed with a minimum follow-up of 12 months. There were 23 females and 13 males. The average age was 60 years. The morphology showed 22 eccentric disciforms, 7 central disciforms and 7 marginal opacities. 30 showed a reduction in the extent of the lipid, 4 no change and 3 an increase. The mean extent pretreatment was compared with mean extent posttreatment was statistically significant (**Table 8.1**).

Table 8.1 Effect of laser on the extent of opacity in 37 patients

	<i>Pretreatment</i>	<i>Posttreatment</i>	X^2
Mean	0.18 (50 +/-0.11)	0.11 (50 +/-0.01)	<0.0001 Wilcoxon

The density of deposits was reduced in 23, the same in 13 and worse in none. The mean density pretreatment was compared with the mean density posttreatment and showed a significant reduction in density (Table 8.2).

Table 8.2. *Effect of treatment on the density of opacities*

	<i>Pretreatment</i>	<i>Posttreatment</i>	X^2
Mean	2.44 (50 +/-0.76)	1.75 (50 +/-0.92)	<0.0001 Wilcoxon

There was improvement in both extent and density in 21. Snellen visual acuity was improved in 18, unchanged in 11, and worse in 7. However, if the patients were divided into two groups, one with vision of 6/18 or worse and the other with 6/12 or better, there was a small but non-significant improvement in both groups (Table 8.3). Combined improvement in all three aspects occurred in 10 cases apart from the case that was grafted.

Table 8.3. *Effect of laser treatment on visual acuity*

	<i>6/18 or worse</i>	<i>6/12 or better</i>	X^2
Before treatment	12	24	
After treatment	10	26	p<0.457

$X^2 = p < 0.457$, non-significant

An example of improvement is shown in **figures 8.3 & 8.4**. One graft was carried out after treatment by laser and urgently because of descemetocoele formation. It was clear after a minimum follow up of 4 years.

It was usually possible to close all the blood vessels at the end of a treatment session but in very vascular keratopathies there was a tendency for some vascular channels to reopen soon afterwards. However, after repeated treatment, all but some very small vessels with very slow flow were successfully closed (as seen with very high magnification on the slit lamp).

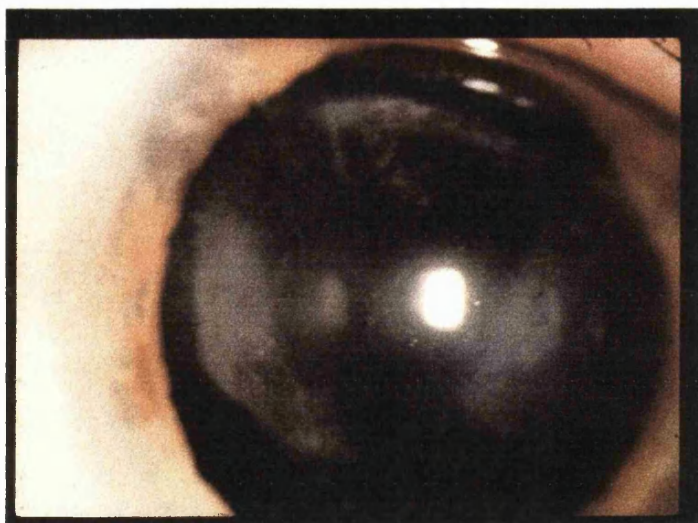
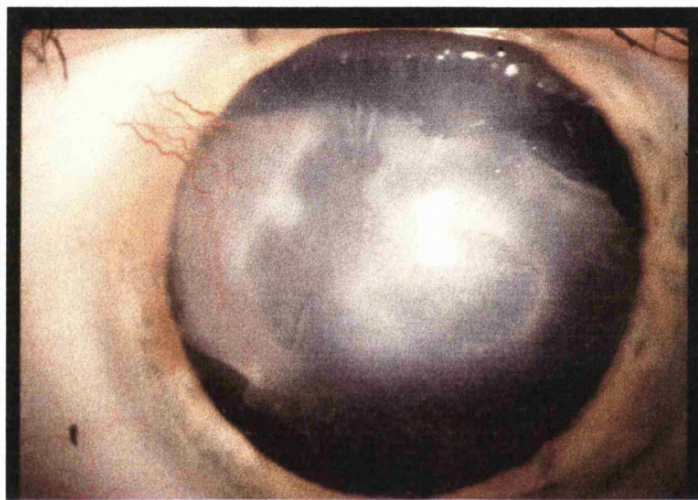


Figure 8.3 *Disciform type of keratopathy.*

Figure 8.4 *Same patient as above 2 years after start of laser treatment.*

8.30 Complications: The commonest immediate complication was haemorrhage around the treated vessels, which rarely spread widely between corneal lamellae. However, this was a temporary phenomenon and, though a little disturbing to the patient, always resorbed. Less commonly there was temporary peaking of the pupil in the sector underlying that treated with the laser. Patients who had multiple laser treatments all developed some degree of iris atrophy (unrelated to previous zoster iris atrophy) underlying the treatment zone. There was occasional reactivation of keratitis, but all except one responded well to increasing topical steroids. One case of dense disciform lipid deposits developed rapid central stromal thinning within one month of treatment culminating in the development of a descemetocele at four months which was successfully treated by a penetrating corneal graft. All cases of disciform keratopathy that responded successfully to treatment showed some degree of stromal thinning. One patient developed appreciable field loss due to a combination of chronic keratouveitis and topical steroids. There did not appear to be any lens or retinal damage as a result of the therapy.

8.4 Discussion: The results were encouraging in that there was some degree of success in reducing the extent and density of the keratopathies but clearing of the lipid was slow and could take several years to be apparent. Generally speaking the moderate and milder cases did best, although there were the odd surprises. Once again, apart from the small number of cases with improved visual acuity, many were subjectively better and symptoms of photophobia improved. It is also notable that a large number failed to progress contrary to the normal natural history which seemed a significant achievement. The Abraham lens provided a great improvement for laser delivery giving less iris damage. Patients also preferred the immobilization and protection it gave them. The new Argon laser (Nova) was a great improvement on the previous machine particularly with its rapid repeat-fire facility speeding up treatment and its argon green wavelength. The results of grafting treated cases were excellent. It seemed best to arrange for laser treatment three days prior to grafting (under topical steroid cover) to render the cornea avascular at surgery and preclude descemetocele formation.

Modification of the laser treatment by incorporating an intravenous complimentary dye may prove useful (Hennessey et al, 1994; Sheppard et al, 1994), particularly for closing very small vessels. In addition it could reduce the amount of laser energy required which in turn could lower the amount of laser-induced iris damage.

The video corneal angiograms proved very useful for identifying feeder vessels and flow. They also clearly showed that many of the eccentric disciform keratopathies and all the marginal and half of the idiopathic deep keratopathies had marked ischaemic changes in neighbouring episclera. They probably had an ischaemic episcleritis at the time of the preceding acute keratitis.

It was important that close follow-up was made on all patients because reactivity of keratitis occurred in some and required topical steroids to suppress the inflammatory response. Thinning of the cornea following treatment was pronounced in some cases and in one case led to descemetocele formation. Prompt corneal grafting after treating dense central disciform keratopathy may therefore be necessary. The thinning seen in the eccentric disciforms was less severe. Up to 15 years none has formed a descemetocele or increased in astigmatism. Patients on the whole tolerated the treatment very well. The main complaint was that the laser beam dazzled their other eye (it was worth covering it with the operator's hand during firing). It should be admitted that prolonged treatment sessions were also uncomfortable for the surgeon and that on the rare occasions when fluorescein angiography had been carried out just previously the dazzle was even more bothersome. The importance of using the postoperative drops was stressed to the patients, and regular applanation was important to find steroid responders.

Prevention of the lipid keratopathy is an important element in any discussion on treatment. Most importantly, vascularising active keratitis should be adequately treated with topical steroid to prevent excessive scarring. For the future better treatment of the precipitating keratitis is required to prevent development of the keratopathy, and better knowledge of lipid metabolism and the mechanism of local deposition of fat. Finally this is a retrospective non-randomised trial and a controlled trial is necessary.

8.40 Pathogenesis The mechanism of lipid clearance after laser is uncertain but is probably due to ingestion by macrophages wandering between corneal lamellae which then migrate to the limbus, whence they gain access to lymph and blood vessels. Successful closure of vessels will obviously prevent further deposition of lipid in most cases. Another factor is the obvious disruption in the corneal tissues caused by the laser burns, which may facilitate diffusion of lipid away from the keratopathy. As expected, fibrous scarring of the corneal stroma did not clear. Thinning occurred as the lipid 'leached out', implying that the lipid deposits had artificially contributed to corneal thickness and in fact revealed how much corneal stroma had been destroyed by the preexisting keratitis.

9 OCULAR PALSIES

9.1 Introduction. Ocular palsies in ophthalmic zoster are well described in the ophthalmic literature with incidences from 5% to 14% (Hybord, 1872; Flament & Bronner, 1974; Desirat, 1903; Worster-Draught, 1923; Nover, 1970; Rebattu et al, 1933; Edgerton, 1945; Hunt, 1909). However, there has been little published on aetiology; the following have been suggested: a direct viral cytopathic effect (Cope & Jones, 1954), an allergic neuropathic response to the virus (Krumholtz & Luihan, 1945) and an occlusive vasculitis (Gordon & Tucker, 1945). More puzzling was a reference in the literature to a contralateral VIth nerve paresis (Norris et al, 1970). It was therefore decided to carry out a careful retrospective and prospective analysis of the prevalence, incidence and natural history of ocular palsies.

9.2 Patients and Methods: Patients were drawn from 2 sources in 1977. Firstly the database from 1972-1975 of 512 patients was surveyed retrospectively for those with extraocular muscle palsy and diplopia with a follow up of at least 1 year who were willing to come to hospital for further examination (36 patients). Secondly, all new patients presenting to the hospital with ophthalmic zoster in an 8 month period from January to August in 1976 were orthoptically examined for their ocular muscle balance (77 patients). Special investigations included haemoglobin concentration, ESR, differential white count, blood film, plasma protein electrophoretic strip, blood sugar, liver function tests and chest x-ray. 2 Orthoptists examined the patients at each attendance regardless of subjective symptoms and they included cover test, ocular movements, convergence, assessment of binocular function, and Lees screen. A note was also made of the position of the upper lid margin.

9.3 Results: Twenty-two cases of paresis were found prospectively in the 77 new patients examined, giving an incidence of 29%. 36 of the old patients attended for examination giving a total of 58 cases of external ocular muscle paresis. Forty-two of them complained of diplopia, 32 constantly. Symptoms appeared within one week of the rash onset. Sixteen of the patients were asymptomatic, although 8 admitted to diplopia on testing in extremes of gaze. Analysis of the 58 pareses showed they fell into 5 categories of laterality (**Table 9.1**).

Table 9.1 *Laterality of external ocular palsy in the 58 patients*

	<i>Ipsilateral</i>	<i>Contralateral</i>	<i>Ipsilateral becoming contralateral</i>	<i>Bilateral</i>	<i>Complete ophthalmoplegia</i>
No. of cases	34	9	6	5	4

The different cranial nerves involved in the ipsilateral and contralateral groups are analyzed in the Venn diagram (Figure 9.1).

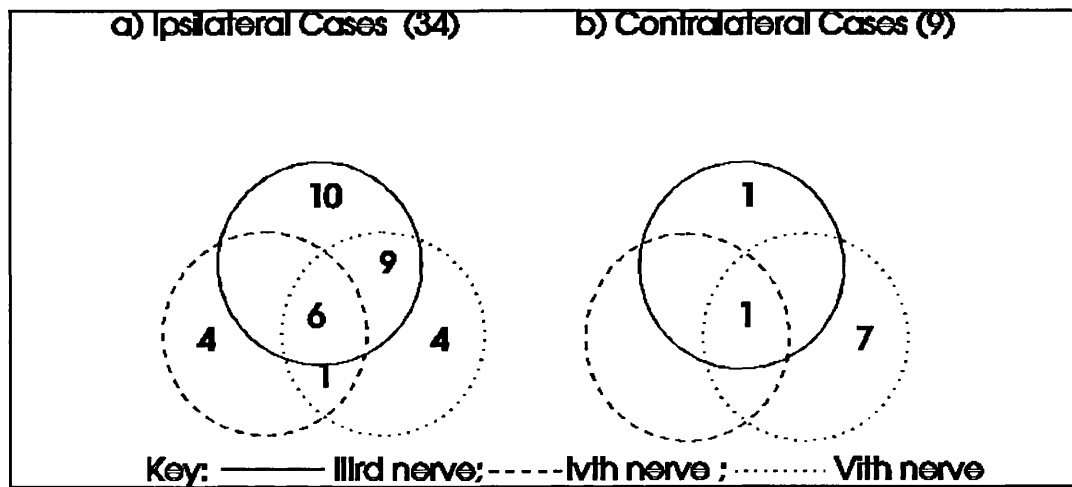


Figure 9.1 *Venn diagram of the distribution of nerve involvement in external ocular palsies (The number of patients with each palsy is included in the appropriate circle and those with ipsilateral becoming contralateral, bilateral and complete ophthalmoplegias, are excluded).*

The third category of laterality revealed slow recovery of the original ipsilateral paresis, and always a contralateral IIIrd nerve palsy superseded, although the same branch was not necessarily affected on each side (Table 9.2). A small percentage of cases had the same muscle paresis on each side from the beginning, but other underactions were present, usually on the side affected by the rash. Complete ophthalmoplegia was accompanied by proptosis in 3 of the 4 cases seen, and 1 of these in fact had bilateral ophthalmoplegia and proptosis.

Table 9.2 *Ipsilateral palsies becoming contralateral*

Cases	<i>Ipsilateral</i>		<i>Contralateral</i>
1	} III	->	III
2			
3	VI	->	III and IV
4	} III and VI	->	III and VI
5			
6	III, VI, and IV	->	III and VI

Figure 9.2 shows the age distribution of the 58 patients with palsies, and it should be noted that the youngest was 46.

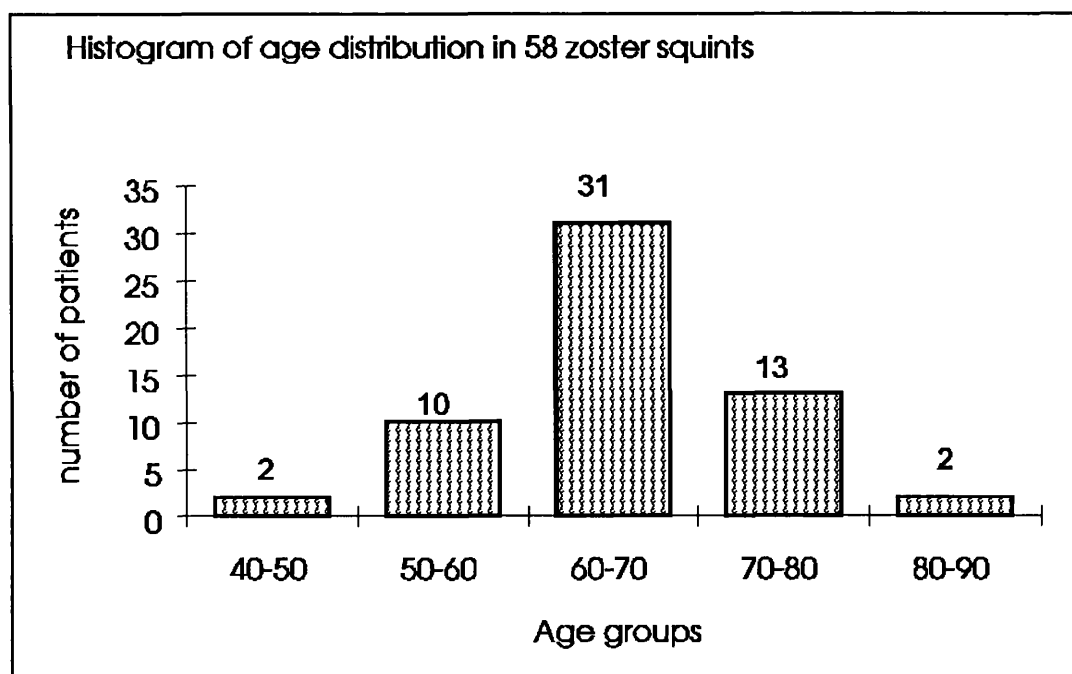


Figure 9.2 *Histogram of age distribution of the 58 squints in zoster.*

All the pareses were detected within the first week of the rash, although it was often difficult to examine eye movements at this stage owing to the lid swelling and malaise of many of the patients. Figure 9.3 shows the

duration of symptoms, and it is significant that there were only 3 cases lasting for more than 18 months. However, an orthoptic defect could always be found in all patients despite the excellent subjective recovery.

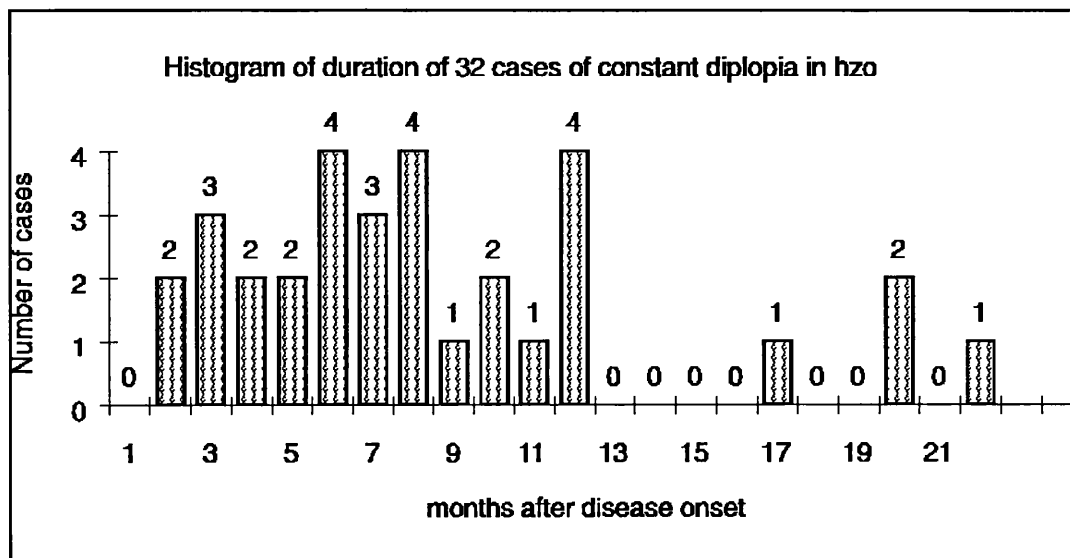


Figure 9.3 *Histogram of duration of diplopia in ophthalmic zoster*

The incidence of other ocular complications of zoster in the ocular motor palsy group was compared with those occurring in a comparison group of 46 patients seen at the same time with no ocular motor defect. The results and statistical analyses are depicted in **Table 9.3**.

Table 9.3 *The association of external ocular palsies with other complications of herpes zoster.*

<i>Complications of HZO</i>	<i>X²</i>	<i>Probability</i>	<i>Remarks</i>
Severity of rash	12-6	P < 0.001	Significant
Neuralgia	5-9	0.05 > P > 0.01	Significant
Iritis	12-6	P < 0.001	Significant
Iris atrophy	10-2	0.01 > P > 0.001	Significant
Sphincter damage	1.8	0.2 > P > 0.1	Non-significant
Corneal sensation	0.8	0.5 > P > 0.3	Non-significant
Corneal involvement	2-1	0.2 > P > 0.1	Non-significant
Episcleritis	0.2	0.7 > P > 0.5	Non-significant
Lid involvement	0.91	0.5 > P > 0.3	Non-significant

There was no clear relationship between any of the sectoral lesions (episcleritis, sclerokeratitis and iris atrophy) and a particular external ocular muscle underaction. Neither was there any significant correlation with the results of the special investigations. Three patients had ipsilateral VIIIth nerve paralysis without auricular involvement. A further 3 developed contralateral hemiplegia within 1 month of the onset of zoster, and a fourth developed an ipsilateral hemiplegia 2 years after the rash.

9.4 Discussion: External ocular motor palsies in ophthalmic zoster appear to be more common than previously indicated. This was probably related to the detailed examination of eye movements in all patients. 28% were asymptomatic owing to the diplopia being present only in extremes of gaze, poor sight in the affected eye, or to the development of suppression at a late age. Recovery was excellent despite the fact that an objective defect could always be found on orthoptic examination. The presence of a squint was significantly associated with the severity of the rash and the later occurrence of severe neuralgia, iritis, and iris atrophy, whereas episcleritis, and corneal and lid involvement were of no greater frequency. No case was seen under the age of 40. Surprisingly we found some of the palsies to be

bilateral and on the side opposite to the skin lesions.

9.41 Pathogenesis: To try to understand the cause of bilaterality of some of the palsies and their relationship to other complications of zoster it is necessary to consider the pathogenesis of the lesions.

Three pathogenic mechanisms should be considered for mediating neural damage in zoster. The first is a direct cytopathic effect from the virus itself on the surrounding neural tissue (Cope and Jones, 1954). The second is an allergic response of the central nervous system to the virus, which is not primarily vascular (Krumholz and Luihan, 1945; Appelbaum et al, 1962; Rose et al, 1964). The third attributes it to an occlusive vasculitis induced by the virus (Gordon and Tucker, 1945; Feyrter, 1954; Anastostopoulos et al, 1958; Wray, 1972). A fourth theory (for which there is little evidence) suggests the varicella/zoster virus activates another latent neuropathic virus within the brain (Appelbalm et al, 1962). Virus may reach the brain in several ways and there cause direct cytopathic or allergic damage to the nervous tissue. The first is a retrograde spread of virus from the trigeminal ganglion to the Vth nerve nucleus. Here it reaches other cranial nerve nuclei, either by axonal spread along established interconnections (Biggart and Fisher, 1938; Godfredson, 1948; Goodbody, 1953), or by random spread (Cope and Jones, 1954; Acers, 1964). The former pathway could be along the proprioceptive neurones of the oculomotor muscles in the Vth nerve (Denny-Brown et al, 1944). Alternatively, virus may reach the brain by means of a basal meningoencephalitis, which is well described in the literature (Schiff and Brain, 1930; Wynne Parry and Laszlo, 1943; Gordon and Tucker, 1945; Godfredson, 1948; Hughes, 1951 ; Norris et al, 1970). The area chiefly involved is thought to be the pontine region (Worster-Drought, 1923). Many features can be attributed to this: headache, general malaise, pyrexia, bilaterality of lesions, multiple cranial nerve palsies, hemiplegia, CSF findings, and the rare cases of cranial nerve lesions secondary to a remote primary zoster lesion (Thomas and Howard, 1972; Keane, 1975). Against this theory is the delayed occurrence of many of the cranial nerve lesions, the lack of symptoms and signs of encephalitis in many of the patients, and the rarity of bilateral lesions other than oculomotor palsies. Thirdly, a separate cranial motor neuritis may occur

simultaneously with the trigeminal lesion, presumably also owing to the presence of latent virus activated by the same unknown stimuli. This could be a satisfactory answer for contralateral palsies and the occurrence of lesions at a different level from the primary rash (Denny-Brown et al, 1944; Keane, 1975). However, it is somewhat unsatisfactory to postulate 2 distinct lesions and could not adequately explain the association of squints with other ocular complications of zoster.

The last pathogenic mechanism to be considered is that of occlusive vasculitis. Various sites have been proposed. The earliest suggestion was that of the muscle cone and orbit with accompanying myositis, perineuritis, and thrombosis (Wyss, 1871; Abadie, 1898; Aubineau, 1914-15; Kreibig, 1938; Von Siegert, 1964). While this would be in keeping with the picture seen in total ophthalmoplegia with proptosis, iritis, and iris atrophy, it does not explain the contralateral ocular palsies seen.

The second site to be described was the cavernous sinus and orbit apex with involvement of the adjacent IIIrd, IVth, and VIth nerves (Rebattu et al, 1933; Edgerton, 1945g; Franceschetti et al., 1955; Walsh and Hoyt, 1969; Scheie, 1970). The difficulty here is to account for hemiplegias and the bilaterality of lesions, although it is true that the cavernous sinuses of both sides intercommunicate freely. The origins of the middle cerebral and ophthalmic arteries are here, and an ascending vasculitis may spread along these, with accompanying thrombosis (Gordon and Tucker, 1945; Anastostopoulos et al, 1958). This may be mediated by a granulomatous angiitis induced by the varicella/zoster virus, involving the carotid artery, ipsilateral to the involved eye and segmental (Rosenblum and Hadfield, 1972; Victor and Green, 1976). In favour of this theory is the delayed onset of contralateral hemiplegias, hemianopias, and aphasias secondary to damage in the region of the internal capsule, and the occurrence of ischaemic optic neuritis and iritis. But it is a rather unsatisfactory mechanism for evoking contralateral ocular palsies.

A third site of vasculitis in the brain stem has been described pathologically by Feyrter(1954). Patchy lesions here would, of course, account for ipsilateral palsies, contralateral hemiplegias (from involvement of the corticospinal tract), and lesions of adjacent cranial nerve nuclei. A

spill over of the vasculitis just the other side of the midline could give rise to the contralateral ocular palsies.

It is possible, of course, that the palsies are of a mixed aetiology and that all the mechanisms and sites mentioned are involved. Overall the palsies are probably due to a vasculitis at different sites and clearly there is a close relationship between active virus in neural tissue at the very beginning of the disease and the later development of adjacent vasculitis. It is to be hoped that new methods of imaging such as NMR and PET scans will clarify the anatomical sites. (Recently I have investigated 5 cases at the National Hospital Queen's Square using Nuclear Magnetic Resonance (NMR) scans. In one case there was clearly a lesion in the homolateral IIIrd nerve nucleus in two there were sparse indeterminate small lesions scattered throughout the brain and in two nothing significant to see). Hopefully new developments in immunology will explain some of the pathogenic mechanisms particularly in immune-complex vasculitis.

9.42: Treatment: In view of the satisfactory recovery without treatment in most cases the question arises, Is any necessary? The minority that suffer very troublesome diplopia may need temporary occlusions.

An overall therapeutic solution to zoster must include an effective, non-toxic, systemic antiviral agent which crosses the blood brain barrier. If given at the very onset of the disease it would prevent both the direct and allergic cytopathic effect of the virus on neural tissue and prevent the initiation of a secondary vasculitis by destroying the virus at an early stage. However, a problem will still exist if cases present later on when these changes have been initiated, especially the vasculitis. As steroids are known to suppress the latter it would therefore seem logical to use them in cases of occlusive vasculitis. Furthermore, it is almost certain that total ophthalmoplegia with proptosis and ischaemic papillitis comes into this category (Marsh, 1976). All the cases of contralateral hemiplegia were treated with intensive systemic steroid and seemed to respond well with good recovery at 6 months. Thus using the same regime of 80 mgm of prednisolone on the first day reduced by 10 mgm per day over the following week and then a maintenance dose of 10 mgm per day would seem appropriate.

10 IRIS ANGIOGRAPHY IN ZOSTER WITH IRITIS AND IRIS ATROPHY

10.1 Introduction: Duke-Elder (1940) divided zoster iritis into two types: diffusely exudative and locally eruptive. The diffuse type was either mild and produced posterior synechiae or severe, with keratitic precipitates, and was occasionally accompanied by hypopyon or secondary glaucoma. The second type was characterized by eruptive lesions on the iris with acute vascular dilatation. These observations were made prior to the introduction of therapeutic corticosteroids, the administration of which markedly alters the course of iritis. More recently it has been described as appearing within 2 weeks of the rash (Marsh et al, 1974), tending to run either an acute or a chronic relapsing course but, with corticosteroid treatment, is in no way so severe as described in the earlier reports. It is characterized by very fine deposits on the corneal endothelium, the aqueous flare is generally minimal and is associated with only a small quantity of cells. Posterior synechiae are unusual. Often there is complicating ocular hypertension (possibly caused by an associated trabeculitis) and overlying corneal stromal oedema (possibly contributed to by an associated with endotheliitis). All these features respond rapidly to topical steroids.

The pathogenesis of iritis and iris atrophy in zoster has not been determined but would seem to be due to either invasion of the pigment epithelium by virus, a local vasculitis, or a neurogenic effect. Vasculitis may produce ischaemia and atrophy. In 1971 iris angiography was a relatively new technique and it seemed appropriate to apply it to zoster patients to see if there was a vasculitis present in the iris. The following project was therefore initiated.

10.2 Patients and Methods: Over an 18 month study period (1973-74) 520 patients were seen of which 140 were new patients and 380 old patients. Of these there were 21 patients with iris atrophy that were suitable for fluorescein angiography from the point of view of safety, volunteering and having blue irides. Three additional suitable new patients with acute iritis had angiograms performed during the acute and convalescent periods. Lastly 2 patients with no iris complications volunteered to have angiograms.

General investigations on all patients included chest x-ray film, haemoglobin concentration, complete blood cell count, erythrocyte sedimentation rate,

plasma proteins, electrophoretic strip, blood glucose, and serum cholesterol.

10.20 Iris angiography: The basic anterior segment angiography equipment was used (as described earlier). Colours pictures of the iris were taken first including transillumination shots of the iris atrophy (Marsh RJ et al, 1974). A B 4 exciter filter (Baird Atomic, UK) was placed in front of the slit objective and a Wratten 15 barrier filter (Kodak, UK) in front of the 35mm camera (Bron & Easty, 1972) and a rapid sequence of exposures was made.

10.3 Results: 14 % (seventy-four) of the 520 combined new and old patients showed iris atrophy. The average age was 60 years; 35 were men and 39 were women; 66 had blue irides and eight had brown. The 140 new patients presenting in the acute stage of the disease over the 18-month period had a 52% incidence of iritis (71 patients), and a 25% incidence of atrophy (36 patients). The discrepancy between the 2 figures of incidence of iris atrophy is because the 380 old patients included showed a lower incidence of iris atrophy, probably due to previous selection for follow-up based on other features of the disease. The 74 cases of iris atrophy fell into three grades of severity: 35 (47%) showed basal sector atrophy only; 35 (47%) had additional sphincter damage and 4 (6%) had massive iris atrophy.

10.30 A normal iris angiogram shows rapid filling of the vessels from the major circle of the iris in a series of arcades. The shortest system of arcades is at the base of the iris (arrow A), lying between large, long, radial vessels, which pass toward the pupil, branching into two at the collarette. One of these forks backward to the base of the iris forming a second series of arcades at the collarette (arrow B), the lesser circle of the iris. The other branch passes to the pupillary edge where it turns back on itself to form the third series of arcades (arrow C.) Leakage is minimal at the pupillary margin (figure 10.1).

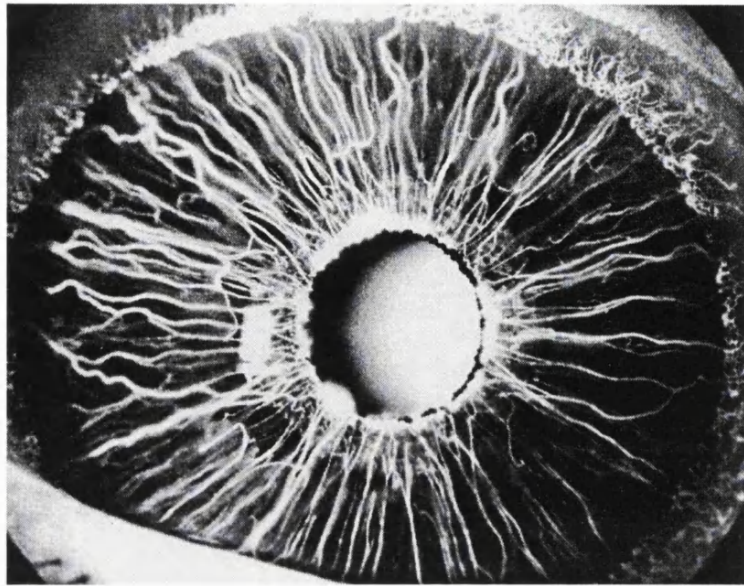


Figure 10.1 *Normal iris angiogram*

10.31 *Angiographic findings in herpes zoster iritis:* Our angiographic findings may be considered under the following headings: Acute iritis (3 cases), and those with different types of iris atrophy, pure iris sector atrophy (Group A, 12 cases), those progressing to additional sphincter damage (Group B, 10 cases); and massive iris atrophy (Group C, 2 cases).

10.31a *Acute zoster iritis:* Three cases were studied with serial angiography from the onset of iritis over the acute phase. Dilatation and early leakage of all iris vessels were seen initially (**figure 10.2**).

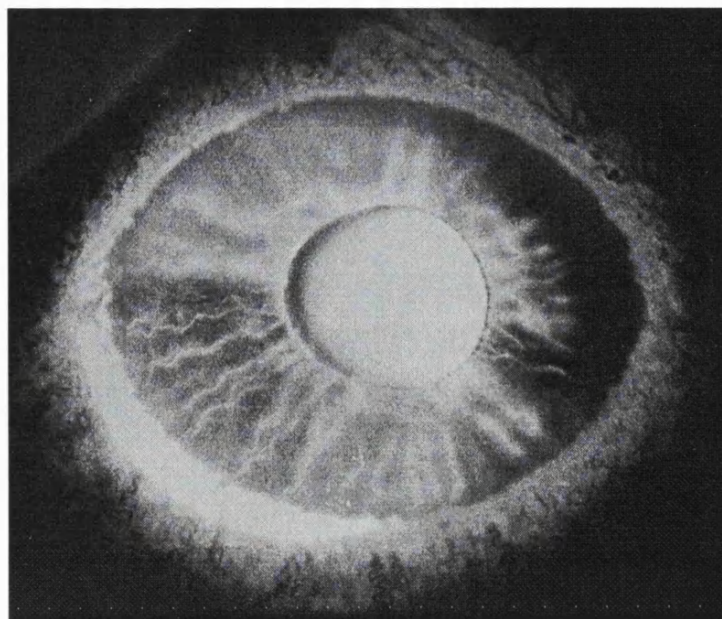


Figure 10.2 *Iris angiogram in early iritis*

Three days later small areas of vascular narrowing and loss of filling appeared in a sectorial distribution against a background of generalized vascular dilatation and leakage. Direct slit-lamp observation revealed deformation of the pupil with accompanying sluggish sphincter action in the affected sector. One week later, more sectors revealed vascular narrowing and closure with less generalized dilatation and leakage. Slit-lamp examination of the iris showed chinks of pigment epithelial loss in the affected sector (**figure 10.3**). Resolution of the vascular dilatation occurred three and a half weeks after the onset of iritis, but the areas of narrowing and closure remained and were directly related to the area of iritis atrophy (**Figure.10.4**). Later pictures showed evidence of filling in vessels that were closed in previous angiograms. Pigment epithelial loss continued to occur in the affected sectors for a month more, despite the resolution of the iritis, and despite the extensive use of local and systemic corticosteroids. Raised ocular pressure did not accompany the loss of pigment epithelium.

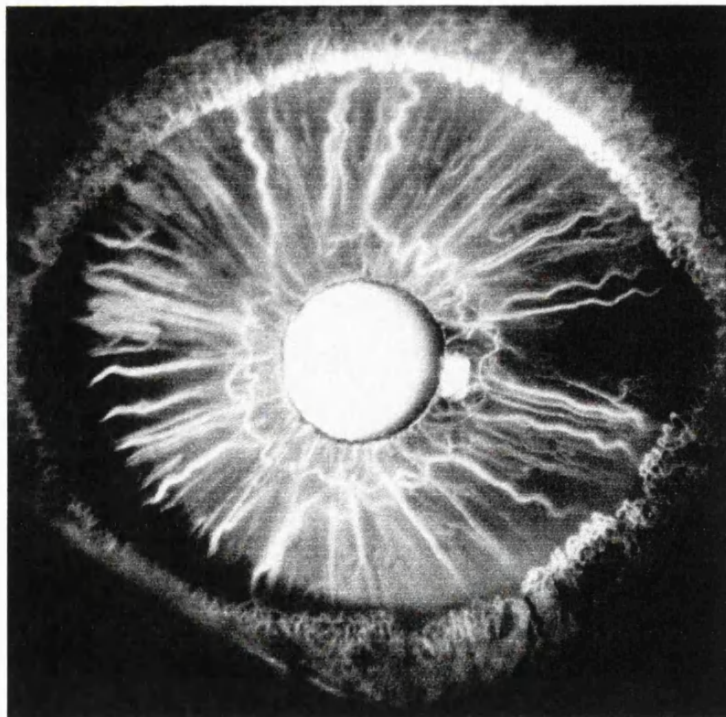
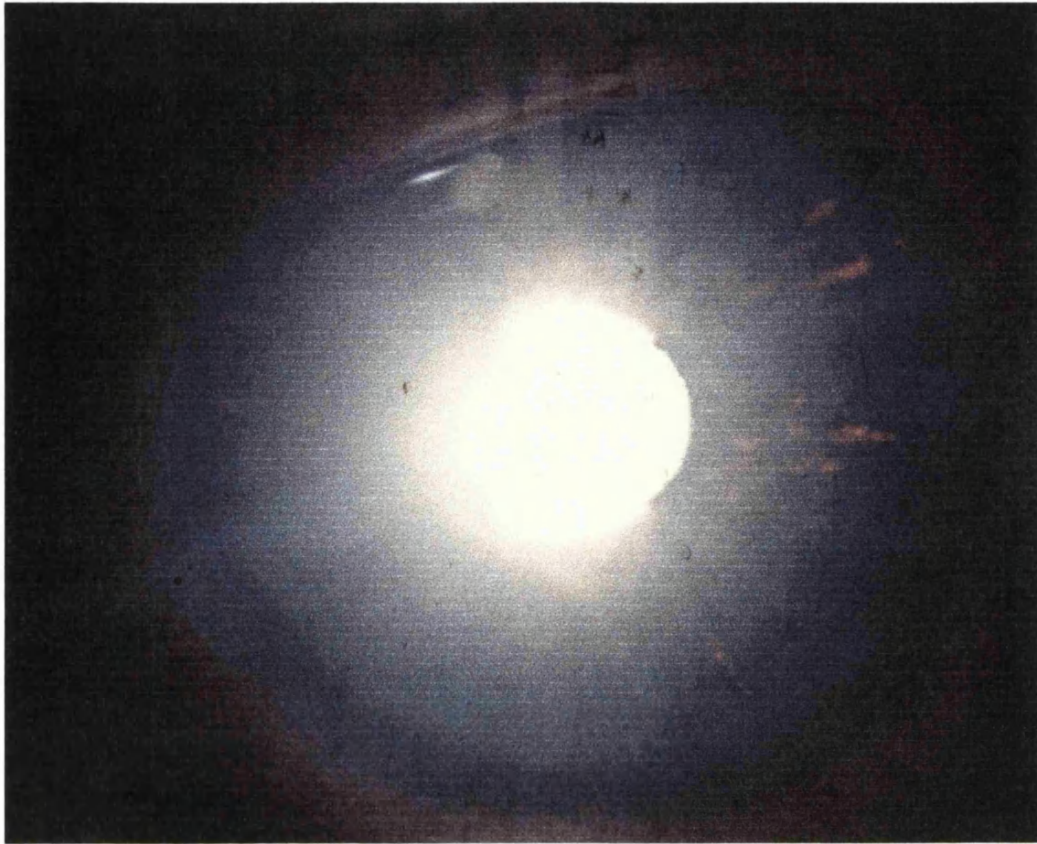


Figure 10.3 *Early sectorial iris atrophy in herpes zoster.*

Figure 10.4 *Fluorescein angiography of iris atrophy show above.*

10.31b *Herpes zoster iris atrophy.* The twelve patients in Group A revealed either delayed or complete loss of filling of basal arcades and long radial vessels in the area of pigment epithelial loss, often accompanied by dilatation of the neighbouring long radial vessels.

The ten patients in Group B, with combined iris atrophy, showed additional changes. There was occlusion of the two distinct arcades normally visible at the collarette and pupil margin, leaving only an ill-defined vascular arcade in the affected sector. Some cases had retrograde filling of the larger and patent vessels in the atrophic areas from dilated neighbouring vessels.

The two patients in Group C showed large areas of iris that did not fill with fluorescein corresponding to the iris pigment epithelial loss. Some leakage occurred at the pupil margin and from the dilated vessels adjacent to the atrophic areas.

10.32 *Herpes simplex uveitis:* Three cases of herpes simplex with sectorial iris atrophy were chosen at random and examined by transillumination, they revealed loss of pigment epithelium, but the stroma appeared to be normal. The atrophy characteristically had scalloped, well-defined edges (**Figure 10.5**) in contrast to that of herpes zoster, which is ill-defined (**Figure 10.3**). Angiography demonstrated filling of basal and radial vessels in the affected areas and there was no sign of occluded vessels (**Figure 10.6**)

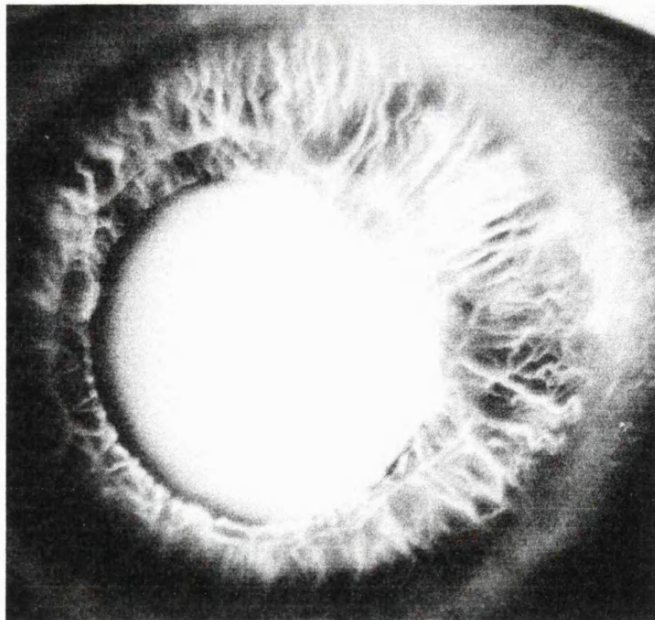
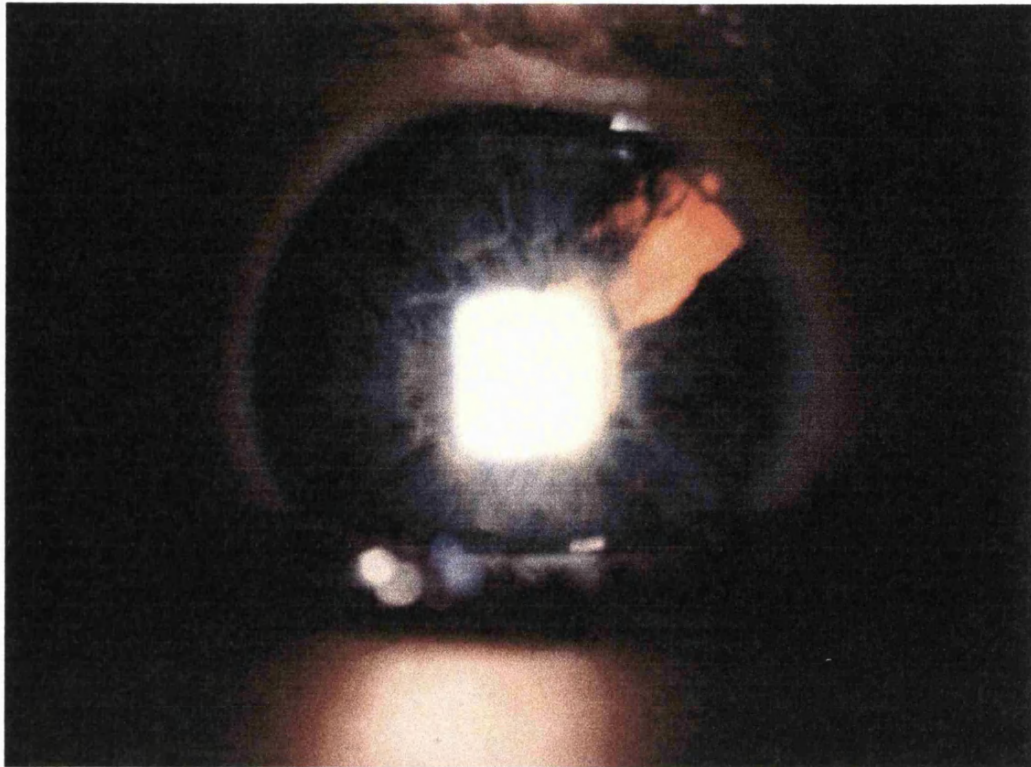


Figure 10.5 *Iris atrophy in herpes simplex.*

Figure 10.6 *Fluorescein angiogram of iris atrophy show above.*

10.4 Discussion: Sectorial iris atrophy together with sphincter atrophy in herpes zoster ophthalmicus follows localized ischaemia. Iris angiograms showed that areas of pigment epithelial loss did not demonstrate vascular filling. In contrast to this, areas of pigment epithelial loss in patients with herpes simplex uveitis demonstrated normal vascular filling. The ischaemia in some patients with gross zoster iris atrophy resembled the angiographic appearances following acute glaucoma or anterior segment necrosis (Chignell & Easty, 1971) but the stromal damage was not as pronounced.

10.40 Pathogenesis: From the pathologic evidence, the ischaemic changes in the iris can be attributed to an occlusive vasculitis (Abadie, 1902; Head & Campbell, 1910; Gardilic, 1937; Naumann et al, 1968; Klein & Farkas, 1964; Kreibig, 1938; Kreibig 1959; Mueller, 1920; Mueller 1923; Feyter, 1954. The pathogenesis of this vasculitis may be direct viral invasion of vessels from the neighbouring nerves in the neurovascular bundles or, conversely, an immune-complex vasculitis with inclusion of complement in response to zoster antigens resulting from viral replication, presumably in nerves in the iris. The chronicity and relapsing nature of the vasculitis may suggest recrudescences of viral replication. However, the favourable response to corticosteroid therapy and the poor response to antivirals is more in keeping with an immune response.

10.41 Differential Diagnosis: The presence of zoster iris atrophy confirms that the patient has at some time suffered from herpes zoster ophthalmicus even though the other signs of the disease may be absent (i.e. skin scarring, and history). 14 cases of disciform keratitis, originally thought to be due to herpes simplex, were found to have the zoster type of iris changes. In 12 of these cases there were other clinical features of zoster present, thus corroborating the diagnosis of herpes zoster ophthalmicus and allowing aggressive topical corticosteroid therapy which led to rapid resolution of the zoster disciform keratitis, without fear of provoking herpes simplex corneal ulceration. Similarly, when this atrophic appearance is seen in an acute iritis it suggests a relapsing case of herpes zoster ophthalmicus.

10.42 Treatment: Topical corticosteroid treatment is especially effective in preventing and treating glaucoma secondary to zoster iritis. Although the corticosteroid does not succeed in opening closed vascular channels, it does

seem to prevent the development of additional closures.



11 APPENDIX

A Proforma for recording types and severity of ocular complications

HERPES ZOSTER

Series Number	[]	
Name	[]	
Sex	[]	1 = Male	2 = Female	
Hospital Number	[]	
Seen at Week	[]	Enter number of weeks		
Right Visual Acuity	[]			
Left Visual Acuity	[]			
Lid Margin Involvement	[]	0 = No	1 = Yes	
Naso-Ciliary	[]	0 = No	1 = Yes	
Rash Severity	[]	0 = None	1 = Mild	2 = Mod
Conjunctival Involvement	[]	0 = None	1 = Mild	2 = Mod
		3 = Severe		
Episcleritis Scattered	[]	0 = None	1 = Mild	2 = Mod
		3 = Severe	4 = Very Severe	
Episcleritis Nodular	[]	0 = None	1 = Present	
Early Corneal Involvement	[]	See late corneal involvement		
Late Corneal Involvement (After 3 months)	[]	Enter a mixture of letter as needed		
		M = Microdendrites	S = Stromal infiltrate	D = Disciform
		P = Pseudodendrite	L = Lipid	K = Sclerokeratitis
		N = Neurotrophic	E = Exposure	O = Other
Corneal Reflex	[]	0 = Normal	1 = Abnormal	2 = Absent
Iritis	[]	0 = None	1 = Mild	2 = Mod
		3 = Severe	4 = Very Severe	
Iris Atrophy	[]	0 = No	1 = Yes	
Pupil Abnormality	[]	0 = Normal	1 = Atrophy	2 = Other
Glaucoma	[]	0 = Normal	1 = Abnormal	2 = Steroid induced
Extraocular Movements	[]	0 = No	1 = Yes	
Neurological Abnormality	[]	0 = No	1 = Yes	
Previous Zoster	[]	0 = No	1 = Yes	
Steroid Response	[]	0 = No	1 = Yes	
Early Neuralgia	[]	0 = None	1 = Mild	2 = Mod
		3 = Severe	4 = Very Severe	
Early Cataract	[]	0 = No	1 = Yes	
Early Tarsorrhaphy	[]	0 = No	1 = Yes	
		After 3 months		
Late Neuralgia	[]	0 = None	1 = Mild	2 = Mod
		3 = Severe	4 = Very Severe	
Late Cataract	[]	0 = No	1 = Yes	
Late Tarsorrhaphy	[]	0 = No	1 = Yes	
Late Pitting	[]	0 = None	1 = Mild	2 = Mod
Late Pigmentation	[]	0 = None	1 = Mild	2 = Mod

B Proforma for treatment of lipid keratopathy

LIPID KERATOPATHY PROFORMA

Name..... Hosp No..... Date of birth..... Consultant.....

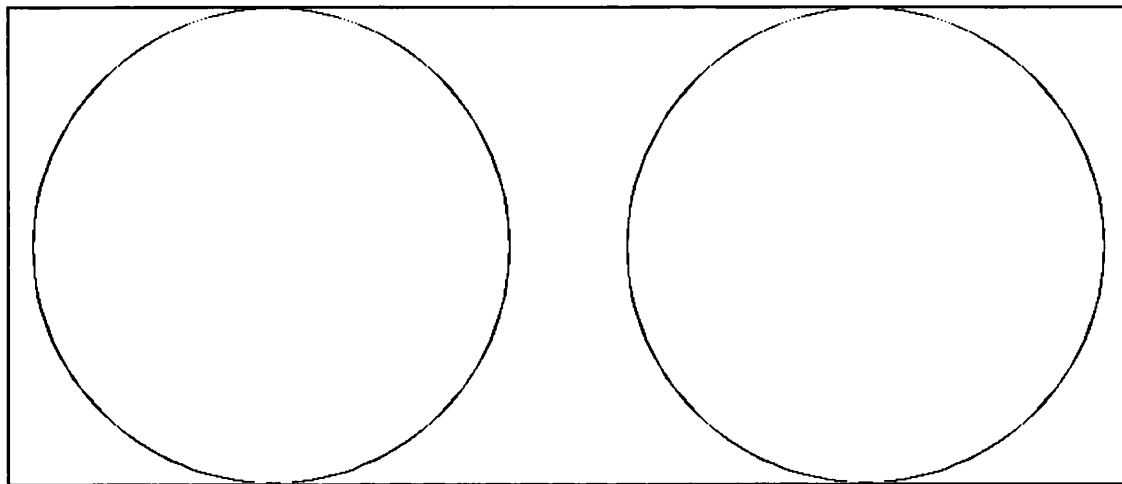
Relevant History:-

Aetiology:-

VR =

VL =

Morphology:- Central Disciform/Eccentric Disciform/Marginal/ Diffuse Interstitial/Diffuse Deep



Date	Laser Burns	Colour Photo	Extent Decimal	Density	Vascularity	VAs	Complications

12 DISCUSSION & CONCLUSIONS

There is a vast spectrum of tissue damage in ophthalmic zoster ranging from one or two skin pox to massive skin loss or scarring and destruction of the globe. The degree of damage does not correlate with other facets of the disease, appears to be quite randomly distributed in patients although there is a tendency for it to be more severe in older age groups (Edgerton 1945) and those with impaired cell-mediated immunity (Wright & Winer, 1961; Sokal & Firat, 1965). By analyzing the figures in Chapter 6 it can be demonstrated that there were significant sight threatening complications in 135 out of 1356 patients (10%). Thus the vast majority of patients recovered well with minimal complications and 341 cases (25%) had no ocular involvement at all. Reference to Chapter 6 (pages 52 & 61) shows that the commonest complication was postherpetic neuralgia which reached a significant level in 157 patients (12%) corresponding with others' findings (Burgoon et al, 1957).

Those ocular complications causing significant visual loss and damage to the globe were neurotrophic keratitis (NTK), mucous plaque keratitis (MPK), lipid keratopathy, 'megaplaque' keratopathy, diffuse epitheliopathy and optic neuritis. These have all been described in this thesis. It has been demonstrated that prompt identification and instigation of appropriate treatment will prevent severe visual loss in the majority of these cases. In most of the inflammatory complications topical steroids were effective but their administration had to be carefully adjusted, supervised and very gradually withdrawn - sometimes over years (Marsh, 1976).

Chapter 5 The incidence of clinical impairments of immunity

This is the first series of ophthalmic zoster patients with long-term follow up to show that there is minimal clinical impairment of immunity. This finding was against the view of many physicians who felt that patients developed zoster because of impaired immunity (Wright & Winer, 1961). Although this study was largely carried out some time ago prior to the appearance of AIDS in the mid 80s, and the development of better tests for impaired immunity, the results still seem valid in this country. Since then most cases of AIDS with ophthalmic zoster have been clinically obvious, and the advice remains that it is not justified to investigate all cases of ophthalmic zoster for

impaired immunity unless there are other very strong clinical clues to suggest an abnormal immune status.

Trigger factors in zoster are poorly understood and for obvious reasons it is difficult to establish if there is a temporary period of impaired immunity just prior to the development of zoster (Marsh & Cooper, 1993). More information is required on the immune status of patients (particularly cell-mediated) during the acute, chronic and relapsing stages of zoster especially when there are severe and prolonged ocular complications. The investigations should include measurements of neutralising antibody levels and circulating antigen/antibody complexes in a series of new patients at onset, 4 days, weeks one, two, three and four, at months three and six. At the same times the intensity of ocular inflammatory complications should be scored (especially lesions putatively associated with immune-complex vasculitis such as iritis and episcleritis). Cellular immunity should also be assessed at the same times by CD4/CD8 lymphocyte ratios (Arvin et al, 1996), improved VZV skin test antigen (Takahashi et al, 1992), analysis of the primary cytotoxic T Lymphocyte response (Arvin, 1992) and T lymphocyte Subsets (Higa et al, 1992). This time the emphasis should be on those complications with infiltrative lesions such as disciform keratitis, superficial stromal infiltrates and MPK. Moreover, it may be that certain strains of varicella/zoster virus induce a brisker immune response so it would be of value to culture and identify the virus strain at the start of the disease in all these cases.

Chapter 6 The incidence of ocular complications in ophthalmic zoster, their correlations and supplementary notes on 3 types of keratitis.

This study has provided a large database with long term follow up. A representative incidence of ocular complications and their correlations is given for a general London population which offers a useful baseline to assess future clinical trials. It also provides information on the natural history giving clues for prognosis and prompt management. Three of the more severe types of keratitis are described in this section.

Neurotrophic keratitis (NTK) must be identified and treated early to prevent the development of severe corneal stromal scarring and loss of vision. Thus Botulinus induced ptosis or a lateral third tarsorrhaphy carried out at the very

onset of ulceration proved most effective (Adams et al,1987). The hypothesis is advanced that these procedures are effective because of the close and constant contact of the cornea with the back of the conjunctiva of the tarsal plate allowing diffusion across of trophic factors which stabilise the corneal epithelium. More research needs to be carried out on these trophic factors and the microscopic and metabolic changes in corneal epithelium after denervation. This could be carried out using corneal epithelial imprints on PMMA spatulas (Thatcher et al 1977) for cytological staining and biochemical microanalysis in particular for levels of acetylcholine, neural and epidermal growth factors. Conjunctival biopsies also need to be taken for similar analysis, for goblet cells and the mucus produced (Nelson & Wright, 1984). In the future it may be possible to provide trophic factors in topical form.

Diffuse epitheliopathy. This is defined for the first time as a distinct entity resembling exposure keratitis but in the absence of lid deficiencies. There is only partial loss of corneal sensation and no associated stromal or inflammatory disease. Taping the lids closed appears to be the only effective treatment. The pathogenic mechanism is completely unknown. Again more information is required about the changes in corneal and conjunctival epithelium both microscopically and metabolically. Surface epithelium should be obtained by impression and excisional biopsies. This should be examined by EM and staining for biochemical changes; in particular the microvilli on the surface (Hoffman & Schweichel, 1972; Pfister & Berstein, 1977; Gipson et al, 1995; Watanabe et al,1995) and the conjunctival goblet cells (Nelson & Wright, 1984). Biochemical analysis should concentrate on the presence of growth factors, the mucin in the goblet cells and the levels of acetylcholine in the cornea. The tears need to be analyzed for their cellular content, lysozymes, quality of mucin and lipids (Maes, 1938). The confocal microscope may be useful here for assessing the tear film (Prydal & Campbell, 1996) and superficial cornea in vivo. Hopefully pharmaceutical agents will become available containing growth factors for correcting mucin and lipid defects in the tear film so that the stability of the precorneal tear film may become reestablished (Holly & Lemp, 1971).

Megaplaque keratitis is described for the first time and is the end stage of

some cases of neurotrophic keratitis and diffuse epitheliopathy. These plaques caused severe visual embarrassment and often were associated with bacterial infection. Their surgical removal was unsatisfactory because it was difficult to dissect them off and leave a smooth corneal surface. When excimer laser became available this became possible and healing was much more rapid. Unfortunately they have a tendency to recur. More needs to be known about the original disease provoking the changes as well as the biochemical chain of events leading up to calcium plaque deposition. The same investigations as above should be undertaken with the addition of biochemical analysis of calcium in the tear film and the substances giving rise to its precipitation. Confocal microscopy may be helpful here too observing in vivo changes (Prydal & Campbell, 1996). Finally biochemical agents may become available to block calcium deposition and stabilise the ocular surface.

Meaning of correlations: There was a clear relationship between the severity of rash and postherpetic neuralgia, iritis, episcleritis and neurotrophic keratitis. This was to be expected because they all reflect the density of viral spread. Iritis and episcleritis were closely related and as both are due to a vasculitis this was to be anticipated.

Comparison with other series: It was difficult to draw comparisons because many of the other series were small or multicentre-based (Burgoon et al, 1957; Harding et al, 1987; Edgerton, 1945). Liesegang's (1985) corresponded to this series more than the rest and this was probably because it was based on a retrospective analysis of a large number of notes from the Mayo Clinic.

Chapter 7 Mucous plaque keratitis

This is the largest series of cases reported. It is the first time that early and late-presenting disease types have been identified, and accurate guide lines have been given on differentiating these dendritic figures from those of herpes simplex (previously they were often confused). Pre-existing conditions and complications are described and the management discussed. There is still doubt if active viral replication occurs in the cornea; cultures for the virus have been negative (Piebenga & Laibson, 1973) but varicella DNA has been found by PCR (Yu et al, 1993), and if replication is occurring it

must be at a very low level. This would seem to be confirmed by the fact that the keratitis does not respond to topical acyclovir (Marsh & Cooper, 1984).

For the future more biopsy specimens of conjunctiva and cornea are required to look for viral replication by culture, RNA PCR and fluorescent antibody staining. Unfortunately DNA PCR merely demonstrates fragments of viral DNA are present but not replicating virus. It may be of course that the mere presence of viral antigen at the onset of the disease is the only stimulus necessary to initiate a prolonged immunological reaction and inflammatory response possibly by modifying the antigenic profile of the neighbouring host tissue. Therefore biopsies should also be analyzed for immunological changes particularly with reference to immune complex vasculitis and cellular immunity. Investigations similar to those described above for the other keratopathies are needed to show what is happening to mucus production, the corneal epithelium (Dilly (A), 1985; Dilly (B), 1985), lipids and precorneal tear film and their relationship to each other (Holly & Lemp, 1971).

Chapter 8 Laser treatment of Lipid Keratopathy in Zoster.

This is the largest series published and is the only one to consistently use fluorescein angiography to define the vessel pattern. It was pointed out that lipid keratopathy usually developed in cases of zoster keratitis that had been inadequately treated with topical steroid (Marsh, 1988). It was always accompanied by vascularisation of the cornea. It was thought that lipids leaked out of these vessels and became deposited in the stroma so that closure of them was desirable (Cogan & Kuwabara, 1958). Successful closure of these vessels could be achieved with the laser, particularly if the treatment was repeated at intervals. This led to a significant improvement in the extent and density of the lesions and a marginal improvement in visual acuity. Most patients said it made them less photophobic. A mechanism of action is proposed in that closing the vessels prevents further lipid deposition, allows phagocytosis to clear interstitial lipid and possibly makes holes within the corneal stroma through which the lipid may percolate.

More knowledge is required of the processes leading up to lipid deposition and why some cases of keratitis go on to develop it and others

not. Vascularisation too is not always associated with lipid deposition (Cogan & Kuwabara, 1958) and it is uncertain if some new vessels are more permeable than others or if the preexisting blood levels of lipids are higher than normal (Cogan 1960). Fluorescein angiography in this series showed the bulk of the leakage occurred from the small vessels and not the large. Therefore those with dense capillary beds showed more leakage than those that were sparse. There may be more effective means of delivering the laser treatment using complimentary dyes for photoactivation particularly with small vessel closure (Hennesy et al, 1994; Sheppard, 1994).

Chapter 9 Ocular palsies in zoster.

This is the largest series of zoster palsies published. On screening a series of new patients with zoster there was a much higher incidence of palsy than found previously. Many were asymptomatic and thought to be so because of development of central cortical suppression (Marsh et al, 1977). This is a well recognised phenomenon in adults with acquired long-standing squints: diplopia can be overcome by fixation with one eye and suppression of the other. It was also demonstrated for the first time that the palsies could be contralateral and bilateral. Most cases recovered well. The mechanisms of the palsies is poorly understood but an attempt was made to speculate on the sites involved and the pathogenesis.

More pathological material on these cases is needed, a small number of patients die within a few weeks of exhibiting zoster and it is vital to obtain a post mortem. More in vivo information is required using more sophisticated NMR and Positron Emission Tomography (PET) scans with enhancement techniques to establish the site and type of lesion. At present the former produces images based on the different water content of tissues and can differentiate between hypertensive infarcts from vasculytic lesions whilst the latter demonstrates large ischaemic lesions in the cerebral cortex but is not good for demonstrating lesions in the posterior fossa.

Chapter 10 Iris Angiography in zoster with iritis and iris atrophy

This was the first in vivo demonstration of vasculitis occurring in iris vessels in patients with zoster iritis. Fluorescein angiography elegantly demonstrated leakage, dilatation, impaired flow and closure of vessels. It showed that subsequent sectoral iris atrophy was related to previous areas

of poorly perfused iris vessels (unlike herpes simplex). The mechanism was not defined but was thought to be due to an immune-complex vasculitis set up by the transient presence of replicating virus. The iritis responded well in all cases to topical steroids but not to topical antiviral agents.

More iris biopsy specimens must be analyzed for microscopical changes, biochemical changes and for the presence of virus and the local immune response. Appropriate iris material becomes available when cataract extraction is carried out on an affected eye. Examinations should include using electron microscopy, DNA and RNA PCR analysis, culture of the virus, fluorescent antibody staining and radio immunoassay. The local lymphocytic effector response also requires detailed examination as do other mediators of the inflammatory response such as complement and interleukins. Better methods of eliminating the unwanted side effects of the inflammatory response such as vasculitis and gross cell death must be found.

General comments on pathogenesis and treatment.

The pathogenesis of zoster is poorly understood due to lack of animal models and a dearth of pathological material. It seems that the phase of acute viral replication is relatively short-lived, perhaps only five to seven days at the start of the disease (Kangro & Harper, 1995). After this time the vesicles disappear and virus cannot be cultured from the skin or eye (Liesegang, 1991; Kangro & Harper, 1995) but it clearly initiates the inflammatory reactions. This is in marked contradiction to most lesions induced by herpes simplex viral disease where large quantities of replicating virus are found. It is uncertain if varicella/zoster virus remains in the tissues in an altered form, undergoes sporadic reactivation where it is difficult to culture but can induce a marked immune-mediated inflammatory response, or, alters susceptible cell membranes inducing an ongoing autoimmune inflammatory response. Variability of the strain of virus may also contribute to the degree and distribution of complications (Liesegang, 1991). It may be that some strains invoke more of a cytopathic response than others or have a predilection for particular tissues like herpes simplex (Stevens, 1987; Liesegang, 1991). It is difficult to explain why the lesions are prone to recurrence. Any of the above mechanisms could explain it and many

autoimmune diseases such as polyarteritis nodosa, scleroderma and SLE are characterised by a tendency to relapse.

There is ignorance of the states of viral latency and reactivation. In latency very few neurones or satellite cells are colonised (Liesegang, 1991) but after reactivation and replication most of the neurones may be destroyed (Head & Campbell, 1900; Kangro & Harper, 1995). If the reactivating factors were known perhaps they could be removed or a protection devised against them. The only characteristic about reactivation is that clearly it is commoner with ageing (Edgerton, 1945).

The immunological responses in zoster have been investigated by assessment of neutralising antibody, and reduced delayed type sensitivity response by blastogenesis of peripheral blood cells and skin testing (Weller, 1982). Perhaps the most important established aspect of humoral immunity is the capacity of specific immunoglobulins to prevent spread of virus infection by blocking viral attachment to susceptible cells. But it is rather difficult to reconcile this with the fact that zoster is not unduly severe in patients with agammaglobulinaemia (Gershon & Steinberg, 1981). The main problem with cell-mediated immunity is the tendency for 'overkill' by sensitised macrophages, PMNs, and killer lymphocytes. That is to say they eliminate the virus by destroying the infected cells. If the response is delayed and the virus has spread and proliferated there may be massive neuronal loss (Straus, 1992). All observations would tend to confirm this. Moreover in some patients there may be an inappropriate overwhelming immune response (Liesegang, 1991).

Therapy Many problems with ophthalmic zoster arise because of late presentation or identification of the disease and its complications. This may be because the patient or GP is late in referring to the ophthalmologist or there is a delay in diagnosis: although it should be emphasised that most GPs refer all cases of ophthalmic zoster directly to the ophthalmologist. On the other hand there may be early referral to an ophthalmologist who is not fully cognisant of the nature of ocular complications and their tendency to relapse. He may prematurely discharge the patient without treatment or start topical steroid and stop it precipitously. Either way the inflammatory response is established and reinforced and becomes more resistant to

treatment. Also at a later stage virostatic antivirals are ineffective because the phase of active viral replication has passed and they cannot destroy latent virus or eradicate sporadically replicating virus (Kangro & Jefferies, 1995). The small number with impaired cellular immunity tend to have prolonged active proliferation of virus and virostatic antivirals are more effective here (Bean et al, 1982). A safe effective viricidal drug administered very early in the course of the disease might prove useful because although it would not destroy true latent virus it should be effective against low grade replicating virus. The latter now appears to be the case in the latent phase because of the levels of messenger RNA present (Dueland, 1996). However, with later presentation of the disease and established inflammation, drugs that will suppress its undesirable aspects are required, and so far only steroids are available to the majority of physicians. They act chiefly by their inhibitory action on cell-mediated immunity, in particular on cytotoxic T cells and macrophages.

In the meantime the most positive and interesting option to be pursued is the action of specific immunoglobulins in blocking spread of the virus. Vaccination has been introduced for protection against varicella using an attenuated strain of the virus (Takahashi et al, 1974) and although trials are not completed it has proved most successful in protecting patients who have impaired immunity, particularly in children with leukaemia. However, our knowledge is limited of its affect in modifying the development of zoster (Sperber et al, 1992). Neutralising antibodies fall to very low levels after one year (Cradock-Watson et al, 1979; Ceretini et al, 1983) and so regular 6 monthly vaccination could conceivably maintain a sufficiently high level of specific antibody to contain spontaneously reactivated virus and prevent the development of clinical zoster and its complications. In view of the relatively late presentation of many cases of zoster, prophylaxis would appear to be a very attractive option (Oxman, 1995). For convenience sake it may be possible to administer it in the elderly population when they attend for other vaccinations such as influenza or for routine screening. From the fiscal point of view it might appear at first sight to be an expensive option. But vaccines are not generally costly, especially when compared with systemic antivirals. Delivery of vaccine is straightforward and reasonably

economical of human resources. It would be well worthwhile setting up a large pilot study in the elderly who have not suffered zoster to see if six monthly vaccinations are effective in preventing zoster. Because of the sporadic nature of zoster this would have to be large, multicentre and long term trial. This would be a formidable organisational challenge in recruiting adequate numbers of volunteers if the younger age groups were included especially in obtaining regular review visits. But it would be easier to base trials on the more vulnerable elderly population in Residential Care where monitoring is easier. It should be randomised, controlled and preferably blind.

Conclusion As a result of the studies presented here it is apparent that ophthalmic zoster, although not a common ophthalmic condition, may pose critical problems in diagnosis and management of its complications. Due to our ignorance of the pathogenesis of most of the treatment options for the ocular complications tend to be rather empirical and mainly confined to antivirals and steroidal antiinflammatories neither of which are particularly effective in preventing some complications. Virostatic drugs have to be administered very early on and topical steroids may prove difficult to withdraw and give unacceptable complications. A promising new approach to therapy is regular active immunisation with an attenuated strain of varicella\zoster virus which, at best, may prevent the development of zoster or minimise the severity of an attack.

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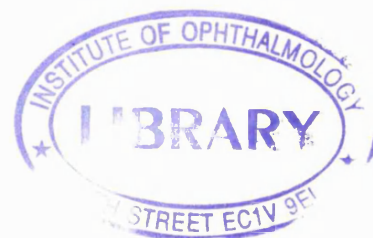
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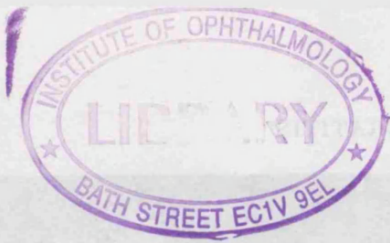
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HERPES ZOSTER KERATITIS

R. J. MARSH (London)

EARLIER descriptions of Zoster Keratitis stress its serious nature and the risk of loss of the eye (Jeffries, 1873; Spicer, 1891; Elliot, 1918; Edgerton, 1945). With the advent of antibiotics, corticosteroids, and viscous artificial tear preparations, the nature and course of the disease have changed for the better. It therefore seems an appropriate time to attempt a revised classification of the different types of keratitis occurring in this condition. I am basing this paper on the observation of over 500 patients suffering from the disease seen in the External Diseases Clinic at Moorfields Eye Hospital.

Just over 7 per cent. of all cases of Herpes Zoster affect the Ophthalmic nerve (Achard, 1924) and the cornea is involved in 35 per cent. of these (Edgerton, 1945). The disease itself is due to the reactivation of latent varicella virus lying in the trigeminal ganglion (Garland, 1943; Hope-Simpson, 1965). The virus replicates in response to an unknown trigger factor and migrates down radicals of the ophthalmic nerve eventually reaching the skin and in 50 per cent. of cases the globe (Duke Elder, 1965). Three major stages in the involvement of the cornea may be recognized; acute, chronic and relapsing. All the tissues of the cornea are involved and will be considered under the headings of acute epithelial keratitis, acute superficial stromal infiltrates (Figs. 1 and 2), disciform keratitis (Figs. 3 and 4), sclerokeratitis and keratitis associated with impairment of corneal sensation (Figs. 5 and 6). The percentage incidences quoted in this paper are based on the last 100 new patients attending the clinic.

The first structure to be involved is the epithelium, either prior to, or, simultaneously with the rash and takes the form of small dendritic type of lesions (Fig. 7) which are raised, multiple and situated close to the limbus. They stain well with Rose Bengal and are occasionally coated with a layer of mucus which stains with Alcian Blue. They differ from those of Herpes Simplex in that they are broader, often stellate, have a simple raised contour and this virus may not be cultured from them. More important is the fact that they are not enhanced by topical steroid. Their course is transient lasting only a few days. They are always accompanied by a catarrhal conjunctivitis and frequently by vesicles on the lid margin. Varicella virus has recently been isolated from them (Pavan-Langston and McCulley, 1973) and would seem to reach the epithelium either from the corneal nerves or from the conjunctival sac. Rarely, a punctate epithelial keratitis is seen (Barrie-Jones, 1962). Steroid antibiotic combination drops should be used to prevent secondary infection and to

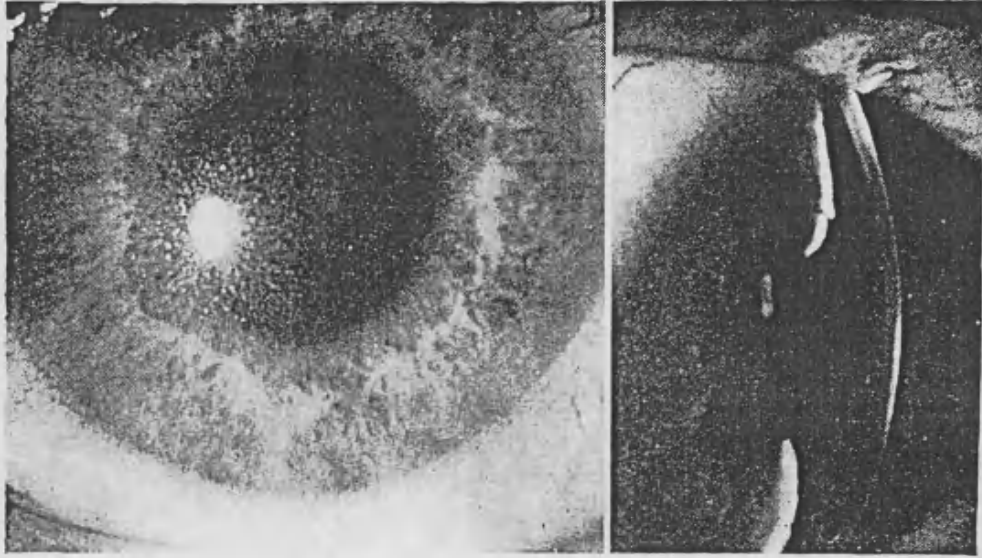


FIG. 1.
Superficial stromal infiltrate.

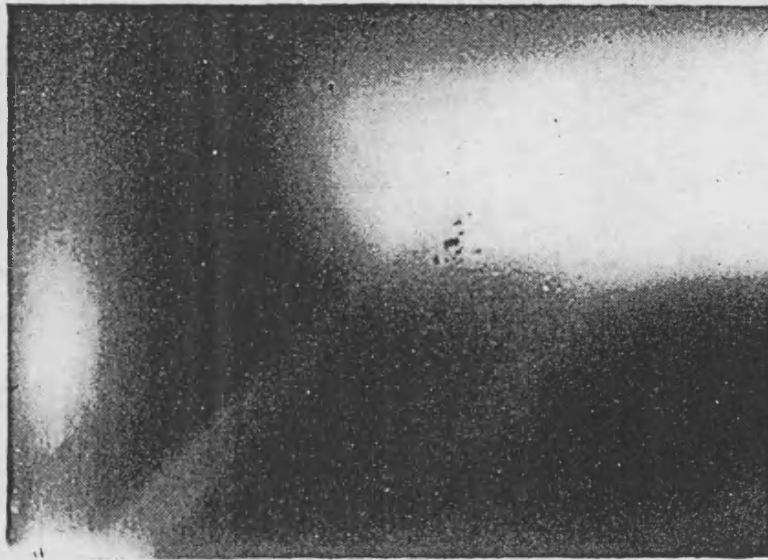


FIG. 2.
Superficial stromal granules. ($\times 10$ magnification.)

reduce the inflammatory response and subsequent scarring of the conjunctiva. If excessive mucus is present acetylcysteine drops may be used to prevent its deposition on the corneal lesions.

The stroma is the next structure to be affected and superficial stromal opacities form the commonest lesion to be seen in the cornea, occurring in 35 per cent. of our cases. They appear about 10 days after the onset of the rash and may succeed the epithelial lesions or arise *de novo*. Their appearance is that of single or multiple areas of ill-defined infiltrate

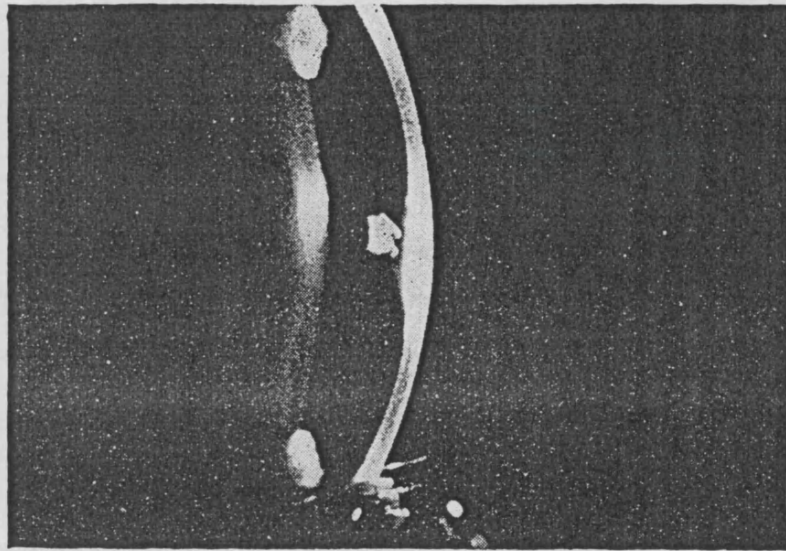


FIG. 3.
Disciform keratitis, slit view.

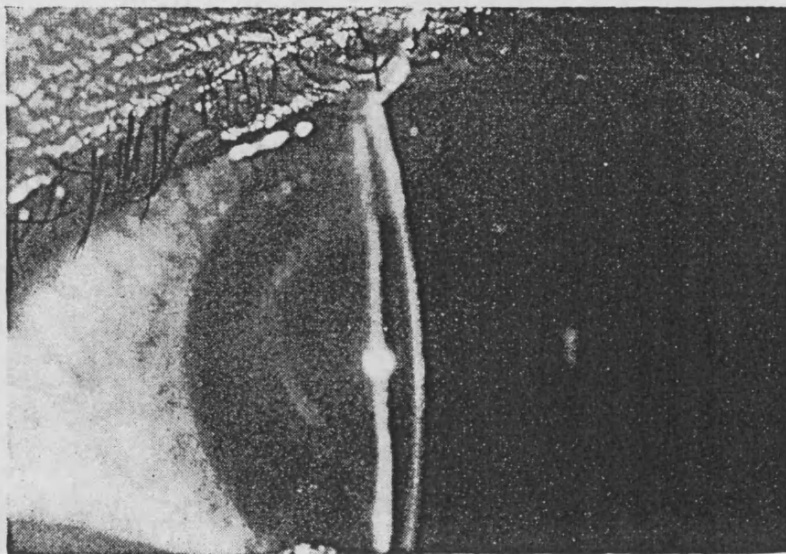


FIG. 4.
Disciform keratitis with immune rings.

varying in size and density lying just beneath Bowmans membrane. They evolve from fine white granules often lying adjacent to enlarged corneal nerves just before they enter the epithelium. Surrounding areas of stromal haze appear very soon after. A week later the white granules turn brown and the stromal interference pattern around them fades. The process of resolution is accelerated by topical steroid but in minority of cases the opacities become chronic with more infiltration and permanent scarring. Rarely, there is a relapse as late as 2 years after the onset of the disease

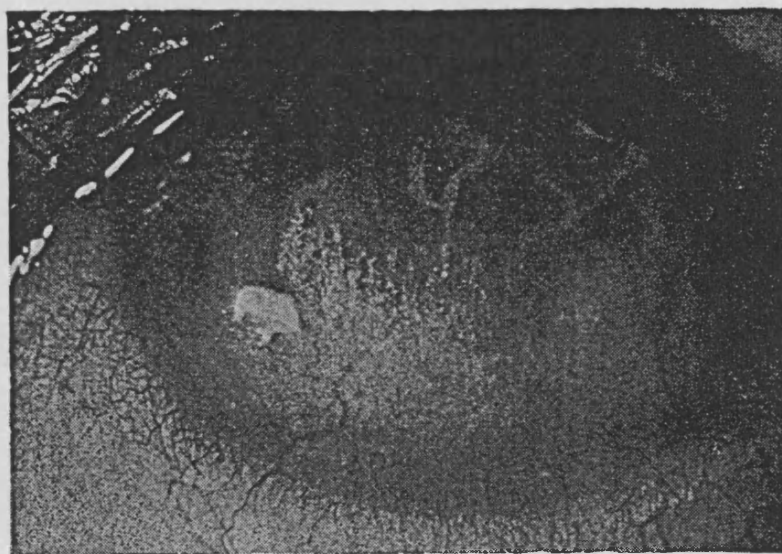


FIG. 5.
Severe corneal scarring from sclerokeratitis.

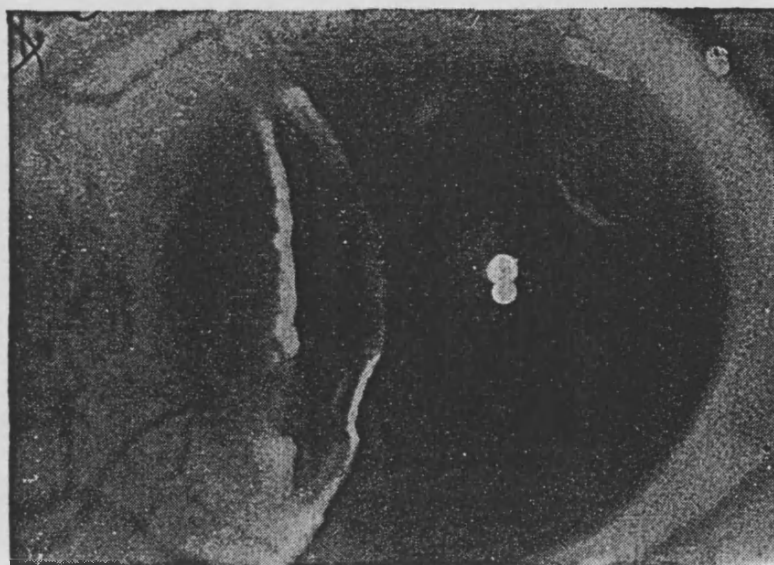


FIG. 6.
Peripheral corneal facets.

and the opacities reappear with much more haze. The early relapse is often provoked by the precipitate withdrawal of topical steroid. Head and Campbell (1900) in their masterly paper on Herpes Zoster stated from pathological evidence that a subepithelial infiltrate of mononuclear cells appears in the substantia propria of the cornea around the terminal nerve fibres. The ætiology of the granules is most likely due to the degeneration of corneal nerves secondary to viral damage. Often these nerves are enlarged and it is possible to trace the course of an involved nerve by the

combined presence of an area of stromal infiltrate, episcleritis and sectorial iris atrophy in the same radius (Redslob, 1923; Bonnet, 1939). Topical corticosteroid reduces their density but must be withdrawn carefully to prevent a rebound keratitis.

A rare form of stromal involvement is disciform keratitis, seen in 6 per cent. of our cases. The appearance is that of central or peripheral stromal infiltrate and swelling. Surrounding immune rings are commonly seen and may reach three in number. If the keratitis is eccentric the rings become C-shaped with the open end facing the adjacent limbus. It is often based

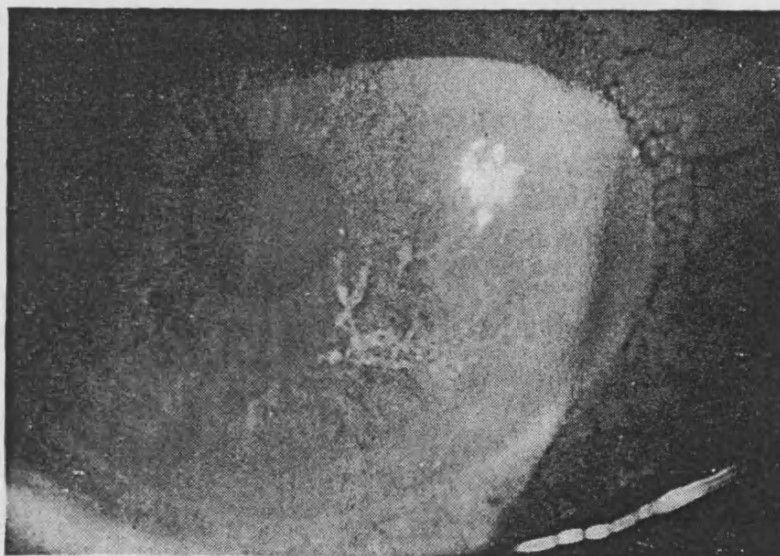


FIG. 7.

Dendritic figures associated with diminution of corneal sensation.

on a preceding superficial stromal infiltrate but lies at a deeper level. It commences at about 1 month after the onset of the disease and if untreated tends to become chronic with increasing infiltration into the lesion itself and the surrounding rings. Lipid deposition appears in approximately 6 months and is followed by vascularization in the superficial half of the cornea. This may lead to a dense central or peripheral nebula formation and in the case of the latter facetting. A most important presentation is the relapsing form which appears between 2 months and several years after the onset of the disease. There is customarily a transient initial keratitis but both this and the rash may have been so mild as to pass unnoticed by the patient. Iritis is invariably present but is mild and often hypertensive. Thus in any new case of disciform keratitis, Herpes Zoster must be considered in the differential diagnosis. The salient features to be looked for are a history of a painful rash, punched out areas of skin scarring, patches of scleral atrophy and sectorial iris atrophy. About 30 per cent. of our cases of Zoster reveal single or multiple patches of sectorial iris pigment

epithelial loss with ill-defined borders and in half there is also involvement of the sphincter. In less than 5 per cent. of Herpes Simplex a sectorial pigment epithelial loss occurs but is well defined and has scalloped edges. The iris angiographic features are distinctive; Zoster revealing no vascular filling in the areas of atrophy unlike the normal filling of Simplex. Some cases of relapsing keratitis progress to corneal anaesthesia, chronic iritis, glaucoma and epithelial defects. Pathological reports are available only on the chronically scarred corneas and describe non-specific chronic inflammatory changes with lipid deposition and vascularization (Hogan and Zimmerman, 1962). The delayed onset, the preceding superficial stromal infiltrate and presence of immune rings suggest a delayed hypersensitivity reaction. The antigenic component would appear to be the original stromal lesion which is either purely degenerated nerve fibre products or persisting virus. The latter has not yet been isolated from corneal buttons trephined from affected patients. The keratitis is extremely steroid sensitive and G. Dexamethasone 0.1 per cent. can be safely used without fear of epithelial complications (unlike Herpes Simplex). However, if steroid is withdrawn rapidly a rebound keratitis is risked. The steroid is best titrated against the activity of the lesion and long term follow-up is necessary.

Sclerokeratitis is an uncommon manifestation of the disease; its incidence in our clinic is 6 per cent. It appears as either a nodular or a brawny scleritis which can involve two-thirds or more of the anterior half of the globe and the smaller the sector of scleritis the smaller the area of corneal involvement. There is cellular infiltration of all stromal layers with marked swelling. It may present at the onset of the disease when it is frequently concealed by an overlying acute conjunctivitis but more often appears 1 to 3 months later, when it can be precipitated by the sudden withdrawal of steroid. It tends to run a chronic course if untreated; the infiltrate spreading across the cornea with increasing stromal swelling. Further progression, as in disciform keratitis, involves extensive infiltration with lipid and vascularization which may either progress to obscure the pupil, or, if it remains localized, develop peripheral faceting. On the other hand the acute keratitis may rapidly resolve to be followed 4 months to several years later by a relapse. An iritis is invariably present and iris atrophy may occur in the same sector (Penman, 1931). Occasionally, a profound loss of corneal sensation develops, especially with the relapsing form. Pathological reports describe non-specific inflammatory changes of the cornea with lipid deposition and vascularization (Naumann, Gass and Font, 1968). Vasculitis is evident in the episcleral and scleral vessels which is most likely an immune complex variety with resultant infiltration and ischaemic affects on the cornea. Chronic activity of the virus in these vessels would seem less likely. The response to topical steroid is good but often potent varieties must be used at frequent intervals. Again, it must

be cautiously withdrawn, possibly over months. Tanderil has been of therapeutic value in some of our severer cases.

The last major type of keratitis is that associated with loss or diminution of corneal sensation. The latter was totally lost in 9 per cent., particularly in 27 per cent. and recovered in 10 per cent. of our cases. Pure loss of sensation does not appear to cause keratitis but when combined with chronic conjunctivitis, an abnormal tear film and other unknown factors, the typical so-called neuroparalytic keratitis occurs. This is characterized by epithelial changes and occasionally by secondary stromal changes. In our series this amounted to 6 per cent., tending to be mild or severe.

The mild form is characterized by a general lack of lustre of the epithelium and at times by very fine vesicles which progress to multiple punctate epithelial erosions in the interpalpebral area. Although these changes can occur immediately after the onset of the disease they are more commonly seen 3 to 6 months later and tend to fluctuate in severity. Lid deformities aggravate the condition; including lid margin scarring, trichiasis and cicatricial ectropion, all resulting from the chronic inflammatory changes of Zoster. The management of the condition is based on maintaining a viscous tear film over the defective epithelium, which can be achieved by the frequent instillation of guttae B.J.6, hypromellose, polyvinyl pyrrolidone 0.5 per cent. or Adapet. Patients often show a marked preference for one of these and so a trial of all four is worthwhile.

A more severe keratitis may ensue with total loss of corneal sensation appearing as diffuse fine vesicular changes of the epithelium with recurrent corneal ulceration. These ulcers are extremely indolent, generally appear in the interpalpebral region and have opaque waterlogged edges. They may extend to involve the whole of the cornea and if the stroma remains uncovered for any length of time it becomes infiltrated by cells, opacifying from the superficial layers downwards. Naturally, the ulcers are prone to secondary infection which, along with thinning, leads to perforation. Fortunately, only one of our series did this but resolved successfully on medical management. The Keratitis tends to fluctuate in intensity and the ulcers usually resolve after 3 months. The majority of them heal with some degree of thinning and vascularization. Histological examination shows degenerative changes in the epithelium and extensive necrosis in the stroma (Duke Elder, 1965). The aetiology is clearly related to viral damage of the ophthalmic nerve and the keratitis is identical with that produced by 5th nerve section, with a similar time lag between denervation and keratitis. Many theories have been advanced to explain the mechanism of corneal damage. Perhaps the best to date are that of 'abnormal cellular metabolism' brought about by deprivation of the control normally carried out by sensory nerve activity (Lewis, 1927), and secondly, that there is a diminution in the wettability of the superficial cells by the tear film with an increase of epithelial permeability (deHaas, 1962; de Simone, 1955).

The management is difficult. Viscous artificial tears should again be used along with topical antibiotics to prevent secondary infection. A severe exacerbation of corneal ulceration may prove uncontrolled by these measures and by padding (Lodge and Lodge, 1923). Tarsorrhaphy has always been invaluable in such cases but in order to be satisfactory, may be so extensive as to embarrass vision. Soft lenses would seem to offer a solution but in my limited experience, have unfortunately proved disappointing.

Another type of keratitis associated with diminution of corneal sensation has emerged as a definite entity in our clinic and its incidence is 5 per cent. It is characterized by initial transitory epithelial lesions followed by permanent stromal haze formation. The onset is sudden, at 2 to 3 months after the start of the disease which is usually distinguished by a transitory disciform keratitis, superficial stromal infiltration or sclerokeratitis. The epithelial lesions are dendritic figures which rapidly increase in number and extent, forming quite complicated configurations. They have a simple raised contour, are whitish in colour and are easily rubbed from the corneal surface without detaching the underlying epithelium. They stain with fluorescein, Alcian blue and best of all with Rose Bengal. There is always a coincident conjunctivitis with ciliary injection and sometimes an episcleritis or iritis. The precorneal tear film is markedly abnormal, failing to cover the dendritics and rapidly producing dry spots on the epithelium in a dendritiform pattern. Indeed the whole tissue becomes hazy with a fine vesicular appearance. The dendritics are, unlike the previously mentioned acute variety, often confused with those of Herpes Simplex. They differ in having a different profile, in not being adversely affected by steroid and by not yielding herpes virus on culture. Fine infiltration next appears in the superficial stroma and slowly spreads deeply, especially centrally. In many cases, the complicating iritis is hypertensive and poorly responsive to topical steroid, depositing many fine white keratitic precipitates on the endothelium with occasional extension of a fine infiltrate into the deep stroma. After 2 to 4 months, when the epithelial lesions have resolved these stromal opacities are more obvious and permanently reduce the visual acuity. There are no pathological reports on this type of keratitis and the aetiology is conjectural, but it clearly has an inflammatory onset with the epithelium initiating the corneal changes. The abnormal tear film is most likely due to the epithelial disturbance because the bilateral Schirmers test is normal and the tear meniscus at the lower lid margin appears satisfactory. Perhaps the deep stromal haze is an unusual form of disciform keratitis. Management is a problem, there seems to be no way of preventing the development of the stromal haze. The episcleritis and iritis slowly improve on topical steroid and in combination with guttae acetylcysteine 5-20 per cent. the dendritic figures disappear. Viscous artificial tear solution som-

times assist in improving the epithelial lesions. The coincident secondary glaucoma may be a problem and acetazolamide must often be used to control it.

Lastly, it is important to point out that corneal oedema frequently accompanies the iritis of Zoster in the absence of a grossly raised intra-ocular pressure. The corneal endothelium appears to be peculiarly vulnerable to this iritis but rapidly recovers with the use of intensive topical corticosteroid.

CONCLUSION

Careful diagnosis and management can favourably influence the course of Zoster keratitis. Especially important is regular and long term follow-up. Many of the patients we see in the Clinic present 6 months and more after the disease onset and have been discharged from supervision by their doctor. Because of the tendency of the disease to relapse it is advisable to maintain the patient on topical corticosteroid for at least 6 months after the resolution of the keratitis. The adequate use of this drug can prevent serious degrees of corneal scarring which is so often seen in neglected cases. Obviously, the undesirable side effects of steroid must be carefully monitored, but at times it is extremely difficult to differentiate the glaucoma induced by these drugs from that of iritis.

It is essential to differentiate the keratitis of Zoster and Simplex. The two are very often confused and are only very rarely seen together (Acers and Vaille, 1967). When this is suspected, on clinical grounds, recourse should be made to virology. Epithelial specimens must be collected in virus transport medium (such as 2 S.P.), and sent directly for culture to a Specialist Centre. Blood should be taken for varicella and herpes antibody estimation. Because varicella virus is so difficult to grow, Zoster is often a diagnosis of exclusion.

I feel the future in the management of this condition will be in finding a potent, safe selective, systemic antiviral agent to eradicate the virus at the onset of the disease. I hope this presentation stimulates more interest in the keratitis of Zoster which despite the extensive geriatric practice does present an extremely varied spectrum of eye disease and stimulating problems in diagnosis and management.

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I would like to thank Professor Barrie-Jones for his help and encouragement. My colleagues in the External Diseases Clinic were a constant stimulus and help in the production of this paper. Lastly, it is a pleasure to thank the Audio-Visual Department of the Institute of Ophthalmology for their many contributions.

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IRITIS AND IRIS ATROPHY IN HERPES ZOSTER OPHTHALMICUS

R. J. MARSH, F.R.C.S., D. L. EASTY, M.D., AND B. R. JONES, B.Sc.

London, England

Herpes zoster ophthalmicus is caused by the reactivation of a latent infection due to the varicella-zoster virus.^{1,2} The virus is widely disseminated in the body during an initial varicella illness and remains apparently inactive in certain tissues. It has been demonstrated in the trigeminal ganglion by Esiri and Tomlinson,³ where it appears to replicate and migrate down the peripheral fibers of the ophthalmic branch of the fifth cranial nerve. On reaching the skin, the virus produces the typical rash from which it can be cultured.

Iritis is a common complication of herpes zoster ophthalmicus; Edgerton⁴ reported an incidence of 20%. Duke-Elder⁵ divided the iritis into two types: diffusely exudative and locally eruptive. The diffuse type was either mild and produced posterior synechiae⁶ or severe with keratitic precipitates, and was occasionally accompanied by hypopyon⁷ or secondary glaucoma. The second type was characterized by eruptive lesions on the iris with acute vascular dilatation.⁸⁻¹⁰ These observations were made prior to the introduction of therapeutic corticosteroids, the administration of which markedly alters the course of iritis. It tends to run either an acute or a chronic relapsing course and, with corticosteroid treatment, is in no way so severe as described in the early reports. The aqueous flare is generally minimal and is associated with only a small quantity of cells. The corneal stroma is frequently swollen in the acute phase; posterior synechiae formation and severe glaucoma are unusual, the latter responding readily to corticosteroids.

A frequent sequel to the inflammation is iris atrophy. The common defect is a triangular sectorial loss of pigment epithelium with

the base lying at the iris root (Fig. 1). Stromal damage is rare. Several areas may be involved, with no predilection for any particular site. Examination with the slit lamp using focal illumination shows migration of pigment clumps from the underlying epithelium into the adjacent stroma.¹¹ In many cases sphincter damage, which may lead to torsion of the iris, occurs adjacent to atrophic areas. A minority of patients develop massive iris atrophy with gross sphincter damage, cataract formation, and ocular hypotension.¹² Herpes simplex, acute angle-closure glaucoma, and anterior segment necrosis also lead to sectorial iris atrophy.

The pathogenesis of the iris atrophy has not been determined but would seem to be due to either invasion of the pigment epithelium by virus, a local vasculitis, or a neurogenic effect. Vasculitis may produce ischemia; fluorescein angiography is a good method for demonstrating such changes in the iris.¹³

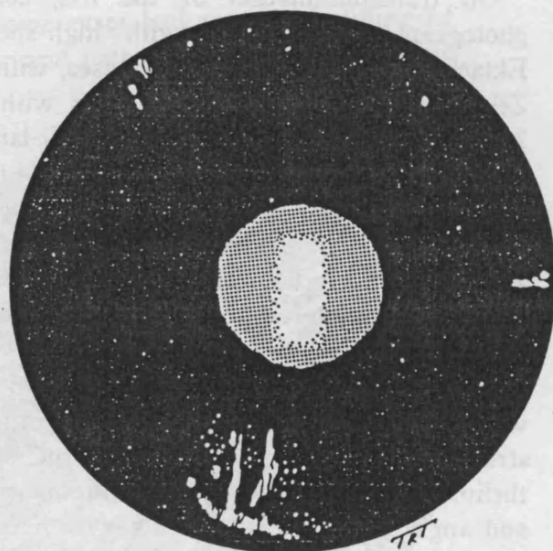


Fig. 1 (Marsh, Easty, and Jones). Drawing of sectorial iris atrophy photographed by transillumination.

From the Moorfields Eye Hospital, London, England.

Reprint requests to R. J. Marsh, Moorfields Eye Hospital, City Road, London EC1V 2PD, England.

PATIENTS AND METHODS

This 18-month study included 520 patients with herpes zoster ophthalmicus attending the External Diseases Clinic at Moorfields Eye Hospital. Of these patients 140 were seen by us from the onset of the disease. The examination routine included careful history taking, especially noting previous eye disease, and complete ophthalmic examination with particular attention to the anterior segment. Abnormalities in the anterior chamber and iris were scored and recorded (in some cases with drawings, photographs, and fluorescein angiograms). The color and architecture of the iris, as demonstrated by focal and transpupillary retroillumination, the appearance of pupil, and ocular tensions were recorded at each visit.

Twenty-one blue-eyed patients with iris atrophy in the quiescent stages and normal ocular pressure had iris angiography by the technique of Easty and Bron.¹⁴ Three further patients had angiograms performed during both the acute and convalescent phases. Two blue-eyed patients with herpes zoster ophthalmicus but not iritis served as controls.

On transillumination of the iris, color photographs were taken with high-speed Ektachrome film, and, in some cases, with a Zeiss photo slit-lamp camera fitted with a $\times 1$ objective. The objective and slit-lamp head apertures were set at maximum, and the illuminating slit enlarged just to fill the pupillary aperture. The slit-lamp head was brought as near to the coaxial position as possible with the beam decentered to avoid troublesome glare from the cornea.

To compare herpes zoster ophthalmicus with other conditions that cause localized iris atrophy and destruction of pigment epithelium, we examined by transillumination and angiography three patients with herpes simplex, three with acute angle-closure glaucoma, and three with anterior segment necrosis subsequent to retinal detachment surgery.

General investigations on all patients included chest x-ray film, hemoglobin concentration, complete blood cell count, erythrocyte

sedimentation rate, plasma proteins, electrophoretic strip, blood glucose, and serum cholesterol.

RESULTS

Seventy-four of the 520 patients showed iris atrophy. The average age was 60 years; 35 were men and 39 were women; 66 had blue irides and eight had brown. The 140 patients presenting in the acute stage of the disease over the 18-month period had a 52% incidence of iritis and 25% incidence of iris atrophy. The other 380 patients showed a lower incidence of iris atrophy, probably due to previous selection for follow-up based on other features of the disease. The iris atrophy fell into three grades of severity: 47% showed pure basal sector atrophy; 47% had additional sphincter damage; and 6% had massive iris atrophy.

Angiography in zoster iris—A normal iris angiogram (Fig. 2) shows rapid filling of the vessels from the major circle of the iris in a series of arcades. The shortest system of arcades is at the base of the iris (arrow A), lying between large, long, radial vessels, which pass toward the pupil, branch-

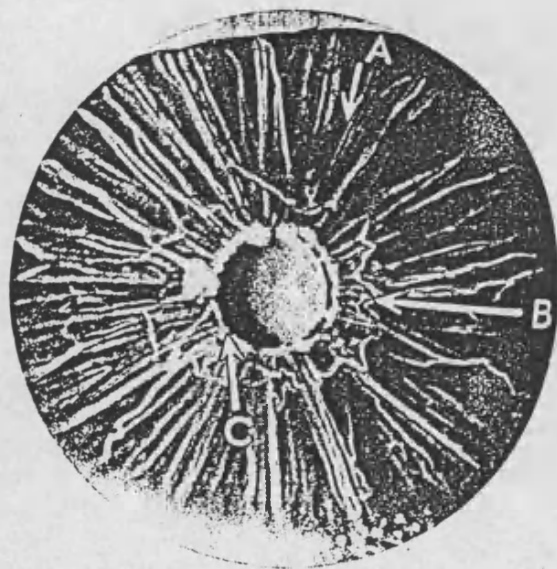


Fig. 2 (Marsh, Easty, and Jones). A normal iris angiogram, showing the basal arcade system (arrow A), the lesser circle of the iris (arrow B), and the arcades at the pupil margin (arrow C).

ing into two at the collarette. One of these branches forks backward to the base of the iris forming a second series of arcades at the collarette (arrow B), the lesser circle of the iris. The other branch passes to the pupillary edge where it turns back on itself to form the third series of arcades (arrow C.) Leakage is minimal at the pupillary margin. Our angiographic findings may be considered under the following group headings: Group A, with pure iris sector atrophy; Group B, with additional sphincter damage; and Group C, with massive iris atrophy.

Herpes zoster uveitis—The 12 patients in Group A revealed either delayed or complete loss of filling of basal arcades and long radial vessels in the area of pigment epithelial loss, often accompanied by dilatation of the neighboring long radial vessels.

Three cases were studied with serial angiography from the onset of iritis over the acute phase. Dilatation and early leakage of all iris vessels were seen initially; three days later small areas of vascular narrowing and loss of filling appeared in a sectorial distribution against a background of generalized vascular dilatation and leakage. Direct slit-lamp observation revealed deformation of the pupil

with accompanying sluggish sphincter action in the affected sector. One week later, more sectors revealed vascular narrowing and closure with less generalized dilatation and leakage. Slit-lamp examination of the iris showed chinks of pigment epithelial loss in the affected sector. Resolution of the vascular dilatation occurred $3\frac{1}{2}$ weeks after the onset of iritis, but the areas of narrowing and closure remained and were directly related to the area of iritis atrophy (Fig. 3). Later pictures showed evidence of filling in vessels that were closed in previous angiograms. Pigment epithelial loss continued to occur in the affected sectors for a month more, despite the resolution of the iritis (Figs. 4 and 5), and despite the extensive use of local and systemic corticosteroids. Raised ocular pressure did not accompany the loss of pigment epithelium.

The ten patients in Group B, with combined atrophy, showed additional changes (Fig. 6, left). There was occlusion of the two distinct arcades normally visible at the collarette and pupil margin, leaving only an ill-defined vascular arcade in the affected sector (Fig. 6, right). Some cases had retrograde filling of the larger and patent vessels in the atrophic

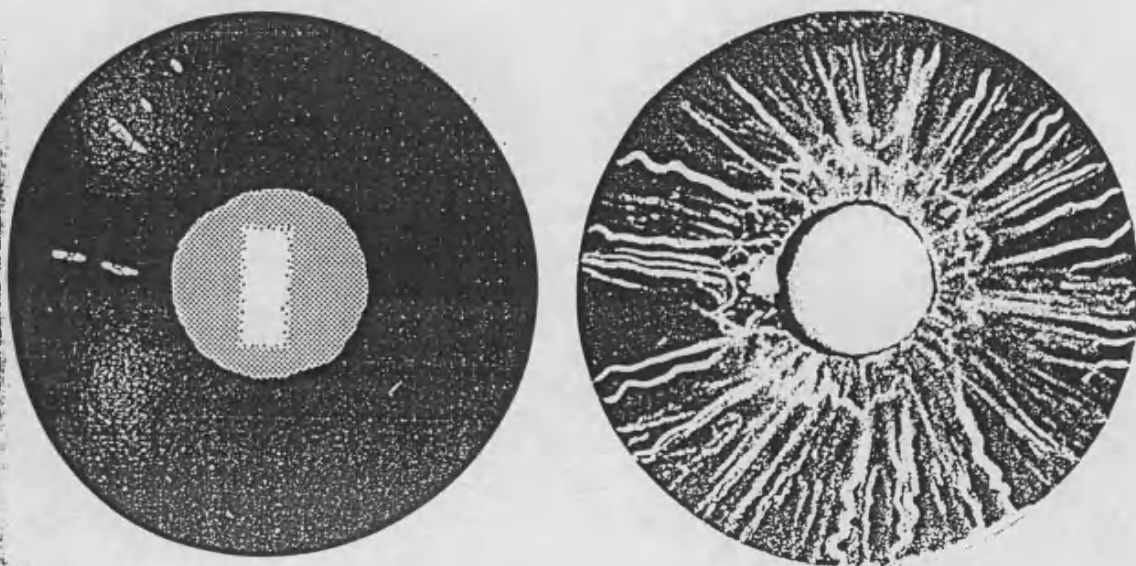


Fig. 3 (Marsh, Easty, and Jones). Left, Drawing of iris pigment epithelial atrophy $3\frac{1}{2}$ weeks after the onset of iritis (photographed by transillumination). Right, Angiogram of the same iris depicted. Note the failure of iris vessels to fill at 9 o'clock and the generalized vasodilatation.

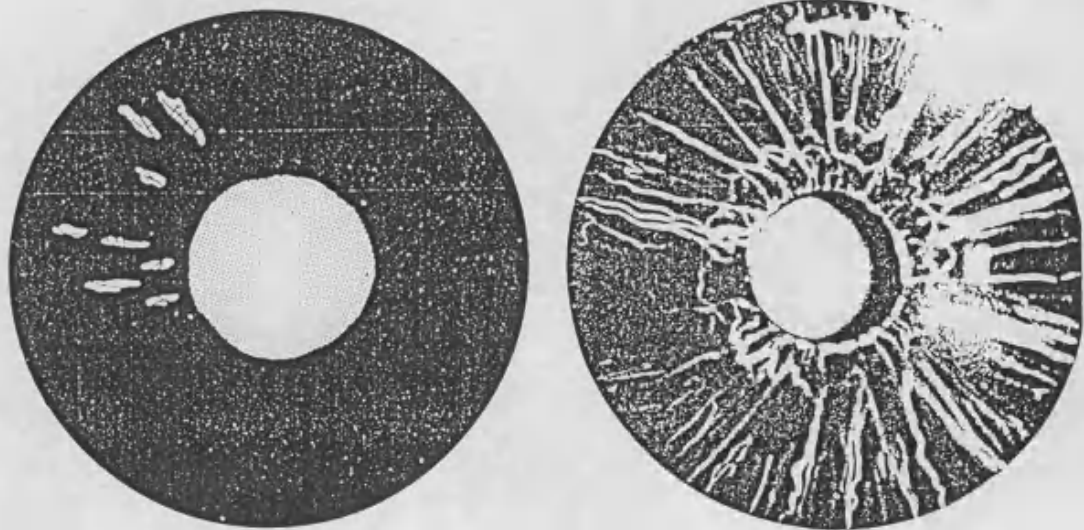


Fig 4 (Marsh, Easty, and Jones). Left, Drawing of iris pigment epithelial atrophy in the same patient as Figure 3, two weeks later. Right, Angiogram of the same iris. Note more extensive leakage of fluorescein into previously avascular filling.

areas from dilated neighboring vessels.

The two patients in Group C showed large areas of iris that did not fill with fluorescein corresponding to the iris pigment epithelial loss. Some leakage occurred at the pupil margin and from the dilated vessels adjacent to the atrophic areas (Fig. 7).

Herpes simplex uveitis—Three cases of

herpes simplex with sectorial iris atrophy, examined by transillumination, revealed loss of pigment epithelium, but the stroma appeared to be normal. The atrophy characteristically had scalloped, well-defined edges—contrast to that of herpes zoster, which is ill-defined (Fig. 8, left). Angiography demonstrated filling of basal and radial vessels in the

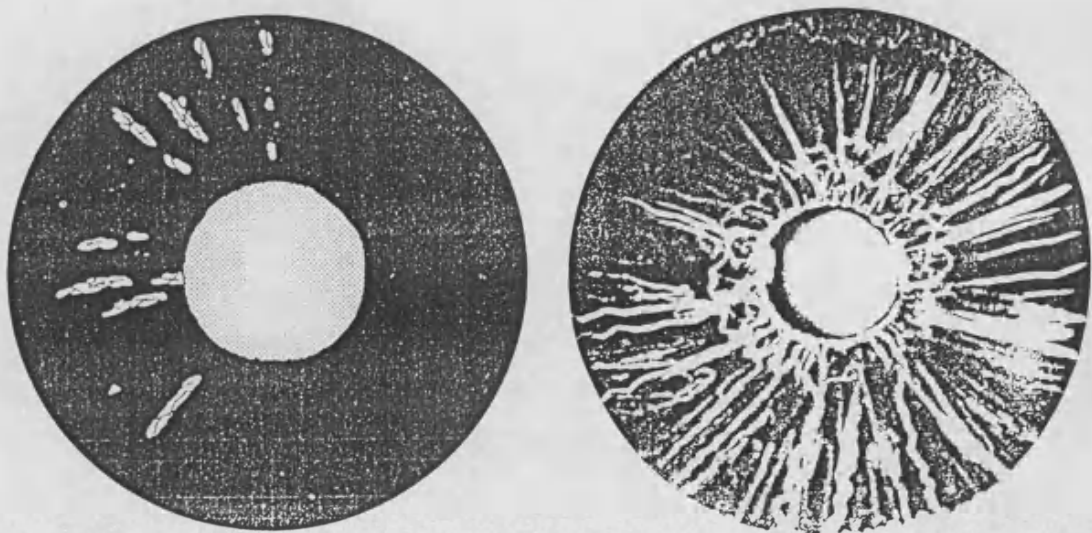


Fig. 5 (Marsh, Easty, and Jones). Left, Drawing of iris pigment epithelial atrophy in same patient as Figure 4 one month later. Right, Angiogram of the same iris. Note the return of some filling in previously avascular areas.

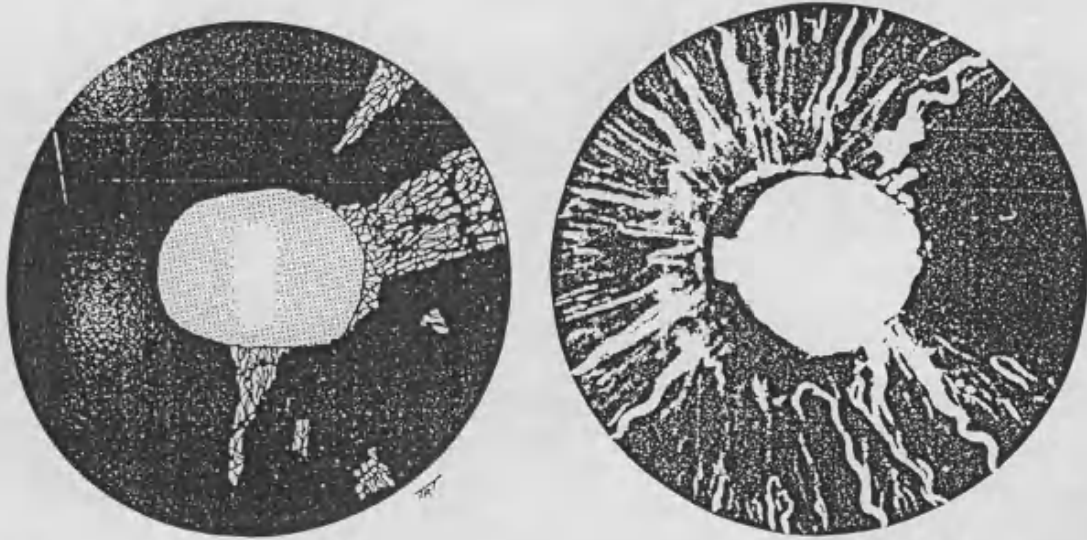


Fig. 6 (Marsh, Easty, and Jones). Left, Drawing of combined iris and sphincter atrophy (photographed by transillumination). Right, Iris angiogram of same iris as Figure 4. Note the lack of vascular filling from 2 to 4 o'clock and the dilatation of neighboring radial vessels.

affected areas, and there was no sign of occluded vessels (Fig. 8, right).

DISCUSSION

Section of iris atrophy together with sphincter atrophy in herpes zoster ophthalmicus follows localized ischemia. Iris angiograms showed that areas of pigment epithelial loss

did not demonstrate vascular filling. In contrast to this, areas of pigment epithelial loss in patients with herpes simplex uveitis demonstrated normal vascular filling. The ischemia in some patients with gross zoster iris atrophy resembled the angiographic appearances following acute glaucoma or anterior segment necrosis. The stromal damage

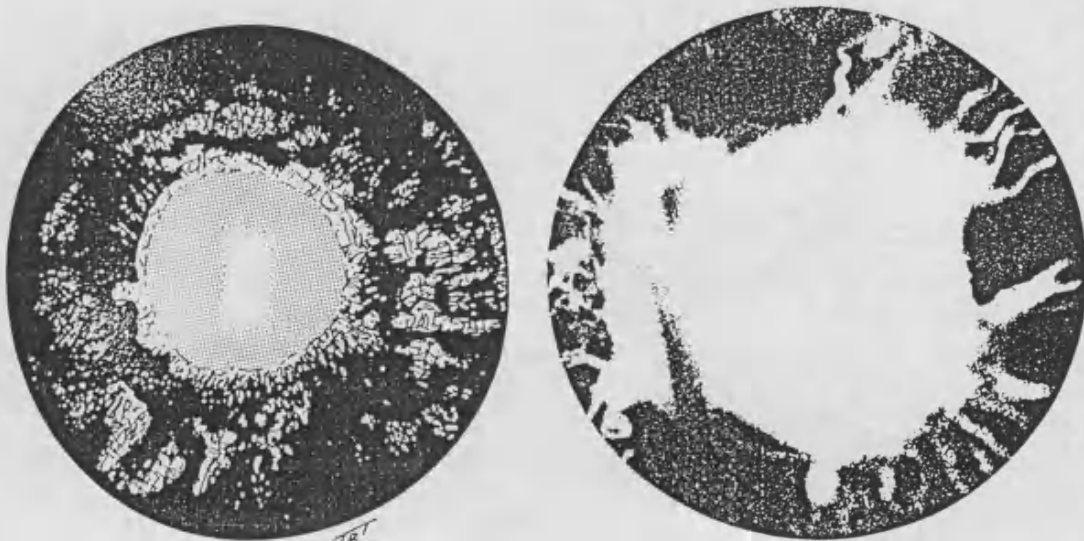


Fig. 7 (Marsh, Easty, and Jones). Left, Drawing of massive iris atrophy (photographed by transillumination). Right, Angiogram of the same iris. Note the loss of vasculature, the dilatation, and leakage of remaining vessels. The pupil is fixed and dilated.

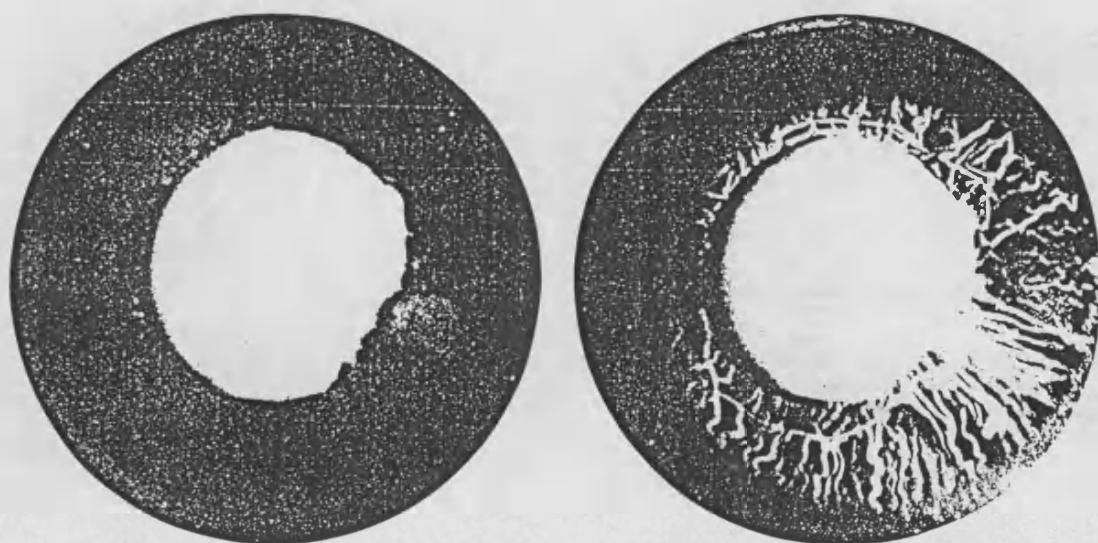


Fig. 8 (Marsh, Easty, and Jones). Left, Iris pigment epithelial atrophy in herpes simplex (photographed by transillumination). Posterior synechiae are present from 4 to 5 o'clock. Right, Angiogram of the same iris. Note the vascular filling occurring in the area of iris epithelial atrophy.

was not as pronounced.

From the pathologic evidence, the ischemic changes in the iris can be attributed to an occlusive vasculitis.¹⁵⁻²⁴ The pathogenesis of this vasculitis may be direct viral invasion of vessels from neighboring nerves or, conversely, immunogenic mechanisms in response to zoster antigens resulting from viral replication, presumably in nerves in the iris. The chronicity and relapsing nature of the vasculitis may be due to recrudescences of viral replication. The favorable response to corticosteroid therapy is in keeping with an allergic response.

The presence of zoster iris atrophy confirms that the patient has at some time suffered from herpes zoster ophthalmicus even though the other signs of the disease may be absent (i.e., skin scarring and history). We have now seen 14 cases of disciform keratitis, originally thought to be due to herpes simplex, in which the zoster type of iris changes were present. In 12 of these cases there were other clinical features of zoster present, thus corroborating the diagnosis. Confirmed diagnosis of herpes zoster ophthalmicus allows aggressive topical corticosteroid therapy with rapid resolution of the

zoster disciform keratitis, without fear of provoking herpes simplex corneal ulceration. Similarly, this appearance seen in an acute iritis suggests a relapsing case of herpes zoster ophthalmicus.

Topical corticosteroid treatment is especially effective in preventing and treating glaucoma secondary to zoster iritis. Although the corticosteroid does not succeed in opening closed vascular channels, it does seem to prevent the development of additional closures.

SUMMARY

We examined 520 cases of herpes zoster ophthalmicus for atrophic changes in the iris. Angiography of sectorial iris changes showed absence of vascular filling in relation to the atrophic areas, suggesting ischemic origin. This type of ischemic iritis has not been seen in other viral diseases such as herpes simplex infection. The pathogenesis of the vasculitis leading to occlusion may be immunogenic. The characteristic appearance of the iris atrophy has proved a useful clinical guide in the differential diagnosis of late keratitis and iritis. Topical corticosteroids limit the progression of the vasculitis and reduce the risk of secondary glaucoma.

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Ophthalmic herpes zoster

R. J. MARSH

ST MARY'S HOSPITAL and MOORFIELDS EYE HOSPITAL, LONDON

OPTHALMIC herpes zoster is a disease varying in severity from devastating, threatening life and sight, to so mild that it may pass unnoticed. The ophthalmic division of the fifth cranial nerve is affected in 7 per cent of herpes zoster patients (Achard, 1924). Ocular involvement complicates approximately 50 per cent of these and very rarely also complicates maxillary herpes zoster (Edgerton, 1945), affecting many of the tissues of the globe and orbit by highly varied types of lesions.

Aetiology

The current theory of aetiology is that after an initial attack of chickenpox, virus is retained in the posterior root ganglion in a latent form that under the influence of unknown trigger factors reactivates, replicates, and migrates centrifugally down the sensory nerves (Garland, 1943; Hope-Simpson, 1965). The virus eventually reaches the skin where it produces the familiar herpes zoster vesicles whence it can be isolated. At this phase of the disease close contacts who have not suffered from chickenpox risk acquiring the infection. However, the converse is not true, as proven by epidemiological studies (Hope-Simpson, 1965). During an attack of herpes zoster there is an anamnestic rise in the level of varicella-neutralizing antibody, demonstrating that the virus has been encountered previously (Miller and Brunell, 1970). Unusually, a second attack of herpes zoster occurs and two areas of the body can be affected simultaneously.

The disease tends to occur in older age-groups, although it can present at any time of life. The trigger factors are largely unknown; trauma has been blamed for many of the attacks (Juel-Jensen and MacCallum, 1972a) but the only convincing evidence has been cases of herpes zoster following retrobulbar or trigeminal ganglion injections.

It is a well established fact that herpes zoster is more frequent and severe in patients with diseases of

the reticuloendothelial system, after deep X-ray therapy, and during immunosuppressive therapy. This type of herpes zoster used to be termed symptomatic. It is interesting that viruses in the same family as varicella-zoster (herpes simplex virus and cytomegalovirus) produce severe infections under the same circumstances. Moreover, segmental herpes zoster with the later appearance of a chickenpox rash elsewhere on the body shows a high incidence of reticuloses (Stevens and Merigan, 1972) and it is well worthwhile thoroughly screening such cases for these diseases.

Onset

There is a prodromal 'flu-like illness, with headache, pyrexia, malaise, depression, and sometimes neck stiffness, which may last a week before the rash appears. This is shortly followed by localized pain over the distribution of the ophthalmic nerve, lymph node swelling in the corresponding drainage areas, and occasionally a red eye.

Rash

This varies enormously in distribution, density, and severity. It commences as macules which rapidly progress to papules, vesicles, and pustules. Crusts start to form from about 6 days onwards. All, or just one, of the cutaneous branches of the ophthalmic nerve are affected. The lesions vary from small, discrete, scattered, and superficial to large, confluent, and deep with haemorrhagic bullae.

Oedema is a variable complication, tending to develop after the first 2 or 3 days. It may be so pronounced as to completely close the lids of the affected eye and spread across the midline to involve the other lids (giving the erroneous impression that the disease is bilateral). It should be stressed that oedema is not due to secondary infection in the majority of cases, since it rapidly resolves without any antibiotic therapy.

The rash can be mimicked by herpes simplex which



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1. *Acta Therapeutica*, 1975, Vol. 1, No. 1.
2. *N.Z. med. J.*, 1970, 72, 183.

can also take on a dermatome distribution (Slavin and Ferguson, 1950). Herpes simplex vesicles are smaller and frequently recurrent; they do not form the large distinct crusts or the typical punched-out scarring of herpes zoster and are not as painful. The two infections may be accurately differentiated by culturing vesicle fluid and assessing serum neutralizing antibodies. Differential diagnosis from impetigo is usually straightforward because of the lack of dermatome distribution.

Ocular involvement

The old rule that cutaneous involvement of the nasociliary nerve heralds ocular complications is a good one but *not* infallible. Similarly, vesicles appearing on the lid margins are invariably associated with ocular involvement, although severe ocular complications may occur with a very mild insignificant rash anywhere on the forehead.

Acute lesions of the globe and orbit develop within 3 weeks of the rash. They frequently take a chronic course, especially if untreated, and may linger for years. Finally, relapsing lesions may develop up to 6 years after the disease onset. The mechanism of ocular involvement is not clearly understood; presumably the virus reaches the eye via the ciliary nerves. The connection between this and subsequent lesions such as perineuritis, perivasculitis (Naumann et al, 1968; Walsh and Hoyt, 1969), and nonspecific chronic inflammatory reaction is a mystery. It is interesting that, at times, lesions of different tissues occur in the same sector of the eye (Redslob, 1923; Bonnet, 1939) confirming the neurological distribution of the disease in the globe.

Acute lesions

Eyelids: Ptosis is common and is usually due to mechanical factors such as inflammation and oedema. Less frequently it is neurological.

Conjunctivae: Mucopurulent conjunctivitis is one of the commonest manifestations of herpes zoster and is always associated with vesicles on the lid margin. It is generally transitory, resolving in a week, and rarely becomes chronic.

Episcleritis and scleritis: These are common complications occurring in approximately 35 per cent of cases. Sectorial or diffuse episcleritis usually appears at the onset of the rash when it is frequently concealed by an overlying conjunctivitis. Less commonly, scleritis appears, usually at the end of the first week; it may be adjacent to the limbus with accompanying corneal stromal infiltrate and swelling, producing sclerokeratitis in 6 per cent of cases (Marsh, 1973). Nodular episcleritis occurs rarely, usually starting in the second week of the disease.

Cornea: Concurrently with acute conjunctivitis, small dendritic figures are often seen on the corneal surface (Fig. 1; Pavan-Langston and McCulley, 1973). These are raised multiple epithelial lesions lying towards the periphery of the cornea, and at

times mucus deposits overlie them. Like the conjunctivitis they are transitory lesions lasting about a week. Less commonly, a punctate epithelial and filamentary keratitis occurs. The commonest corneal lesion is a nummular keratitis seen in 35 per cent of cases (Marsh, 1973). It is characterized by multiple fine granular deposits in the stroma just beneath Bowman's membrane which are surrounded by a halo of stromal haze (Fig. 2). They appear 10 days after onset of the disease and are at first white but later become brown. Sometimes they underlie a preceding epithelial lesion but more often they are seen in close proximity to a thickened corneal nerve (Head and Campbell, 1900). The lesions fluctuate in density and can become chronic.

Disciform keratitis develops in 6 per cent of cases and generally presents 3–4 weeks after the disease onset. It is usually centrally sited but can be eccentric, varying in the degree of stromal oedema and infiltrate. It seems to be based on preceding nummular keratitis; new infiltrate appears in the stroma underlying this and occasionally surrounds it as an immune ring which may be multiple and concentric. Generally, there is associated iritis with fine keratitic precipitates underlying the swollen stroma. Eccentric disciform keratitis often merges into sclerokeratitis.

Total loss of corneal sensation occurs at the onset of the disease in 9 per cent of patients, and 6 per cent develop immediate neuroparalytic keratitis with corneal ulceration.

Iritis: This is another common complication, occurring in about 52 per cent of cases and appearing within 2 weeks of the rash (Marsh et al, 1974). It is characterized by very fine deposits on the corneal endothelium, faint flare, and a small to moderate number of cells. Often there is complicating ocular hypertension and overlying stromal oedema. All these features respond rapidly to topical steroids. In 25 per cent of cases pupillary distortion occurs 4–5 days after the onset of the iritis, and a few days afterwards iris atrophy develops. This is distinguished by sectorial loss of iris pigment epithelium, migration of pigment into the overlying stroma, and occlusive vasculitis (Fig. 3a). The atrophy is readily seen by transpupillary transillumination (Fig. 3b; Abrams, 1964), especially in blue irides, and is distinguished by a rather moth-eaten sectorial distribution. In 12 per cent of cases there is permanent iris sphincter damage.

The glaucoma observed in the acute phase of herpes zoster is due to hypertensive iritis. Very rarely, choroiditis (Meller, 1920), choroidal detachment (Lincoff et al, 1956), and retinal vasculitis (Collier, 1959) have been described.

Optic neuritis is well documented (Edgerton, 1945; Walsh and Hoyt, 1969) and occurs in about one per cent of cases. It is probably ischaemic, is often accompanied by posterior scleritis, and has a poor prognosis for vision.

External ocular muscle palsies are common,

appearing in 31 per cent (Kelly and Dulley, 1976) at the onset of the disease. All cranial nerves are involved, the third most commonly then the fourth and fifth. Rarely, a total third nerve palsy is accompanied by proptosis, scleritis, and iritis which suggests orbital vasculitis (Wyss, 1871; Edgerton, 1945; Siegert, 1964). The majority of palsies recover subjectively within 3 months but an orthoptically detectable lesion remains (Kelly and Dulley, 1976). Very rarely contralateral palsies occur. The aetiology of such lesions is difficult to construe but it is known that the virus can reach motor nuclei (Thomas and Howard, 1972).

Encephalitis develops very rarely, usually in severe cases of herpes zoster with systemic spread of virus and a defective reticuloendothelial system. Another rare cerebral complication is contralateral hemiplegia which occurs at about 7 weeks and commonly recovers well (Laws, 1960; Acers, 1964).

At the onset of the disease, neuralgia is severe and constant in the majority of cases but it tends to remit at the end of the first week. It is localized to the dermatome distribution of the rash.

Chronic lesions

Skin: Varying degrees of scarring develop, ranging from undetectable lesions to extensive areas of deep scarring resembling that seen after third degree burns, and even to cicatrix production. Generally, the typical punched-out geographical scars appear early with differing amounts of pigmentation or depigmentation, loss of hair, and some acne formation. These lesions frequently fade with time.

Eyelids: Chronic ptosis is common and nearly always of mechanical aetiology due to chronic inflammation, oedema, and scarring. Chronic blepharitis secondary to scarring of the lid margin is less commonly seen. This may lead to trichiasis, loss of lashes, abnormal tear film distribution, and occasionally ectropion or entropion. Very rarely, columnar epithelium migrates forwards over the lid margin to replace squamous epithelium.

Conjunctivas: Mucus-producing conjunctivitis is a common chronic lesion. This mucus is abnormal and adversely affects the tear film, making it greasy and unstable. Less often, large lipid-filled granulomas (Fig. 4) appear under the subtarsal conjunctiva and severe submucosal scarring similar to that of old trachoma can develop.

Episcleritis and scleritis: These lesions are often chronic, particularly scleritis and nodular episcleritis which frequently leave patches of scleral atrophy (Fig. 5). Neglected sclerokeratitis runs a very chronic course with progressive deposition of infiltrate, vascularization, and lipid in the cornea. It may remain confined to the periphery of the cornea to form a faceted type of scarring or may migrate across the cornea causing severe scarring and visual embarrassment.

Cornea: Nummular keratitis behaves like the

superficial stromal infiltrates of adenovirus type 8 in that it fluctuates in density and can diminish visual acuity. The peripheral infiltrates may form facets which later become vascularized with lipid deposition.

Disciform keratitis nearly always becomes chronic if untreated, with progressive accumulation of infiltrate in its centre and immune rings. This is followed by lipid deposition and vascularization (Fig. 6) and very dense nebulae can form, often adversely affecting vision.

Neuroparalytic keratitis: Total loss of corneal sensation does not necessarily lead to this type of keratitis. Other factors are required, such as chronic conjunctivitis and lid margin deformities. Chronic corneal epithelial swelling initiates the keratitis and produces punctate epithelial erosions leading to ulceration in the interpalpebral area (Fig. 7) and infiltration of the underlying stroma. If untreated the ulcer tends to deepen and perforate.

Mucous plaque keratitis: A strange form of keratitis develops in 5 per cent of cases of herpes zoster. It commences one week to 3 years after the onset of the rash and most commonly between 3–6 months. It is characterized by transitory epithelial lesions followed by permanent stromal haze formation. The onset is sudden, with ciliary injection and the production of mucous plaque deposits on the surface of a diffusely swollen corneal epithelium. The overlying tear film becomes unstable and rapidly forms dry spots, often in dendriform shapes. The plaques look like fragments of white blotting paper and in the branching form often resemble dendritic ulcers. They stain brilliantly with rose Bengal (Fig. 8) and moderately well with fluorescein and Alcian blue. The plaques can be easily removed from the surface of the cornea without any damage to the underlying epithelium. They vary in size, shape, and number from day to day and are accompanied by diffuse stromal haze in both the superficial and deep layers of the cornea. There is always underlying iritis with formation of small white keratitic precipitates.

The keratitis progresses with loss of corneal sensation and increased stromal haze. After 3–4 months the plaques disappear and the tear film stabilizes, revealing more clearly the large sheets of stromal haze. There is a resulting drop in visual acuity, and some danger of the corneal sensation being lost altogether and of ensuing neuroparalytic keratitis.

It is important to differentiate these plaques from the dendritic ulcers seen in herpes simplex. The features mentioned above greatly facilitate clinical diagnosis, but culturing of the epithelial lesions for virus clearly differentiates herpes simplex from herpes zoster.

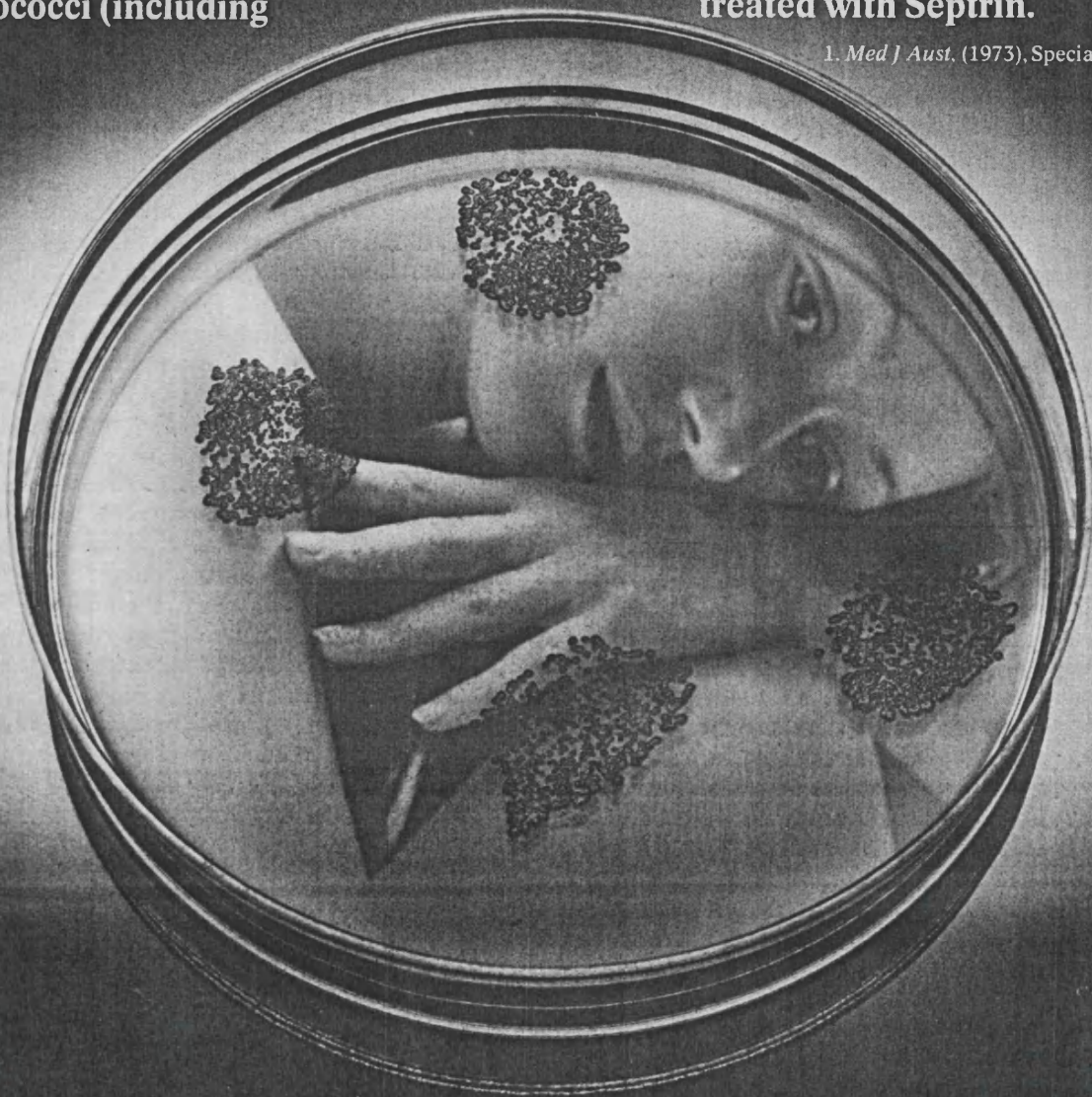
Iritis: This often becomes chronic and if untreated in the acute stages posterior synechiae develop. The iritis may progress in its ischaemic manifestations to massive iris atrophy in 6 per cent of cases (Marsh et al, 1974). It is interesting that this resembles the iris changes sometimes seen after cases of acute closed-

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studies reported from different parts of the world in which over 4,900 strains of *Staphylococcus aureus* were tested showed that 87% were sensitive to cephalosporins.¹ Septrin decisively eradicates staphylococci (including

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1. *Med J Aust.* (1973), Special Suppl, 1, 10



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angle glaucoma or following retinal detachment operations, and may be termed an anterior segment necrosis (Crock, 1967). Posterior subcapsular lens opacities often develop early in this 6 per cent and a sector of subcapsular lens opacity may underlie a sector of iris atrophy.

Glaucoma: Hypertensive iritis may persist with a minimum of flare and cells. Unfortunately, confusion can occur during the management of this condition owing to the development of a steroid glaucoma.

Optic atrophy follows optic neuritis with a profound loss of vision. Permanent external ocular muscle palsies rarely occur and the affected muscle usually lies adjacent to an area of chronic scleritis and iris atrophy.

Neuralgia: Severe chronic neuralgia occurs in approximately 7 per cent of patients. It may take on different forms and can be a chronic constant pain or ache, an intermittent severe stabbing pain closely resembling tic douloureux, or an intermittent very unpleasant paraesthesia (formication or a sensation of crawling under the skin). The pain is often aggravated by touch and heat, and is worse at night. The majority of patients improve slowly over one year; the proportion who do not usually suffer depression and there may be severe exhaustion and even a danger of suicide.

Recurrent disease

Perhaps the strangest aspect of ophthalmic herpes zoster is the recurrent nature of the ocular complications. These can reappear as late as 7 years after the onset of the disease and appear to be unrelated to the severity of the initial illness. They are frequently precipitated by the sudden withdrawal or reduction of topical steroid therapy. Mucus-producing conjunctivitis recurs infrequently, but episcleritis and scleritis do so more often. A particularly severe form of scleritis can cause much resulting scleral atrophy. When nummular or disciform keratitis relapses there is an increase in stromal infiltrate, haze, and thickness. Neuroparalytic keratitis is very prone to recur with repeated disruption of corneal epithelium and with ulcer formation. Mucous plaque keratitis also readily reactivates with consequent formation of plaques, ciliary injection, and iritis. Profuse creamy coloured keratitic precipitates usually accompany relapsing iritis, although hypertensive iritis may show practically no flare, cells, or keratitic precipitates. In this it closely resembles the Posner-Schlossman syndrome and can even mimic chronic open-angle glaucoma.

It should be borne in mind that all these recurrent lesions may be separated by some time from a previous attack of herpes zoster and, indeed, the original attack may have been forgotten or so mild as to have passed unnoticed. It is therefore worthwhile bearing the diagnosis of herpes zoster in mind when any of the lesions described above are seen in a patient for the first time.

Treatment

Ophthalmic herpes zoster offers a great challenge in management. Such is the nature of the complications that effective treatment early in the disease can prevent many disasters at a later stage. Of necessity, treatment must be intensive at first and in severe cases must include a long-term follow-up. The factors in treatment are:

1. Admission
2. Antivirals
3. Anti-inflammatory agents
4. Analgesics
5. Antibiotics
6. Artificial tears
7. Antidepressants.

Admission or, failing this, bed-rest at home is preferable for the first week of the disease. It is vital, at this time, that full analgesia be given. Patients must be screened for reticuloses and their general health checked. They are often distressed and frightened of the disease and must be reassured that the acute stage is short-lived and recovery usually follows with the correct management.

Skin: The main objective of treatment is to achieve healing without the massive crust formation that often gives rise to severe scarring. This may be achieved simply by the use of an antibiotic-steroid combination ointment (for instance Neo-Cort cream (such as Betnesol-N), or spray (for example Terra-Cortril). Careful application three times a day generally leads to resolution of the rash in about 7 days, barring a few crusts. It may be necessary to use hot sterile saline washes to remove much of the debris (especially if prior treatment has been with calamine or starch powder, the use of which is to be strictly deprecated). Ointment softens the large crusts and allows easy separation.

More recently, I have been using the form of ointment recommended by Juel-Jensen (1972b), in which a solution of 40 per cent idoxuridine in dimethyl sulfoxide is used to impregnate a large square of lint which is applied to the lesions on the forehead. A lint dressing is then placed on top and both are held in place by Tubogauze put on the head like a balaclava helmet. The small inaccessible lesions on the side of the nose and at the inner canthus may be covered

- Fig. 1. a Small epithelial dendritic figures b Magnification x 400 of epithelial dendritic figures.
- Fig. 2. Superficial stromal infiltrates (nummular keratitis).
- Fig. 3a. Sector iris atrophy.
- Fig. 3b. Iris angiogram of the patient shown in Fig. 3a. No area of vascular closure, most marked from 7—10 o'clock.
- Fig. 4. Lipid-filled conjunctival granulomas.
- Fig. 5. Scleral atrophy.
- Fig. 6. Lipid keratopathy following chronic disciform keratitis.
- Fig. 7. Neuroparalytic perforated corneal ulcer. Note the secondary cataract.
- Fig. 8. Mucous plaque keratitis stained with rose Bengal. Note the hazy corneal epithelium.

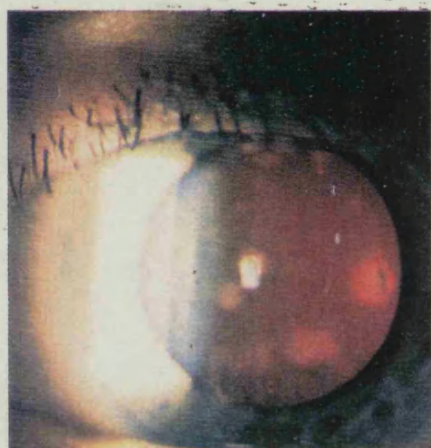
Ophthalmic herpes zoster

R. J. MARSH



1a

1b



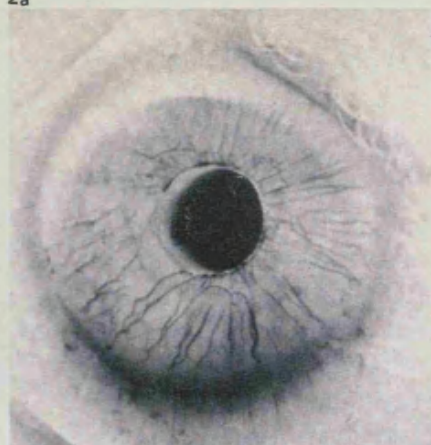
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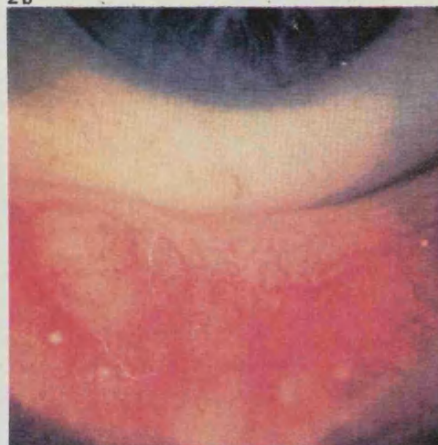
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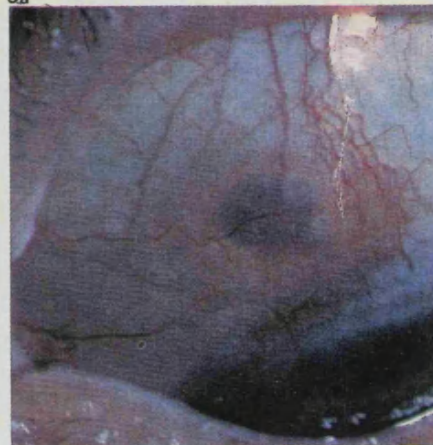
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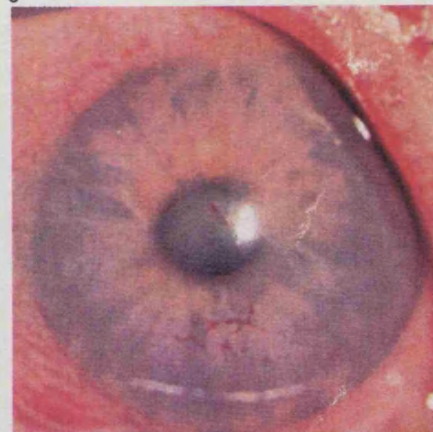
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4



5



impregnated band-aid strips. Dressings are changed once daily for 4 days. Healing is very rapid, crust formation occurring in 4 days, and the treatment seems to prevent the lesions coalescing. Five per cent idoxuridine in dimethyl sulphoxide (Herpid) is available for application by paint brush, but clinical trials have revealed the stronger solution to be more effective (Juel-Jensen, 1972b, c). Unfortunately, the very severe haemorrhagic type of rash seems to respond poorly to any treatment.

Lids: The same treatment as described for the skin may be used, but in view of the ocular toxicity of dimethyl sulphoxide (Noel et al, 1975) it is best kept away from the lid margins. If there is severe scarring of the lids it may be necessary to epilate and electrolyse the trichiasis or to correct lid deformities by plastic surgery. Chronic blepharitis should be treated by the application of antibiotic ointment to the lid margins twice a day.

Neuralgia: Fortunately, acute neuralgia, although severe at first, is short-lived. Full analgesia should be given in the early stages (for instance Panadol, Distalgic, or DF 118) and in very severe cases pethidine may be necessary. Chronic neuralgia and paraesthesia are extremely difficult to treat. The list of remedies recommended in the literature is legion, indicating their overall inefficacy. It is often a good idea to advise a strong analgesic in the evening as the pain is worse at night. It has been suggested that idoxuridine in dimethyl sulphoxide reduces the incidence of post-herpetic neuralgia (Juel-Jensen, 1972a), but in my experience there is little decrease in the severer forms.

Depression: This is fairly common, especially 2 weeks after onset of the disease, and it is often advisable to use antidepressants such as amitryptiline at this time.

Ocular involvement

Unfortunately, topical antivirals such as idoxuridine seem to be ineffective on ocular complications. Anti-inflammatory agents have proved to be the most valuable tool for treatment. I tend to use topical steroids fairly freely in nearly all the complications of herpes zoster, matching the potency and frequency of application with the severity of the lesion. I find dexamethasone alcohol 0.1 per cent particularly effective in scleritis, sclerokeratitis, disciform keratitis, and iritis. Predsol 0.3 per cent is usually effective in treating conjunctivitis, episcleritis, and nummular keratitis. The main principle in their use is to start with frequent application and titrate the dosage thereafter on the degree of activity of the lesion. When using dexamethasone I cautiously reduce it to Betnesol and then Predsol until a low dose of Predsol contains the lesions. An abrupt withdrawal of steroid or too rapid a transfer to a weaker strength frequently precipitates a relapse. Indeed, it may be necessary to prolong the withdrawal period over 2 years.

It is interesting that the nummular keratitis of herpes zoster behaves in a very similar way to the

stromal infiltrates of adenovirus infection when treated with topical steroid. Both fade initially but intensify on the cessation of therapy.

Obviously, routine safeguards must be taken with long-term steroid administration. Intraocular pressures must be frequently checked and patients possessing an unstable corneal epithelium or frank ulceration must be closely observed. Steroids should always be covered with a topical antibiotic. Lastly, the risk of fungal superinfection should always be borne in mind. The other long-term complications of topical steroids are of course ptosis, pupil dilatation, and the formation of lens opacities.

Neuroparalytic keratitis: This must be carefully and frequently observed. The precorneal tear film must be stabilized by the use of artificial tears such as BJ6, hypromellose, or PVP (adapt or adapet). Any co-existing ulcerative blepharitis should be treated with antibiotic ointment. Abnormal plugs of mucus in the tear film may be dispersed by mucolytics such as acetylcysteine. In my own experience severe indolent ulceration of the cornea is best treated by a large lateral half tarsorrhaphy at an early stage — an old but well proven therapy. Recovery after this small operation is remarkable, with stabilization of the tear film and rapid healing of ulceration. A year or two after this procedure it may be possible to open the tarsorrhaphy very slowly. My own experience with soft lenses in this condition has been disappointing.

Mucous plaque keratitis is a difficult problem in management. Topical steroids treat the underlying iritis, mucolytics frequently clear the plaques, and artificial tears stabilize the tear film. The chief problem is in those cases that progress to lose all corneal sensitivity and develop chronic corneal ulceration. Again, tarsorrhaphy is indicated.

Severe cases of corneal scarring (especially lipid keratopathy) occluding the pupillary area should be considered for grafting. Broadly speaking, patients with some remaining corneal sensitivity and a small number of feeder vessels do extremely well. Those with marked vascularization and poor sensation fare less well.

External ocular muscle palsies generally recover subjectively and require no treatment. However, I feel that total third cranial nerve palsies that are accompanied by proptosis, posterior scleritis, and possibly optic neuritis are best treated with systemic steroids in an attempt to prevent ischaemic damage to the optic nerve. The routine use of systemic steroids in cases of ophthalmic herpes zoster is controversial. I think that it is rather hazardous; there are not only the normal complications caused by systemic steroids in old people but also the lowering of patients' immunity, thus risking systemic spread of the virus.

Systemic antivirals: Several antivirals have been suggested for use in herpes zoster. Cytosine arabinoside has been used in several centres (Hall, 1969; Juel-Jensen, 1972c; Pierce and Jenkins, 1973) with favourable results, but a recent double-blind trial

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found the placebo more effective (Stevens et al, 1973). Adenine arabinoside is a more recent discovery, but equivocal results were obtained in a recent blind trial at Moorfields using 10 mg/kg. Nevertheless, higher doses may well prove effective. It is to be hoped that more effective antivirals will soon become available for safe systemic use. However, if viral replication is confined to the onset of the disease and if the later lesions are, as seems likely, due to immunologically mediated reactions not dependent on the presence of live virus, the results will not prove useful unless the drug is administered at the very onset of the disease.

CONCLUSION

The pathogenesis of herpes zoster and even more so its ocular complications are still poorly understood. At the moment our strongest weapons are anti-inflammatory drugs, but these do not act on the source of the disease. It is to be hoped that future research will throw some light on these problems and give us more effective therapy for this extremely distressing condition.

I would like to thank Professor Barrie R. Jones for his continuing encouragement, and Mrs Jane Field for her secretarial assistance.

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INFLUENCE OF ORAL ACYCLOVIR ON OCULAR COMPLICATIONS OF HERPES ZOSTER OPHTHALMICUS

G. W. AYLWARD, C. M. P. CLAOUÉ, R. J. MARSH and N. YASSEEM

London

SUMMARY

The role of oral acyclovir (ACV) in the management of immunocompetent patients with herpes zoster ophthalmicus remains controversial. We have performed a retrospective, comparative, case-control study of cases seen in the Zoster Clinic at Moorfields Eye Hospital over the last 5 years. A standard proforma was used during this period to collect data on the rash, ocular involvement and treatment. There were 419 immunocompetent patients of whom 77 were treated with oral ACV prior to attending the clinic. We compared these with paired controls matched for age, sex and severity of rash. No difference in the rate of ocular complications between treated and untreated patients could be detected. This suggests that oral ACV as currently prescribed has little or no preventive effect on the ocular complications of ophthalmic zoster.

Zoster is due to reactivation from latency of varicella-zoster virus,¹ a member of the Herpesviridae. Primary infection causes systemic disease (varicella), but reactivation causes a disease usually localised to a single dermatome (zoster). The virus which can be isolated from zoster vesicles is identical to that of varicella.²

Herpes zoster ophthalmicus (HZO) is associated with a high rate of ocular involvement, often resulting in serious morbidity.³ Most eye complications arise very shortly after the rash and are assumed to be induced by the presence of replicating varicella-zoster virions in the tissues. The majority of these complications are inflammatory: conjunctivitis, episcleritis, keratitis and uveitis. Conjunctivitis and episcleritis tend to be transitory and self-limiting, but the other inflammatory lesions can become chronic or recurrent, and can result in significant scarring of the corresponding tissue with loss of function. There is no incontrovertible evidence of replicating virus remaining in ocular tissues after the rash, but some have assumed its presence is associated with chronic inflammation. The lack of an animal model for HZO renders an understanding of the underlying pathophysiology difficult.⁴

Correspondence to: Mr G. W. Aylward, Bascom Palmer Eye Institute, PO Box 016880, Miami, FL 33101, USA.

Acyclovir (ACV) inhibits the replication of some members of the Herpesviridae and is active against varicella-zoster virus *in vitro*.^{5,6} The use of systemic ACV reduces the duration and spread of the rash and acute neuralgia in immunosuppressed patients,⁷ but its role in the immunocompetent remains controversial.⁸⁻¹⁰ Two prospective, controlled clinical trials have examined the effect of oral ACV on ocular complications of HZO,¹¹⁻¹³ both of which reported a beneficial effect. We believe, however, that there are serious statistical and methodological flaws in both studies which cast doubt on this conclusion. Cobo *et al.*¹² reported a significant reduction in the rate of corneal complications and anterior uveitis in the ACV-treated group which they attributed to the effect of treatment. This would indeed be a valid conclusion if treated and control groups were similar. However, although randomisation was employed, the treatment and placebo groups were different in an important respect, in that there was a higher incidence of ocular involvement in the placebo group at the start of the study. The authors admit that the difference 'may introduce a bias to more ocular complications in the placebo group'.¹² The reported reduction in keratitis and anterior uveitis was not confirmed by the second study which used a higher dose of ACV. Of seven outcome measures investigated, the authors found a statistically significant difference for only one (the presence of active ocular disease 6 months after rash onset).¹³

In both studies a large number of outcome measures were investigated, which can introduce a subtle form of bias in favour of treatment. In order to claim a treatment effect, only one outcome measure has to be significantly different between the two groups at, say, the $p = 0.05$ level. However, in order to reject a treatment effect, *all* of the outcome measures must be similar in each group. Hence the probability of either study finding no significant difference ($p = 0.05$) if no difference exists, is 0.95^n , where n is the number of outcome measures examined. In the first study¹¹ the number was 18, giving a probability of $0.95^{18} = 0.4$, i.e. a less than evens chance that the study would accept the null hypothesis. This form of bias can be

avoided either by deciding in advance how many outcome measures have to be different in order to claim a treatment effect, or by combining the outcome measures into a single score.

Doubts about the quality of the evidence for a beneficial effect of ACV on ocular complications in HZO prompted us to perform a comparative case-control study on a large number of patients with HZO, specifically to detect an effect of oral ACV on ocular complications.

PATIENTS AND METHODS

A standard proforma has been used in the Zoster Clinic at Moorfields Eye Hospital for the past 5 years to collect data on all new patients referred with a diagnosis of HZO. The information recorded included name, age, sex, severity of skin rash, treatment with oral ACV, and details of ocular involvement. The severity of the skin rash was graded at the first clinic visit on a 3-point scale. The dosage of oral ACV and the interval between the onset of the rash and first dose were recorded. Treatment was defined as 'adequate' if an oral dose of 800 mg, five times a day, was begun within 3 days of onset of the skin rash and taken for 7 days.

The presence or absence of the following ocular complications at the first or subsequent clinic visits was recorded: episcleritis, nodular episcleritis, corneal involvement, anterior uveitis. Corneal complications were subclassified as epithelial disease, stromal keratitis, mucous plaque keratitis, corneal oedema and neurotrophic keratitis. The use of topical steroid and topical ACV were also noted, and whether the patient was still receiving treatment for active ocular disease 6 months following the onset of HZO.

Statistical Methods

The subgroup of immunocompetent patients who had been given oral ACV were identified and control patients were selected from the remainder. Each control was matched for severity of rash, age and sex to one of the treated patients. A full match was achieved for grade of rash and sex, with the match for age being within 1 year for all cases. Where items of data were missing, the matched pair concerned was excluded from the corresponding analysis. The proportions of treated and control patients free of each ocular complication were analysed using techniques for matched pairs with a dichotomous outcome.¹⁴ McNemar's test for significant difference was followed by point and interval estimation of the simple difference between the two outcome proportions. There were four possible outcomes for each matched pair of case and control with respect to any of the outcomes (e.g. presence of keratitis): (a) neither patient had the outcome, (b) the control patient had the outcome but the treated patient did not, (c) the treated patient had the outcome but the control patient did not and (d) both patients had the outcome. These data can be presented as in Table I, where the numbers of matched pairs in each category is represented by *a*, *b*, *c* and *d*. The proportion of control patients free of the outcome (e.g. keratitis) is therefore

$$p_1 = (a + c)/n$$

where *n* is the number of pairs. The proportion of treated patients free of the outcome is

$$p_2 = (a + b)/n$$

The simple difference is $p_2 - p_1$, which has an expected value of zero in the absence of any treatment effect.

In order to combine all the outcome measures into a single variable, a total ocular involvement score (OIS) was constructed as the simple sum of the values for each outcome. A value of 2 was attached to the presence of each measure, with the exception of episcleritis which was assigned a value of 1, reflecting its lesser clinical importance. Hence a patient with episcleritis, stromal keratitis and anterior uveitis would score 5. The distribution of this score was not normal, but the *difference* between the OIS of each member of a matched pair was normally distributed, confirmed using the Shapiro-Francia *W'* test.¹⁵ Statistical analysis of this quantity was therefore carried out using parametric analysis based on the Student *t* distribution.

Separate analyses were carried out on a subgroup of matched pairs in which the treated patient had received 'adequate' treatment.

RESULTS

There were 419 immunocompetent patients referred to the Zoster Clinic with an acute episode of HZO over the 5 year period. The number of immunocompetent patients who had been treated with oral ACV was 77 (18%), of which 42 patients (10%) received 'adequate' treatment. The analyses that follow were therefore carried out on 77 matched pairs of treated and control patients (a total of 154 patients), and 42 pairs of 'adequately' treated patients and control patients (84 patients). The sex distribution was 34 men and 43 women, with an average age at presentation of 63 years (range 33-86 years). The prescribing doctor was the general practitioner in 66 cases (86%), a referring ophthalmologist in 7 cases (9%) and was not recorded in the remaining 4 cases (5%). The distribution of the grade of severity of the rash is shown in Fig. 1.

In the results that follow, a positive difference indicates a higher proportion free of the outcome in the ACV-treated group (i.e. a beneficial effect of ACV). The proportions of patients free of *any* ocular involvement along with the results of statistical analysis are shown in Table II. A small difference of 6.5% is estimated but this is not statistically significant ($p = 0.44$). The proportions free of the various types of ocular involvement are shown in Table III, which also includes the results for the status of treatment at 6 months. There is a suggestion of a beneficial effect of treatment on nodular episcleritis but the statistical significance of this difference is low ($p = 0.07$). The difference in OIS between treated patients and controls and the results of statistical analysis are shown in Table IV. There is a small negative effect of ACV which is not statistically significant ($p = 0.46$).

Table I. 2 × 2 table with letters *a-d* representing the number of matched pairs in each category (see text)

	No acyclovir	
	No keratitis	Keratitis
Acyclovir: No keratitis	<i>a</i>	<i>b</i>
Keratitis	<i>c</i>	<i>d</i>

Table II. Presence or absence of ocular involvement (episcleritis, nodular episcleritis, keratitis, iritis) for all 77 matched pairs of treated and control patients

	No acyclovir	
	No	Yes
Acyclovir: No	0	16
Yes	11	50

Proportion of untreated cases without ocular involvement (p_1): 0.14
 Proportion of treated cases without ocular involvement (p_2): 0.21
 $\chi^2 = 0.59$ ($p = 0.44$)
 Simple difference: 0.065
 95% confidence interval (CI): -0.08 to 0.21.

Table III. Proportions free of particular complications

	p_1	p_2	χ^2	p	$p_2 - p_1$	95% CI
Episcleritis	0.62	0.66	0.098	0.76	0.039	(-0.14 to 0.22)
Nodular episcleritis	0.88	0.97	3.3	0.07	0.091	(-0.004 to 0.19)
Corneal involvement	0.48	0.51	0.028	0.86	0.026	(-0.14 to 0.19)
Anterior uveitis	0.70	0.58	1.6	0.20	-0.12	(-0.29 to 0.054)
On treatment at 6 months	0.45	0.44	0.001	0.97	-0.013	(-0.18 to 0.16)

Table IV. Difference in ocular involvement score (OIS) between treated cases and controls

Mean difference	95% CI	<i>t</i>	<i>p</i>
-0.29	(-1.1 to 0.49)	-0.74	0.46

Table V. Ocular involvement (episcleritis, nodular episcleritis, keratitis, iritis) for 42 matched pairs for which the treated patient received 'adequate' treatment

	No acyclovir	
	No	Yes
Acyclovir: No	0	8
Yes	8	26

Proportion of untreated cases without ocular involvement (p_1): 0.19
 Proportion of treated cases without ocular involvement (p_2): 0.19
 $\chi^2 = 0.063$ ($p = 0.8$)
 Simple difference: 0.00
 95% confidence interval (CI): -0.21 to 0.21

Table VI. Proportions free of particular complications for the 42 matched pairs for which the treated patient received 'adequate' treatment

	p_1	p_2	χ^2	p	$p_2 - p_1$	95% CI
Episcleritis	0.63	0.63	0.056	0.81	0.00	(-0.23 to 0.23)
Nodular episcleritis	0.90	0.95	0.17	0.68	0.048	(-0.09 to 0.18)
Corneal involvement	0.50	0.40	0.45	0.51	-0.095	(-0.33 to 0.13)
Anterior uveitis	0.76	0.50	4.3	0.04	-0.26	(-0.49 to -0.029)
On treatment at 6 months	0.50	0.36	1.2	0.27	-0.14	(-0.37 to 0.085)

Table VII. Difference in ocular involvement score (OIS) between treated cases and controls for 42 matched pairs for which the treated patient received 'adequate' treatment

Mean difference	95% CI	<i>t</i>	<i>p</i>
-0.69	(-1.7 to 0.28)	-1.4	0.15

Table VIII. Difference in ocular involvement score (OIS) between treated cases and controls for various sub-groups of matched pairs

Sub-group	<i>n</i>	Mean difference	95% CI	<i>t</i>	<i>p</i>
Rash grade 1	20	-0.85	(-2.6 to 0.86)	-1.0	0.32
Rash grade 2	43	-0.48	(-1.5 to 0.52)	-0.97	0.34
Rash grade 3	14	1.1	(-1.0 to 3.2)	1.1	0.30
Age up to 60 yr	28	-1.2	(-2.5 to 0.094)	-1.9	0.07
Age 61-75 yr	31	0.84	(-0.32 to 2.0)	1.4	0.16
Age 76 yr and over	18	-0.83	(-2.6 to 0.98)	-0.94	0.36

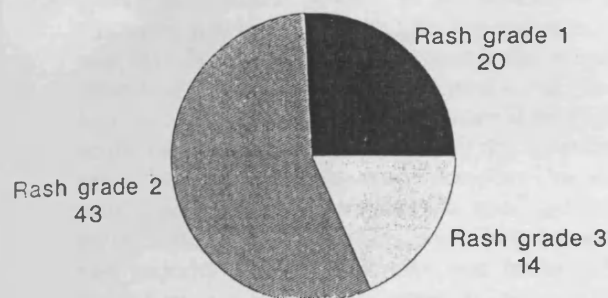


Fig. 1. Pie chart showing the distribution of grade of severity of rash among the 77 patients who received oral acyclovir.

Table X. Patients who received topical steroid

	No acyclovir	
	Yes	No
Acyclovir:		
Yes	38	16
No	17	4

Proportion of untreated cases given topical steroid (p_1): 0.73

Proportion of treated cases given topical steroid (p_2): 0.72

$\chi^2 = 0.00$ ($p = 0.97$)

Simple difference: -0.013

95% confidence interval: -0.17 to 0.15

A subgroup of matched pairs were considered in which the treated cases had 'adequate' treatment (800 mg five times a day for 7 days, begun within 3 days of the onset of the rash). There were 42 such pairs and the results are shown in Tables V, VI and VII. A negative effect of ACV on anterior uveitis is the only statistically significant result ($p_2 - p_1 = -0.26$, $p = 0.04$). Further analysis of the OIS was undertaken within subgroups broken down according to the grade of rash and three age bands (up to 60 years, 61-75 years, over 75 years). The results are shown in Table VIII. No statistically significant difference was found. In order to investigate the effect of the time interval between the onset of rash and the start of treatment, the 'adequately' treated group was divided into subgroups according to the number of days before treatment (Table IX). No significant difference was found.

The possible confounding effect of topical therapy was also examined (Tables X, XI). There was no significant difference in the proportion receiving topical steroid between treated and untreated groups ($p_2 - p_1 = -0.013$, $p = 0.97$). Topical ACV was used more frequently in patients who had been prescribed oral ACV ($p_2 - p_1 = 0.20$, $p = 0.004$).

DISCUSSION

A beneficial effect of oral ACV, as currently prescribed, on the ocular complications of HZO, was not detected by this study. Is it possible that a benefit exists but that the study failed to find it? The 95% confidence interval for the difference in OIS between the treated and untreated cases was -1.1 to 0.49 , and in the subgroup of cases with 'adequate' treatment was -1.4 to 0.28 . Therefore, even if the 'true' value of the difference was at the upper end of

Table IX. Difference in ocular involvement score (OIS) between treated cases and controls for sub-groups of matched pairs of 'adequately' treated patients according to the interval between onset of rash and start of treatment

Interval (days)	n	Mean difference	95% CI	t	p
0	5	-1.8	(-4.8 to 1.1)	-1.2	0.31
1	11	-0.36	(-2.5 to 1.8)	-0.34	0.42
2	12	-0.75	(-2.6 to 1.1)	-0.82	0.32
3	14	-0.50	(-1.9 to 0.90)	-0.72	0.38

Table XI. Patients who received topical acyclovir

	No acyclovir	
	Yes	No
Acyclovir:		
Yes	1	18
No	3	54

Proportion of untreated cases given topical acyclovir (p_1): 0.05

Proportion of treated cases given topical acyclovir (p_2): 0.25

$\chi^2 = 9.33$ ($p = 0.004$)

Simple difference: 0.20

95% confidence interval: 0.075 to 0.32

the first confidence interval, say 0.5, then the clinical effect of ACV would be weak, accounting for an improvement of only half a point in a system by which episcleritis scores 1. Thus, if a clinically significant effect of ACV exists, then it should have been detected by this study.

It is possible that ACV may have a different effect on some ocular complications compared with others. For example, the results suggest a beneficial effect on nodular episcleritis with a 9% difference between the two groups ($p = 0.07$). This result should be interpreted with caution, however, for two reasons. Firstly, the level of statistical significance is not high. Secondly, several 95% confidence intervals have been calculated, and as we described in the introduction, there is therefore a reasonable chance of a spurious result arising (only five 95% confidence intervals have to be calculated to make the chance of a spurious result nearly 1 in 4). This point also applies to the apparent negative effect of oral ACV on anterior uveitis in Table VI.

The use of topical therapy was not controlled for in this study, but has not confounded the results. The proportions of treated and untreated patients receiving topical steroid are virtually identical. This was not the case for topical ACV, which was much more likely to be prescribed in patients given oral ACV. This difference would be expected to enhance a treatment effect rather than mask it, however.

The design of this study was retrospective, but that is not an intrinsic disadvantage. A common problem with a retrospective design is missing data, but this was only a minor problem in the present study because the data were collected in a prospective fashion. An advantage of the retrospective design is the large number of patients available, which, combined with the use of matched pairs,

gives high statistical power. The major disadvantage of this study, however, is the lack of randomisation which may have introduced bias. Is it possible that a beneficial effect of ACV is being obscured because it was prescribed for cases which already had or were more likely to develop ocular complications? We believe that this is unlikely for several reasons. Firstly, the ocular complications of zoster tend to appear several days after the rash¹⁶ and may not present until after ACV has been prescribed. Secondly, the vast majority of ACV treatment was initiated by the general practitioner, who is generally not equipped to diagnose ocular involvement. Thirdly, there is no evidence that any practitioner had a selective prescribing policy towards ophthalmic zoster, such that they prescribed ACV only for those cases with established ocular involvement.

The results of this study cast doubt on claims that oral ACV as currently prescribed reduces the incidence of ocular complications. It is of course possible that earlier administration of ACV may yield benefits. For example, a hastening of rash healing was not seen in patients who began therapy after 48 hours in a large multicentre study of non-ophthalmic zoster.¹⁷ The number of patients in our study treated early is small and the confidence intervals for treatment effect correspondingly large (Table IX). Therefore a treatment benefit from early treatment is compatible with our data. Unfortunately delays in presentation are likely to mean that early treatment is impractical in the majority of patients.

Key words: Acyclovir, Episcleritis, Herpes zoster ophthalmicus, Keratitis, Uveitis.

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Herpetic Corneal Epithelial Disease

Ronald J. Marsh, FRCS; Frederick T. Fraunfelder, MD; James I. McGill, D Phil, FRCS

• The clinical differentiation of corneal epithelial lesions due to herpes simplex or herpes zoster may be confusing. Practical clinical tests, including the use of topical ocular stains, are useful to differentiate corneal epithelial lesions caused by these two viruses. Two distinctive types of zoster corneal epithelial disease may be seen: an early dendritic form, and a delayed form characterized by corneal mucus plaques that may take a dendri-form pattern. These plaques are composed of mucus that is adherent to swollen, degenerating epithelial cells. The clinical differentiation between these two viruses is essential since topically applied corticosteroids are contraindicated in epithelial herpes simplex and often are indicated in the management of epithelial herpes zoster.

(*Arch Ophthalmol* 94:1899-1902, 1976)

It has recently been reported that dendritic ulcers unassociated with herpes simplex infection may occur with ophthalmic zoster.¹⁻³ Previously, when dendritic figures were seen in patients with ophthalmic herpes zoster, a superimposed herpes simplex infection was suspected. Since the epithelial diseases caused by these two viruses may appear similar biomicroscopically, the clinician is in need of

rapid practical differentiating procedures.

This paper describes methods to differentiate the dendritic pattern of herpes zoster from that of herpes simplex and describes two distinctively different patterns of corneal epithelial disease seen in patients with ophthalmic herpes zoster.

SUBJECTS AND METHODS

Patients attending the External Diseases Clinic, Moorfields Eye Hospital (City Road), with either ocular herpes simplex or zoster were examined for corneal epithelial lesions during the course of their disease. Approximately 1,100 new cases of herpes simplex and 283 cases of herpes zoster with ocular involvement were seen between January 1972 and September 1974. If corneal epithelial lesions were present, they were stained with solutions of 1% rose bengal, sodium fluorescein, and, in a few cases, 1% alcian blue. In addition to a complete ocular examination, detailed corneal drawings were made, and in selected cases, and $\times 10$ macrocorneal photographs were taken.⁴ In all cases of ophthalmic zoster, the corneal sensitivities were measured with an esthesiometer (Luneau and Coffignon).

RESULTS

Herpes zoster epithelial lesions fall into two distinct groups based on biomicroscopical appearances, time of onset, duration, and behavior. These lesions are best described as those of acute epithelial dendritic keratitis and delayed corneal mucus plaques. Of the 283 patients with ophthalmic zoster, 37 (13%) had acute epithelial dendritic

keratitis and 20 (7%) had delayed corneal mucus plaques.

Acute Epithelial Keratitis

This is characterized by small, fine, multiple dendritic or stellate lesions. Biomicroscopically, they appear slightly raised but are only intraepithelial (Fig 1, B). They are located generally in the peripheral part of the cornea, and occasionally small plaques of opaque desquamated epithelium overlie them. These epithelial lesions stain moderately well with rose bengal and fluorescein but only minimally with alcian blue. They are self-limiting, appearing within a few days of the onset of the rash, resolving within four to six days, and are always associated with catarrhal conjunctivitis. These dendritic lesions may or may not be followed by an underlying superficial stromal infiltrate.

Corneal Mucus Plaque Keratitis

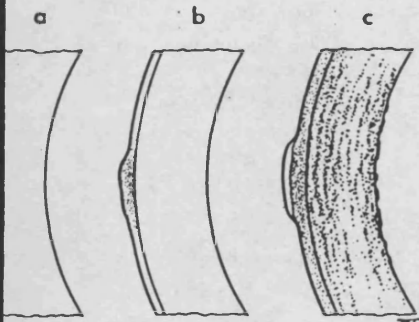
The typical lesion is a whitish-gray plaque with sharp margins that lies on the surface of the epithelium (Fig 1, C) and is linear (Fig 2) or branching (dendri-form) in shape (Fig 3). These plaques are usually multiple, are variable in size and shape, and may appear anywhere on the cornea. Indeed, they may change in configuration, number, and size from day to day. Fluorescein stains these lesions somewhat, while rose bengal stains the whole lesion vividly. Alcian blue stains the lesions and the associated mucus debris in the

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From the External Diseases Clinic, Moorfields Eye Hospital, London. Dr Fraunfelder is currently on sabbatical leave from the University of Arkansas, Little Rock, Ark.
Reprint requests to External Diseases Clinic, Moorfields Eye Hospital, City Road, London, EC1V 2PD, England.

Differences Between Herpes Simplex and Zoster Epithelial Keratitis

Disease	Epithelium	Stroma	Tear Film	Staining Characteristic	Mechanical Debridement	Steroid Response	Cutaneous Manifestation
Herpes simplex	Fine, lacy dendrites with or without terminal end bulbs	Variable involvement	Usually normal	Edges stain with rose bengal; denuded ulcer base stains with fluorescein	Can only be removed with epithelium	May cause enlargement	Current or history of cold sore
Herpes zoster acute	Smaller lesions, often stellate; simple raised contour; usually peripheral	None	Mucoid discharge	Stains sparingly with rose bengal and fluorescein	Can only be removed with epithelium	No apparent effect	Typical zoster rash and vesicles
Delayed (corneal mucus plaques)	Coarse, elevated gray-white plaques	Diffuse haze	Unstable with rapid drying time	Brilliant staining of whole lesion with rose bengal, moderate with alcian blue, and sparingly with fluorescein	Can be removed with minimal damage to underlying epithelium	No apparent effect	Typical zoster scarring on same side

Fig 1 (Marsh, Fraunfelder, McGill).—A, Area of involvement in herpes simplex epithelial disease with epithelial edema and ulceration. B, Area of involvement in herpes zoster epithelial disease with epithelial edema prior to ulceration. C, Herpes zoster keratitis with corneal mucus plaques on surface of elevated edematous epithelium, stroma edema, and keratotic precipitates.



film. Corneal mucus plaques appear as early as seven days and as late as two years after the first signs of acute cutaneous herpes zoster. The major lesions, however, are seen three to four months after the onset of the cutaneous lesions. Corneal mucus plaques are ushered in by ciliary and tarsal conjunctival injection, mild iritis, and profuse deposition of fine keratic precipitates. The whole of the corneal epithelium shows bedewing and swelling with an unstable overlying tear film. Frequently, rapid formation of

infrequently these take a dendriform shape. Interestingly, results of the Schirmer test are usually within normal limits, but corneal sensation is always impaired. Retroillumination and slit-lamp examination show faint superficial stromal haze over most of the cornea. The mucus plaque deposition tends to continue for several months, but eventually the tear film and epithelium stabilize, although relapses can occur at a later date.

Herpes Simplex Corneal Lesions

The dendritic ulcers of herpes simplex have a characteristic arborescent pattern with irregular but sharply defined borders. Terminal end bulbs are present, and the profile on fine slit-lamp examination demonstrates the elevated epithelial borders of the ulcer (Fig 1, A). The margins are serrated, opaque, and may be associated with varying amounts of superficial stromal haze. Occasionally, there are overlying plaques of desquamated epithelium. Fluorescein stains the ulcer crater intensely where there is epithelial loss but does not stain the margin of the ulcer. In contrast, rose bengal brightly stains the damaged cells of the epithelial defect. Alcian blue does not, in general, stain this

Fig 2.—Corneal mucus plaques in patient with herpes zoster keratitis.



Cytology
Ballooned epithelial cells, syncytial multinucleated giant cells, occasional epithelial cells with intranuclear eosinophilic inclusions; mononuclear leukocytes may be present
Ballooned epithelial cells, multinucleated giant cells, margination of chromatin and glassy basophil, intranuclear inclusion bodies
Mucus adherent to ballooned epithelial cells with occasional multinucleated giant cells

Fig 3.—Dendritiform corneal mucus plaque seen in patient with herpes zoster keratitis.



considerable amount of mucus in the tear film. The lesions frequently start as plaques of opaque cells on the epithelial surface. They may appear in a coarse, punctate, stellate, or dendritic pattern, and within a few days the center of the plaque desquamates to form a linear or arborescent ulcer. Mild iritis with keratitic precipitates and a ciliary injection may occur with

symptoms often disproportionate to the clinical findings.

DIFFERENTIATION

Methods to differentiate corneal epithelial herpes simplex from herpes zoster include the following.

Biomicroscopy

While the previously described epithelial lesions caused by herpes simplex and zoster differ as to size, shape, distribution, and appearance (Fig 1), it is difficult with many lesions to make a clinical diagnosis by biomicroscopical examination alone.

Staining Differences

Rose bengal brilliantly stains the entire corneal mucus plaque and the margins of herpes simplex dendritic ulcers, but it stains only moderately well the small acute dendritic zoster lesions. Fluorescein stains the ulcer bed of herpes simplex dendritic ulcers intensely; however, the delayed corneal mucus plaques and the acute dendritic zoster lesions are only moderately well stained. Alcian blue stains the corneal mucus plaques well, but the lesions of the acute herpetic zoster and simplex are stained poorly.

Mechanical Debridement

The dendritic lesions due to herpes simplex and zoster can be removed only if the corneal epithelium is removed. Since the corneal mucus plaques are on the surface of the epithelium, they can be removed easily by gentle scraping with minimal damage to the underlying epithelium.

Response to Corticosteroids

Topical corticosteroids applied to the acute lesions of herpes zoster do not appear to be detrimental, since the lesions disappear within about the same length of time as those that do not receive this medication. Corticosteroids do not have a notable effect on corneal mucus plaques, since they vary in size, number, appearance, and frequency regardless of whether or not this medication is used. Topically applied corticosteroids seem to provide most patients increased ocular comfort and are necessary in some

cases for the accompanying inflammation. Corticosteroids must be used with caution in cases of herpes zoster because of loss of corneal sensation and neurolytic paralytic ulceration because of the danger of perforation. Topically administered corticosteroids can often do appreciably increase the width of individual branches as well as the overall size of dendritic lesions caused by epithelial herpes simplex.

Associated Cutaneous Lesions

Patients with acute herpetic zoster will have the typical acute skin lesions of herpes zoster; the corneal mucus plaques generally appearing later in the course of the disease will be associated with old typical zoster scarring on the same side of the face. Of course, herpes simplex can also be associated with vesicles around the lids and the lips.

Cytology

Scrapings from the margins of herpes simplex and the acute zoster lesions show degenerating cells with large multinucleated cells with molding of nuclei and margination of chromatin. The cytology of the corneal mucus plaques shows no viable cells but strong positive staining for mucus (alcian blue and Southgate mucicarmine). Scrapings of the underlying epithelium demonstrate typical large multinucleated cells similar to those others with swollen and degenerated surrounding epithelium.

Virology

Herpes simplex virus can be readily isolated from the edges of its ulcers. In ten cases, we have failed to isolate varicella zoster virus from the delayed zoster corneal mucus plaques.

COMMENT

There are specific zoster corneal epithelial lesions that can be distinguished from those of herpes simplex. These lesions can be differentiated on the bases of biomicroscopical appearance, staining characteristics, facility of debridement, cytology, and virus isolation techniques. In addition, herpes zoster keratitis can be differentiated into two groups: acute—dendritic lesions, and delayed—corneal

mucus plaques. The acute epithelial lesions were described by Pavan-Langston and McCulley,¹ who obtained varicella zoster virus from three cases within the first four days of the disease. The delayed lesions described here seem to be the same as those reported by Piebenga and Laibson,² who did not succeed in culturing a virus in 11 cases.

Our figure of 13% acute zoster-induced dendritic keratitis is probably low, since most cases were not seen within the first three to four days of onset and the cutaneous involvement was so severe in others that the cornea could not be adequately examined at an early stage in the disease.

The differentiating features of ocular herpes simplex and zoster epithelial disease are reviewed in the Table. An important differentiation is between the herpes simplex and the zoster-induced corneal mucus plaques, both of which may take a dendritic pattern. Prior to reports of pure zoster-induced dendritic epithelial lesions, there have been several cases of herpes simplex epithelial disease reported occurring in eyes of patients who have suffered from zoster (without viral cultures).³⁻⁷ A recent article reported three cases of cutaneous periocular herpes simplex that mimicked herpes zoster.⁸ A review of 500 cases of ocular zoster seen in this institution during a five-year period showed only two cases of clinical ophthalmic zoster with virologically proved herpes simplex keratitis. The two diseases affecting the same eye were separated by eight years in one patient and by two weeks in the other. The herpes simplex keratitis superseded the herpes zoster in both instances. We, therefore, conclude that coincident corneal epithelial infection with the two viruses is an extremely rare event, and that herpetic epithelial keratitis with cutaneous periocular zoster and dendriform lesions on the involved side are caused by zoster until proved otherwise. Rose bengal stain is a particularly important test to differentiate these two conditions, and mechanical debride-

ment is a very helpful additional factor.

The appearance of the corneal mucus plaques associated with zoster keratitis in a dendritic pattern is almost characteristic enough that one can identify them as such even in the absence of a recent history or mild initial attack of zoster. The diagnosis would be reinforced by finding typical zoster skin scarring, iris atrophy,⁹ and scleral atrophy.¹⁰ Corneal mucus plaques, however, are also found in other conditions, especially with keratitis sicca; thus far in sicca they have not been seen in a dendriform pattern.¹¹

The cause of herpes simplex and acute zoster dendrites is clearly due to viral invasion and replication in the corneal epithelial cells.^{1,12} It is interesting that a recent paper describes typical virus-like particles in the epithelium of the cornea in a case of chickenpox with complicating conjunctivitis.¹³ The cause of the corneal mucus plaques is more difficult to explain. As yet, no virus has been grown from these lesions by ourselves or by others,² but cytologic study shows the epithelial cells underlying the plaques to be swollen with large multinucleated cells. In keratitis sicca, these plaques tend to form in areas of extreme drying, such as in corneal areas where the tear film is the most unstable. Possibly if the corneal tear film break-up takes a dendriform shape, these areas may allow mucus plaque to adhere in a dendritic pattern. Fluorescent antibody staining of cells under a probable plaque in one case has shown features suggestive of viral infection.¹⁴ On the other hand, the clinical findings, such as preceding disciform keratitis with immune rings, accompanying iritis, and episcleritis, may suggest that some form of immunologic mechanism is involved.

Perhaps the most important value of differentiating these lesions is in the management of the disease. Topical ocular corticosteroids are contraindicated in epithelial herpes simplex lesions; however, they are of value

with corneal mucus plaque keratitis of zoster, mainly for treating the complicating episcleritis and iritis that so often occur. Corneal mucus plaques have been decreased by topical ocular acetylcysteine application.¹¹ Furthermore, in our experience, idoxuridine preparations, although invaluable in herpes simplex keratitis, adversely affect the already compromised corneal epithelium in the delayed zoster lesions.

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Nonproprietary Names and Trademarks of Drugs

Idoxuridine—*Dendrid, Herplex, Stoxil.*
Acetylcysteine—*Mucomyst, Nac.*

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**CURRENT MANAGEMENT OF OPHTHALMIC
HERPES ZOSTER**

**BY
R. J. MARSH**

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Current management of ophthalmic herpes zoster

R. J. MARSH

Department of Clinical Ophthalmology, Institute of Ophthalmology, Moorfields Eye Hospital, London

Ophthalmic herpes zoster is a disease ranging from trivial to devastating. Poor management can lead to disastrous skin scarring, neuralgia, and loss of the eye. Methodical and regular care can prevent many of the severe complications. In about 50 per cent of cases ocular complications develop (Edgerton, 1945), and these fall into three broad categories: those associated with inflammatory changes; those resulting from nerve damage; and those secondary to tissue scarring.

The inflammatory changes may be expressed directly in the form of nummular, disciform, and mucus-plaque keratitis, or indirectly as a vasculitis in cases of episcleritis/scleritis, iritis, papillitis, and proptosis with total 3rd nerve palsy. The complications associated with nerve damage are neuroparalytic keratitis, ocular muscle palsies, and neuralgia. Chronic tissue scarring, especially of the skin, lids, and conjunctiva, leads to neuralgia, exposure keratitis, trichiasis, lid margin deformities, and tear film problems.

These ocular complications may be considered in three phases: acute, chronic, and relapsing. The acute changes usually occur 2 or 3 days after the onset of the rash, but may rarely precede it. The acute lesions include those associated with inflammatory changes, external ocular muscle palsies, and some cases of neuroparalytic keratitis. The vasculitis tends to become chronic, leading to ischaemic atrophy, and the inflammatory changes in the cornea lead to dense cellular infiltrates and lipid keratopathy. Energetic treatment in the acute stage can prevent many of the later and chronic complications, especially those related to scarring. Ophthalmologists are fortunate in that cases present in the early stages of the disease, most patients being referred to the eye casualty department by the general practitioner at the first sign of the rash.

One of the most important aspects of the ocular complications is their tendency to relapse—even years after the rash. The stimulus to the relapse is often unknown, although the precipitate withdrawal of topical steroids is a potent cause. It should be remembered that some relapses may occur when the original

attack of herpes zoster has either been forgotten or was so mild as to pass unnoticed.

A small proportion of patients with ophthalmic zoster go on to develop a systemic varicella-like rash 1 to 2 weeks after the onset of the disease. A large number of these cases turn out to have reticuloses, other malignant tumours, or defective immunity, or to be receiving immunosuppressive therapy (Stevens and Merigan, 1972). Thus all patients who develop a systemic rash should be carefully examined, preferably by an oncologist. I now screen all new patients by haemoglobin, white blood count, differential count, erythrocyte sedimentation rate, blood film, liver function tests, plasma protein electrophoretic strip, blood sugar and cholesterol, and radiography of the chest. It is also important for ophthalmologists to be aware that in rare cases encephalitis (Appelbaum, Kreps, and Sunshine, 1962) may occur in the acute stage, and that a delayed mild contra-lateral hemiplegia may occur after 7 weeks (Laws, 1960; Acers, 1964).

Management

This may be considered under eight headings.

Admission

Patients with acute ophthalmic herpes zoster are often very ill, aged, and infirm. It is very difficult for them to take their treatment, feed themselves, and rest at home, and by far the best and kindest course is to admit them for one week to hospital. This offers the patient rest in bed, nursing care, proper diet, and correct administration of treatment. The patient should be barrier nursed in a side ward until all the vesicles have dried (usually within 5 days). It is preferable that all nurses in contact with the patient at this stage have had chickenpox, since this can be acquired from patients with herpes zoster by previously uninfected individuals. The converse, however, is not true (Hope-Simpson, 1965).

Analgesia

Pain in this condition is notoriously difficult to treat. It is nearly always severe in the first 2 weeks, but

usually eases at the end of this time. During this acute phase patients should be given sufficient drugs to suppress their pain. There is an old, distinct, and widely held clinical impression that, if pain is adequately treated at the start of the disease, troublesome post-herpetic neuralgia is less common. The correct analgesic has to be found by trial and error—I usually start with Distalgescic, then move to Fortral, DF118, and finally to pethidine (the anti-inflammatory content of these drugs is also useful).

Post-herpetic neuralgia is a poorly understood phenomenon. It can be expressed by varying degrees of paraesthesia, may closely resemble *tic douloureux* (although on the whole it responds very poorly to Tegretol), or can take the form of a constant ache. I find the incidence of severe neuralgia to be about 7 per cent and this can be so bad as to lead to suicide. The mechanism of pain is speculative—sometimes it is associated with severe skin scarring, suggesting fibrotic constriction of nerves (as after burns and amputations), but in other cases there may be minimal scarring. Pain and paraesthesia generally tend to be worse at night and aggravated by heat and wind. It is obviously best to suggest extra analgesia at these times. Unfortunately, the older inhabitants of the United Kingdom, being rather stoical, seem to loathe taking analgesics and much encouragement may be necessary.

Antidepressants

Depression frequently occurs in the acute phase of herpes zoster, especially after the first week, and is also an important component in some cases of post-herpetic neuralgia. It is important to treat this in addition to other complications. I have found amitriptyline particularly useful.

Antibiotics

These are indicated where secondary infection of the skin or eye is threatened. I have found that topical application is usually sufficient for this purpose. At Moorfields Eye Hospital I routinely use an antibiotic/steroid combination ointment such as Neocortef for the skin and lids. This seems to prevent adequately the development of undesirable large crusts and severe secondary infection. It should be emphasized that the acute oedema which occurs shortly after the onset of the rash is not due to bacterial cellulitis and will settle without antibiotics within a few days.

Similarly, in the eye, I use an antibiotic/steroid combination drop (Predsol-N) in the acute stage of the disease when lid vesicles are discharging and forming crusts, and when there is a mucopurulent conjunctivitis.

In the case of later complicating corneal ulceration, usually of neuroparalytic origin, it is vital to use a topical antibiotic to prevent infection until the epithelium has healed.

Lastly, antibiotic ointment (chloramphenicol) should be applied morning and evening to the chronically scarred and inflamed lid margins which occasionally complicate herpes zoster. Left untreated, lid margin scarring becomes a focus for staphylococcal secondary infection and chronic conjunctivitis.

Anti-inflammatory agents

The main drugs in current use in this group are systemic or topical steroids and systemic oxyphenbutazone.

In my opinion steroids are the bulwark of therapy in many of the ocular complications of herpes zoster. Treatment of the skin and lids with a steroid antibiotic combination ointment or cream has already been mentioned. This is applied three times a day and continued until all the crusts have separated (usually within 3 weeks of the onset of the rash). It has proved a safe form of therapy with no evidence of severe topical or systemic toxic effects in over 600 cases.

The main use of steroids is, however, in the eye. It may be used for all inflammatory lesions, and is essential for lesions linked with vasculitis: *i.e.* episcleritis/scleritis, sclerokeratitis, and iritis. At the first evidence of these I usually start dexamethasone alcohol 0.1 per cent drops 4-hrly, with Betnesol ointment at night. My principle is to strike hard and swiftly at the start of vasculitis to cut down the ischaemic and fibrotic scarring which usually develops. Once control is achieved the potency and frequency of administration can be reduced. The iritis of herpes zoster is frequently hypertensive and it is interesting that high intraocular pressures can occur with small amounts of flare, cells, and keratic precipitates. Fortunately, it is very responsive to steroid therapy, control usually being achieved with this drug alone within a few days. This complication usually occurs at the onset of the disease, but it may constitute a late relapsing phenomenon years after the acute attack. I have now seen several cases of unilateral chronic open angle glaucoma that have been referred from the Glaucoma Clinic after the typical iris, scleral, and skin scarring of herpes zoster have been noticed on the appropriate side (Marsh, Easty, and Jones, 1974).

The inflammatory keratitis of herpes zoster responds well to steroid therapy, but does not require such high doses as the above. Disciform keratitis, in particular, responds well and is unlike the keratitis of herpes simplex in that epithelial ulceration does not occur. The nummular keratitis fades on low doses of Predsol drops, but as in adenovirus keratitis the opacities recur if the drug is suddenly withdrawn. Mucus-plaque keratitis is a strange complication of herpes zoster, occurring in 5 per cent of cases at any time from 1 week to 3 years after the rash (Marsh, 1973). Superficially it resembles herpes simplex dendritic ulcers with a stromal keratitis. On closer inspection it proves to consist of dendritiform mucus plaques deposited

on swollen epithelium with underlying mild diffuse stromal keratitis and iritis. The last two are distinctly benefited by topical steroids without adverse effect on the mucus plaques or the formation of ulcers. In contrast, treatment with antivirals and no steroids causes marked deterioration in the keratitis. Therefore it is important to be aware of the differential diagnosis here, and to remember that herpes simplex superinfection of the affected cornea is very unusual (Marsh, Fraunfelder, and McGill, in press).

All these complications have a great propensity to relapse, especially on too rapid withdrawal of steroid therapy. Indeed, some of the worst ocular complications I have seen in cases of herpes zoster have been due to this phenomenon. In this respect the condition resembles many other systemic and ocular diseases requiring steroids, such as rheumatoid arthritis, ulcerative colitis, collagen disease, etc., vernal catarrh, and herpes simplex stromal keratitis. I like to titrate the dose of topical steroids against the degree of disease activity in the eye. This, of necessity, is a slow, cautious process and may extend over a period of years. As well as reducing the frequency of administration of the drug, serial logarithmic dilutions can be made, or a change to another weaker steroid may be made, e.g. from dexamethasone drops to Betnesol drops to Predsol drops. It is interesting that many of the more intelligent patients can titrate their own dose, which may be reduced to as little as Predsol drops 0.03 g/100 ml strength once a day to maintain control.

The important essentials of steroid management are careful follow-up and examination to detect toxic side-effects. In particular, the danger of steroid-induced glaucoma must be remembered and regular measurements of intraocular pressure made. Steroids should be used sparingly in patients with diseased corneal epithelium and not at all when neuroparalytic ulcers are present. The long-term dangers are fungal superinfection and the development of lens opacities (although it is often difficult to know whether to attribute the lens opacities to chronic iritis or to the steroids). Regular slit-lamp examination of the cornea and lens is therefore essential.

Systemic steroids are routinely used in some departments for all cases of ophthalmic herpes zoster (Elliott, 1964; Scheie, 1970), but there has been much controversy over this, especially with the risk of systemic spread of the disease (Rado, Tako, Geder, and Jeney, 1965; Haggerty and Eley, 1956). I use them only in cases of progressive proptosis with total 3rd nerve palsy and at the onset of optic neuritis. These conditions are most probably due to occlusive vasculitis threatening sight and are therefore a logical indication for this means of therapy. I start with 60 mg per day and rapidly reduce to a maintenance dose.

Systemic oxyphenbutazone (Tanderil) is useful in cases of severe scleritis and sclero-keratitis that have not fully responded to the strongest doses of topical

steroids. The dosage is that recommended by Watson, Lobascher, Sabiston, Lewis-Faning, Fowler, and Jones (1966).

Artificial tears and mucolytic agents

A fairly common ocular complication in herpes zoster is loss of corneal sensitivity and damage to the mechanisms producing a stable pre-corneal tear film. This results in toxic changes of the corneal epithelium, rapid formation of dry spots on the cornea, and deposits of abnormal mucus aggregations in the tear film. A combination of artificial tears and mucolytics will help to stabilize the tear film and improve the health of the corneal epithelium. The particular agents to use are largely determined by trial and error—I usually start with hypromellose, and then try BJ₆, PVP at differing concentrations, Adapt and Adapette, and varying concentrations of acetylcysteine.

I have not found the high water content soft contact lens of very much use in this complication, although it has proved useful in two cases of chronic neuroparalytic ulceration not totally controlled by a lateral tarsorrhaphy.

Surgery

The older methods of treatment are often the best, and this certainly applies to the tarsorrhaphy in cases of the neuroparalytic ulcers of herpes zoster. After several years of trying the more progressive treatments I have found an immediate lateral half tarsorrhaphy invaluable at the start of neuroparalytic ulceration. It can be difficult to persuade patients to accept it, but it gives such rapid healing and security, reducing out-patient visits dramatically, that they can usually be won round.

Lid surgery may have to be considered for lid margin deformities such as ectropion and trichiasis.

Grafting

Neglected disciform keratitis and sclero-keratitis frequently give rise to dense scarring and lipid deposits in the central cornea. Rarely a strange, progressive fatty lipid keratopathy may spread across the cornea causing severe visual embarrassment. All of these cases, providing the cornea is not too vascularized, tend to do well with perforating corneal grafts; this may be because of the overall preservation of corneal sensation.

Emergency grafting may have to be done in cases of neuroparalytic ulceration with perforation. The prognosis is not as good in these cases as considerable difficulty may be encountered in establishing a stable corneal epithelium over the graft.

Antivirals

Over the last decade a new group of compounds has appeared for the treatment of viral disease. They

include cytosine arabinoside, adenine arabinoside, trifluorothymidine, and idoxuridine.

Several trials have been carried out using intravenous cytosine arabinoside (Hall, Wilfert, and Jaffe, 1969; Mann, 1971; Juel-Jensen, 1971; Pierce and Jenkins, 1973), but a recent double-blind trial (Stevens, Jordan, Waddell, and Merigan, 1973) showed that patients taking the placebo seemed to do better. A recent blind trial of systemic adenine arabinoside, using intravenous doses of 10 mg/kg daily for 7 days, showed equivocal results (Marsh and others, unpublished).

I have used Dr. Juel-Jensen's technique of treatment with 40 per cent idoxuridine in dimethyl sulphoxide topically for the last 2 years at the Western Ophthalmic Hospital (Juel-Jensen and MacCallum, 1972). While there is undoubted improvement in comfort and the rash in the acute phase, my impression is that, in the late stages, the incidence of post-herpetic neuralgia is not significantly altered. Results of topical treatment of the rash with adenine arabinoside and trifluorothymidine have not been published. In my experience, idoxuridine applied topically to the eye does not significantly affect the course of the lesions. In fact, it seems to have an adverse effect on an already compromised corneal epithelium. However, as ophthalmic herpes zoster and its complications are initiated by a virus, it would seem logical to continue

to seek an effective antiviral agent. For maximum effect this must be given at the onset of the disease when virus replication is occurring, it must reach the site of replication in adequate concentrations, and it must be non-toxic. Lastly, but practically, it must be easy and economical to produce.

Conclusions

Ophthalmic herpes zoster presents many problems of management in both the short and the long term. It is vital to follow the ocular complications regularly and to withdrawn topical steroids slowly and cautiously. It should be remembered that the complications have a tendency to relapse and that when they do so after a long interval may account for apparently new cases of ocular inflammation. Lastly, the pathogenesis of the disease is still very poorly understood. In particular, the way in which the virus infection is linked to many of the ocular lesions is totally unknown. Therefore, treatment in many cases is palliative rather than directed at the cause of the disease. It is to be hoped that further advances in immunology and virology will eventually provide an effective treatment.

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DISCUSSION

In answer to a question by Mr H. Cheng, Mr Marsh said he was not aware of the toxic side-effect mentioned of dissolution of keratin, but was aware of the lens toxicity

side-effect of DMSO. This was dose-related, but the amount used in the 4-day closed dressing technique was well below the danger level.



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External ocular motor palsies in ophthalmic zoster: a review

R. J. MARSH, B. DULLEY, AND V. KELLY

From the External Diseases Clinic, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London

SUMMARY Seventy-seven new patients suffering from ophthalmic zoster and a selected group of 69 old patients were carefully examined with regard to external ocular movements. An incidence of 31% of ocular pareses was found in the new patients, and 58 in all were analysed. We were surprised to find several of these were contralateral and bilateral palsies. 28% of the palsies were asymptomatic, due to diplopia being present only in extremes of gaze and the rapid development of suppression in the affected eye. The theories of aetiology of these pareses are discussed.

Herpes zoster ophthalmicus produces widely varying lesions of the eye in 50% of cases (Edgerton, 1945a) and rarely involves other parts of the central nervous system (Edgerton, 1945b; Walsh and Hoyt, 1969; Thomas and Howard, 1972; Marsh, 1976a). It is thought to arise by reactivation of varicella virus lying latent in the trigeminal ganglion after a prior attack of chicken pox (Garland, 1943; Hope-Simpson, 1965), the virus replicating and migrating peripherally to skin, orbit, and centrally to the brain stem (Godfredson, 1948; Esiri and Tomlinson, 1972).

The cranial involvement takes many forms. A meningoencephalitis may develop (Schiff and Brain, 1930; Krumholz and Luihan, 1945; Worster-Drought and Sargent, 1949; Appelbaum *et al.*, 1962; Rose *et al.*, 1964; Norris *et al.*, 1970). Contralateral hemiplegia occurs rarely, either in an isolated form (Baudouin and Lantvejoul, 1919; Rollett and Colrat, 1926; Biggart and Fisher, 1938; Hughes, 1951; Cope and Jones, 1954; Minton, 1956; Laws, 1960; Acers, 1964), or accompanied by hemianopia (Franceschetti *et al.*, 1955), aphasia and agraphia (Gordon and Tucker, 1945; Leonardi, 1949; Anastostopoulos *et al.*, 1958). Other cranial nerves may be implicated simultaneously. Optic neuritis has been well described (Duke-Elder, 1940; Edgerton, 1945c; Pemberton, 1964; Harrison, 1965; Ramsell, 1967). The VIIth nerve is occasionally involved (Hunt, 1909; Edgerton, 1945d), and a contralateral VIIth nerve paresis has been described in 1 case (Norris *et al.*, 1970). Third, IVth, and VIth nerve palsies occur more frequently (Edgerton, 1945e;

Goldsmith, 1968), the IIIrd being the commonest (Kelly and Dulley, 1975). All 3 may be involved together as a total ophthalmoplegia and are usually accompanied by proptosis (Carmody, 1937; Edgerton, 1945f; Lister, 1948; Pincus, 1949; Von Siegert, 1964). Many series have been published giving the incidence of extraocular muscle palsies as 5% (Hybord, 1872; Flament and Bronner, 1974), 7% (Desirat, 1903; Worster-Drought, 1923), 10% (Nover, 1970), 12% (Rebattu *et al.*, 1933), 13% (Edgerton, 1945g), and 14% (Hunt, 1909).

In this paper we present our own series based on a large number of patients.

Patients

The patients included in this study were drawn from those attending the zoster division of the External Diseases Clinic at Moorfields Eye Hospital, City Road, London, over a 4-year period. All were carefully examined with special reference to severity of rash, degree of neuralgia, the presence of nasociliary or lid margin involvement, episcleritis/scleritis, keratitis, iritis, and iris atrophy, and any complaints of diplopia were noted. A special note was added on the sectoral distribution of the lesions. Corneal sensation was measured centrally and in the 4 outer quadrants with the aesthesiometer of Cochet and Bonnet. Special investigations included haemoglobin concentration, ESR, differential white count, blood film, plasma protein electrophoretic strip, blood sugar, liver function tests and chest x-ray.

Two of the authors examined in detail the ocular movements of all new patients passing through the clinic in an 8-month period (77 patients) and a

Address for reprints: R. J. Marsh, FRCS, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD

a) Ipsilateral Cases (34)

b) Contralateral Cases (9)

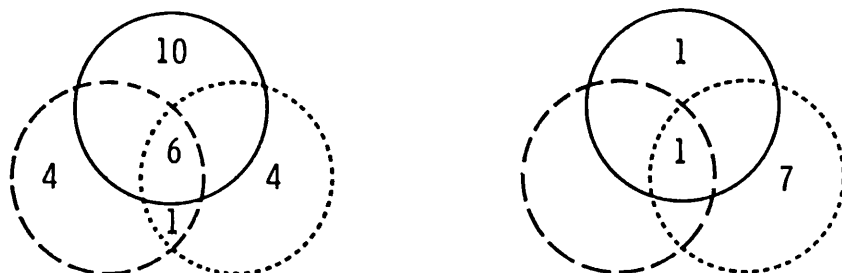


Fig. 1 Distribution of nerve involvement in external ocular palsies

Key: ——— IIIrd nerve; - - - - IVth nerve; - - - - - VIth nerve

selected group of old patients attending for follow-up (69 patients), many of whom had been previously diagnosed as having ocular palsies due to zoster. Tests were carried out at each attendance regardless of subjective symptoms and included cover test, ocular movements, convergence, assessment of binocular function, and Lees screen. A note was also made of the position of the upper lid margin.

Results

Twenty-two cases of paresis were found in the 77 new patients examined, giving an incidence of 29%. A total of 58 cases of external ocular muscle paresis were discovered among the new and old patients. Forty-two of them complained of diplopia, 32 constantly. Sixteen of the patients were asymptomatic, although 8 admitted to diplopia on testing in extremes of gaze. Careful analysis of the 58 pareses showed they tended to fall into 5 categories (Table 1). The different cranial nerves involved in the ipsilateral and contralateral groups are analysed in the Venn diagram (Fig. 1). The third category revealed slow recovery of the original ipsilateral paresis, and always a contralateral IIIrd nerve palsy superseded, although the same branch was not necessarily affected on each side (Table 2). A small percentage of cases had the same muscle paresis on each side from the beginning, but other underactions were present, usually on the side affected by the rash. Complete ophthalmoplegia was accompanied by proptosis in 3 of the 4 cases seen, and 1 of these in fact had bilateral ophthalmoplegia and proptosis.

Fig. 2 shows the age distribution of the patients

with palsies, and it should be noted that the youngest was 46.

All the pareses were detected within the first week of the rash, although it was often difficult to examine

Table 2 Ipsilateral palsies becoming contralateral

Cases	Ipsilateral	→	Contralateral
1 } 2 }	III	→	III
3	VI	→	III and IV
4 } 5 }	III and VI	→	III and VI
6	III, VI, and IV	→	III and VI

Table 1 Laterality of external ocular palsy

	Ipsilateral	Contralateral	Ipsilateral becoming contralateral	Bilateral	Complete ophthalmoplegia
No. of cases	34	9	6	5	4

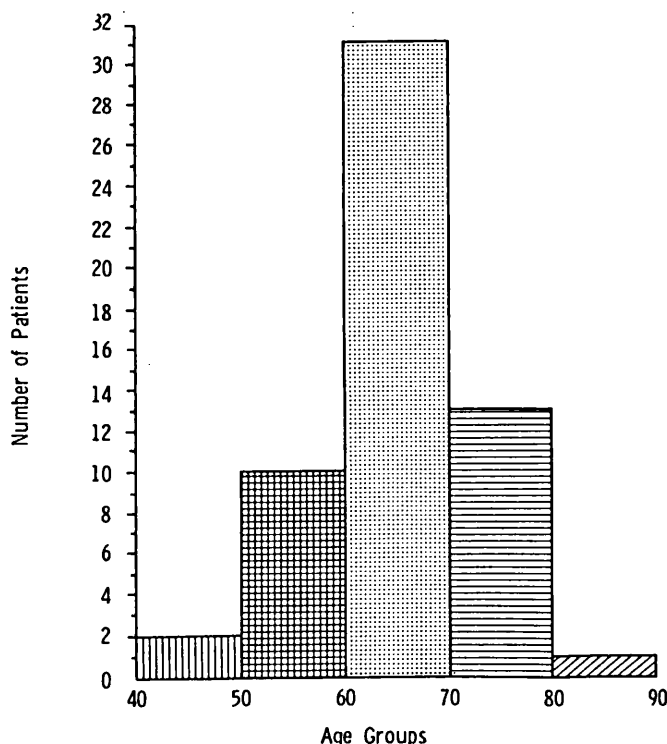


Fig. 2 Histogram of age distribution in zoster

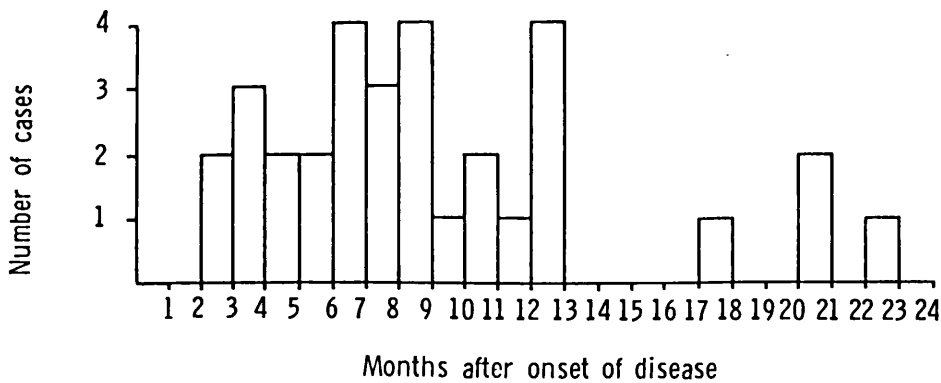


Fig. 3 Histogram of duration of diplopia in ophthalmic zoster

eye movements at this stage owing to the lid swelling and malaise of many of the patients.

Fig. 3 shows the duration of symptoms, and it is significant that there were only 3 cases lasting for more than 18 months. However, an orthoptic defect could always be found in all patients despite the excellent subjective recovery.

The incidence of other ocular complications of zoster in the ocular motor palsy group was compared with those occurring in a comparison group of 46 patients seen at the same time with no ocular motor defect. The results and statistical analyses are depicted in Table 3. There was no clear relationship between any of the sectoral lesions and a particular external ocular muscle underaction. Neither was there any significant correlation with the results of the special investigations.

Three patients had ipsilateral VIIth nerve paralysis without auricular involvement. A further 3 developed contralateral hemiplegia within 1 month of the onset of zoster, and a fourth developed an ipsilateral hemiplegia 2 years after the rash.

Table 3 The association of external ocular palsies with other complications of ophthalmic zoster

Complications of ophthalmic zoster	χ^2	Probability	Remarks
Severity of zoster	12.6	P < 0.001	Very highly significant
Neuralgia	5.9	0.05 > P > 0.01	Highly significant
Iritis	12.6	P < 0.001	Very highly significant
Iris atrophy	10.2	0.01 > P > 0.001	Highly significant
Sphincter damage	1.8	0.2 > P > 0.1	Non-significant
Corneal reflex	0.82	0.5 > P > 0.3	Non-significant
Corneal involvement	2.1	0.2 > P > 0.1	Non-significant
Episcleritis	0.2	0.7 > P > 0.5	Non-significant
Lid involvement	0.91	0.5 > P > 0.3	Non-significant

Discussion

We found external ocular motor palsies in ophthalmic zoster to be more common than previously indicated. This was probably related to the detailed examination of eye movements in all patients. 28% were asymptomatic owing to the diplopia being present only in extremes of gaze, poor sight in the affected eye, or to the development of suppression at a late age. Recovery was excellent despite the fact that an objective defect could always be found on orthoptic examination. The presence of a squint was significantly associated with the severity of the rash and the later occurrence of severe neuralgia, iritis, and iris atrophy, whereas episcleritis, and corneal and lid involvement were of no greater frequency. No case was seen under the age of 40. Surprisingly we found some of the palsies to be bilateral and on the side opposite to the skin lesions.

PATHOGENESIS

To try to understand the cause of bilaterality of some of the palsies and their relationship to other complications of zoster it is necessary to consider the pathogenesis of the lesions.

Three pathogenic mechanisms should be considered for mediating neural damage in zoster. The first is a direct cytopathic effect from the virus itself on the surrounding neural tissue (Cope and Jones, 1954). The second is an allergic response of the central nervous system to the virus, which is not primarily vascular (Krumholz and Luihan, 1945; Appelbaum *et al.*, 1962; Rose *et al.*, 1964). The third attributes it to an occlusive vasculitis induced by the virus (Gordon and Tucker, 1945; Feyrter, 1954; Anastostopoulos *et al.*, 1958; Wray, 1972). A fourth theory (for which there is little evidence) suggests the varicella/zoster virus activates another latent neuropathic virus within the brain (Appelbaum *et al.*, 1962).

Virus may reach the brain in several ways and there cause direct cytopathic or allergic damage to

the nervous tissue. The first is a retrograde spread of virus from the trigeminal ganglion to the Vth nerve nucleus. Here it reaches other cranial nerve nuclei, either by axonal spread along established interconnections (Biggart and Fisher, 1938; Godfredson, 1948; Goodbody, 1953), or by random spread (Cope and Jones, 1954; Acers, 1964). The former pathway could be along the proprioceptive neurones of the oculomotor muscles in the Vth nerve (Denny-Brown *et al.*, 1944). Alternatively, virus may reach the brain by means of a basal meningoencephalitis, which is well described in the literature (Schiff and Brain, 1930; Wynne Parry and Laszlo, 1943; Gordon and Tucker, 1945; Godfredson, 1948; Hughes, 1951; Norris *et al.*, 1970). The area chiefly involved is thought to be the pontine region (Worster-Drought, 1923). Many features can be attributed to this: headache, general malaise, pyrexia, bilaterality of lesions, multiple cranial nerve palsies, hemiplegia, CSF findings, and the rare cases of cranial nerve lesions secondary to a remote primary zoster lesion (Thomas and Howard, 1972; Keane, 1975). Against this theory is the delayed occurrence of many of the cranial nerve lesions, the lack of symptoms and signs of encephalitis in many of the patients, and the rarity of bilateral lesions other than oculomotor palsies. Thirdly, a separate cranial motor neuritis may occur simultaneously with the trigeminal lesion, presumably also owing to the presence of latent virus activated by the same unknown stimuli. This could be a satisfactory answer for contralateral palsies and the occurrence of lesions at a different level from the primary rash (Denny-Brown *et al.*, 1944; Keane, 1975). However, it is somewhat unsatisfactory to postulate 2 distinct lesions and could not adequately explain the association of squints with other ocular complications of zoster.

The last pathogenic mechanism to be considered is that of occlusive vasculitis. Various sites have been proposed. The earliest suggestion was that of the muscle cone and orbit with accompanying myositis, perineuritis, and thrombosis (Wyss, 1871; Abadie, 1898; Aubineau, 1914-15; Kreibig, 1938; Von Siebert, 1964). While this would be in keeping with the picture seen in total ophthalmoplegia with proptosis, iritis, and iris atrophy, it does not explain the isolated and contralateral ocular palsies we have seen or the rarer cases of contralateral hemiplegia.

The second site to be described was the cavernous sinus and orbit apex with involvement of the adjacent IIIrd, IVth, and VIth nerves (Rebattu *et al.*, 1933; Edgerton, 1945g; Franceschetti *et al.*, 1955; Walsh and Hoyt, 1969; Scheie, 1970). The difficulty here is to account for hemiplegias and the bilaterality of lesions, although it is true that the cavernous

sinuses of both sides intercommunicate freely. The origins of the middle cerebral and ophthalmic arteries are here, and an ascending vasculitis may spread along these, with accompanying thrombosis (Gordon and Tucker, 1945; Anastostopoulos *et al.*, 1958). This may be mediated by a granulomatous angiitis induced by the varicella/zoster virus, involving the carotid artery, ipsilateral to the involved eye and segmental (Rosenblum and Hadfield, 1972; Victor and Green, 1976). In favour of this theory is the delayed onset of contralateral hemiplegias, hemianopias, and aphasias secondary to damage in the region of the internal capsule, and the occurrence of ischaemic optic neuritis and iritis. But it is a rather unsatisfactory mechanism for evoking contralateral ocular palsies.

A third site of vasculitis in the brain stem has been described pathologically by Feyrter (1954). This would, of course, account for ipsilateral palsies, contralateral hemiplegias (from involvement of the corticospinal tract), and lesions of adjacent cranial nerve nuclei. A spillover of the vasculitis just the other side of the midline could give rise to the contralateral ocular palsies.

It is possible, of course, that the palsies are of a mixed aetiology and that all the mechanisms and sites mentioned are involved.

TREATMENT

In view of the satisfactory recovery without treatment in most cases the question arises, Is any necessary? The minority that suffer very troublesome diplopia may need temporary occlusions.

An overall therapeutic solution to zoster must include an effective, non-toxic, systemic antiviral agent which crosses the blood brain barrier. If given at the very onset of the disease it would prevent both the direct and allergic cytopathic effect of the virus on neural tissue and prevent the initiation of a secondary vasculitis by destroying the virus at an early stage. However, a problem will still exist if cases present later on when these changes have been initiated, especially the vasculitis. It would seem logical to use systemic steroid in cases of occlusive vasculitis, and it is almost certain that total ophthalmoplegia with proptosis and ischaemic papillitis comes into this category (Marsh, 1976b).

It is quite clear that much work needs to be done on the pathogenesis of zoster and its complications. The disease is still a great mystery and despite its clearly proved association with varicella virus the theory of latency is not proved. The connections between the virus and lesions seen are also not understood. Neither is it known whether continuing presence of virus is necessary for the production of chronic lesions. There are many difficulties in

rifying these issues. No animal model exists for zoster, and there is a great problem in obtaining post-mortem information on well-documented patients with zoster, especially in processing material for immediate histological, virological, and immunological checking. It is to be hoped that advances in these techniques will provide the therapist with the information he needs for the effective handling of this disabling disease.

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Cine photography of anterior segment fluorescein angiography of iris tumours

S. M. FORD AND R. J. MARSH

A description is given of the apparatus and technique for carrying out cine photography of anterior segment fluorescein angiography with special emphasis on its application in the recording and diagnosis of iris tumours.

History

Anterior segment angiography was introduced 22 years ago on the fundus camera (Jenson and Lundback, 1968) and 21 years ago on the slit-lamp camera (Brun-Jenson, 1969; Mitsui *et al.*, 1969). It was found to provide useful information on conjunctival and corneal lesions, especially in lipid keratopathy (Bron and Easty, 1970). Abnormal vascularity of the iris is particularly well demonstrated in anterior segment ischaemia (Chignell and Easty, 1971; Marsh *et al.*, 1974), in glaucoma (Vannas, 1969), in diabetes (Cobb, 1968; Jenson and Lundback, 1968) and after central retinal vein and artery occlusions (Raitta and Vannas, 1969; Maptson, 1970; Kottow, 1976; Laatikainen and Blach, 1977).

Technique

One of the major defects which soon became apparent in anterior segment angiography was that standard machines do not give a fast enough sequence of photographs during the early phase of fluorescein filling. This is important because in diseased states of the anterior segment significant changes in the vascular pattern and permeability occur within the first 5 s of the fluorescein appearing in the eye. In our experience with the Carl Zeiss

photo-slit lamp, at best we could obtain six consecutive exposures at 1.2 s intervals.

We therefore set out to develop a cine technique so that these very early stages of vascular fluorescein filling could be analysed (Marsh and Ford, 1978). We decided at the same time that we should take standard 35 mm photographs at 1.5 s intervals. The basic unit was a Carl Zeiss photo-slit lamp. The flash was driven by the Siemens power pack which was shared with a Zeiss fundus camera. The foot pedal and motor drive were also shared. A special beam splitter 70/30 (301591) was placed in the optical pathway. A 220 mm photographic adaptor (3015129903) with a motorized Nikon camera back-attached to it was fitted on one limb. A cone containing a Spectrotech SB5 barrier filter was mounted in the camera. The diaphragm setting on the photographic adaptor was $f/14$. On the other limb of the beam splitter we connected the 74 mm cine adaptor (301 586), together with the intermediate piece with C-thread (301590), containing a Spectrotech SE5 barrier filter in its upper aperture. A Beaulieu R16 cine camera was fitted to the C-thread and correctly orientated (Figure 1). This was driven by a mains unit and was fired by manual control. The aperture on the camera support was set at $f/4$ and the cine camera set at 12 frames s^{-1} . We found that with this combination the whole of the iris could be encompassed in one frame of the cine film. A Kodak no. 15 gelatin filter was cut out and fitted into one of the eye pieces so that the fluorescence could be directly observed.

The sources of illumination for the still photography were two-fold. The slit-beam aperture was fully opened

and set at $f/9$ and covered by a Spectrotech exciter filter, SE4 of 7 mm diameter. In front of it was opposed a -4.0 sphere lens of the same diameter. This was effective in increasing the field of illumination to encompass the whole iris. An additional exciter filter was mounted in front of the background illuminator. The lighting for the cine camera was provided by the Zeiss fluorescein iris illuminator (308164) with the halogen lamp unit (308166) driven by an accessory power source, 120-VA power supply unit (309608) fitted on the central spindle of the photo-slit lamp, and a Spectrotech exciter filter SE4 was fitted in the appropriate holder (Figure 2). The magnification was set at $\times 16$. After all settings had been carefully checked we injected 5 ml of 20 per cent fluorescein into an antecubital vein, turned up the halogen light source to maximum and

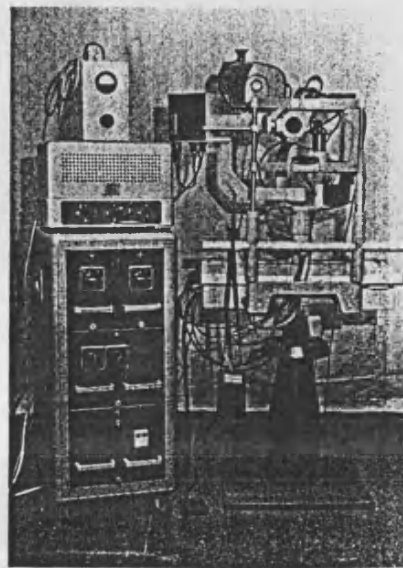


Figure 1. View of the equipment used.

Miss S. M. Ford, ARPS, AIMI, is Chief Medical Photographer and Mr R. J. Marsh, FRCS, is a Consultant Ophthalmic Surgeon at the Western Ophthalmic Hospital, Marylebone Road, London NW1 5YE, UK.

This paper was presented at the 1989 BOPA meeting in Birmingham, UK.

after 6 s we started the cine camera. The foot pedal was depressed and the flash fired when the fluorescein was first seen entering the anterior segment. The film used in the Nikon camera was 35 mm Ilford HP5 and that in the cine camera was 16 mm Kodak Eastman 4-X negative film

7224. The HP5 film was processed in Kodak D76 developer, undiluted, in a deep tank for 14 min at 27°C (80°F). The 4-X negative film was processed in a methol-hydroquinone developer of D76 standard and force developed by one stop. It was projected at 12 frames s⁻¹ and observed in greater detail at 2 frames s⁻¹ on a Specto 16 mm motion analysis projector (Figure 3).

Clinical applications

The features demonstrated by anterior segment angiography are the vascular pattern and any abnormalities in the filling sequence, and the presence of vessels (Figures 4 and 5, respectively). It is possible to identify the veins, arteries and capillaries (Figure 6). In addition you can see if there is any dilation or closure of vessels, if the

vessels are permeable, or if there is any masking of vessels (Figures 7, 8 and 13, respectively) (Marsh and Ford, 1980).

The practical uses of anterior segment angiography are in assessing the vasculature of conjunctival tumours and also abnormalities in the filling pattern and abnormal dilation of vessels in the sclera and episclera (Figures 9 and 10, respectively) (Meyer and Watson, 1987; Meyer, 1989). The degree of corneal vascularization can be assessed as in lipid keratopathy (Figure 11). It has found an established place in assessing the blood supply of the anterior segment before complicated squint surgery, in particular, involving vertical and multiple muscle surgery and in patients with exophthalmos (Figure 12) (Fells and Marsh, 1978). It is used in assessing either obvious or suspected lesions of the iris as with iris tumours (Figures 13–18).

In evaluating iris tumours, fluorescein angiography allows assessment of the degree of the iris tumour vasculature, as well as secondary effects of tumour growth on surrounding tissue. (Dart *et al.*, 1988). Masking of fluorescence by the lesion is considered as indicative of a benign lesion if there is no vascular circulation within the tumour (Figure 13). Sclerotic iris melanomas are characterized by distortion of the pupil, combined with masking of fluorescence and abnormal vascularization (Figure 14). Figure 15 shows a large iris tumour slightly distorting the pupil, there is a vascular circulation within the tumour showing through the masking. Figure 16a shows a highly vascularized tumour which is again distorting the pupil and leaking relatively early on; 2 years later there is no increase in size (Figure 16b). Figure 17a shows a well vascularized tumour which fills and leaks very early on and there is no distortion of the pupil. Three years later the tumour has increased in size and distorted the pupil; there are large feeder vessels on each side of the tumour (Figure 17b). This proved to be a malignant melanoma and was excised. Ciliary body melanomas are characterized by very straight dilated vessels extending from the angle to the centre of the iris (Figure 18).

The limitations of anterior segment angiography are: (1) patients with brown irides, where the vascular pattern is masked by the iris pigment; (2) corneal opacities; and (3) if the

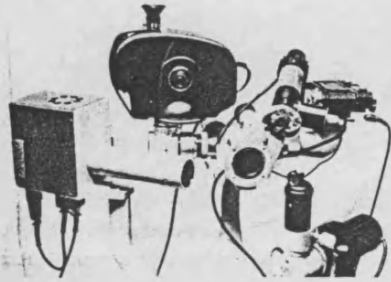


Figure 2. Close up view of the lighting equipment used.



Figure 3. Cine iris angiogram showing early filling of a neoplasm by abnormal tumour vessels. (Continuous sequence running from top left and finishing at bottom right)

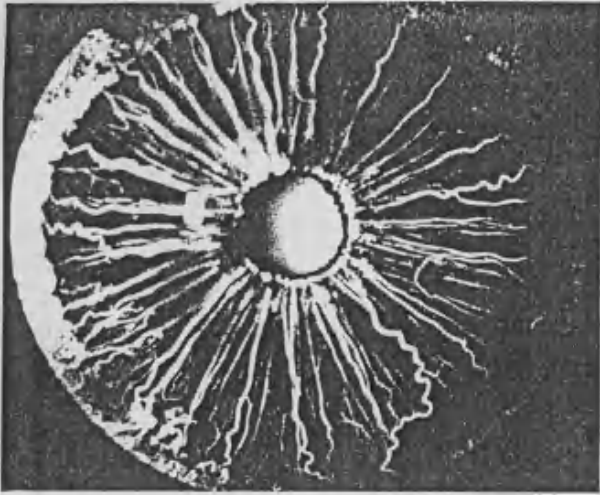


Figure 4. Iris angiogram showing normal vascular pattern.

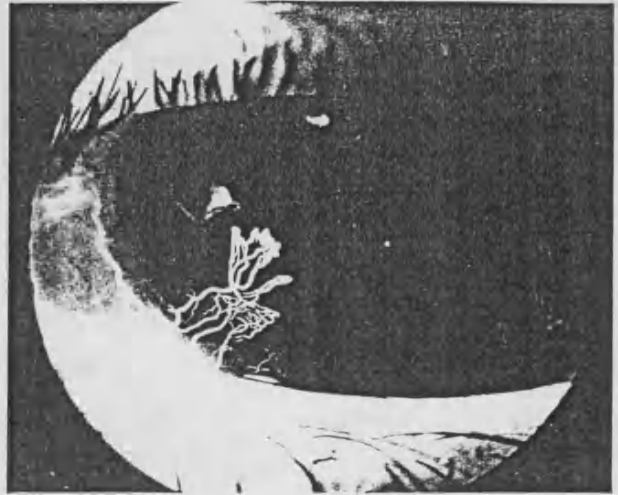


Figure 5. Angiogram of lipid keratopathy showing abnormal presence of corneal vessels.

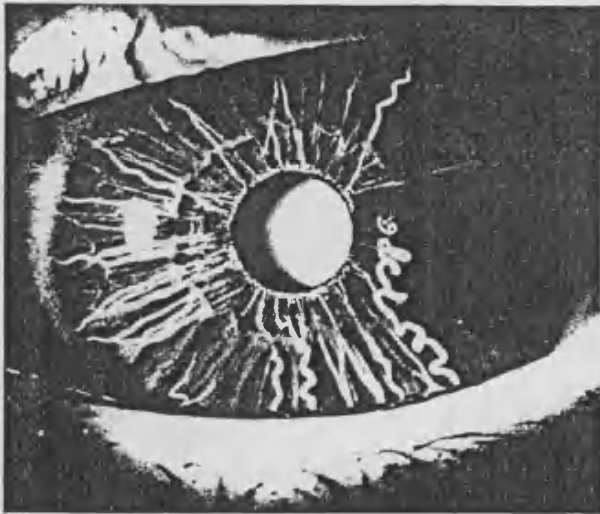


Figure 6. Angiogram of anomolous shunt iris vessels showing a distinct artery on a tortuous course starting at 4 o'clock and a fine capillary network at the pupil margin.

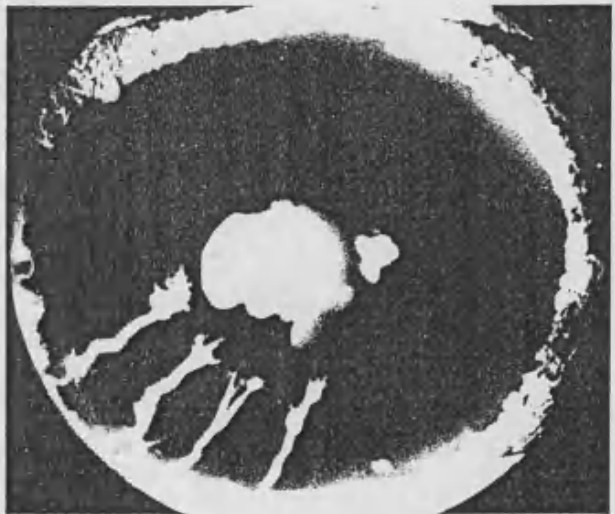


Figure 7. Iris angiogram of thrombotic glaucoma showing posterior synechiae, dilation and closure of vessels.

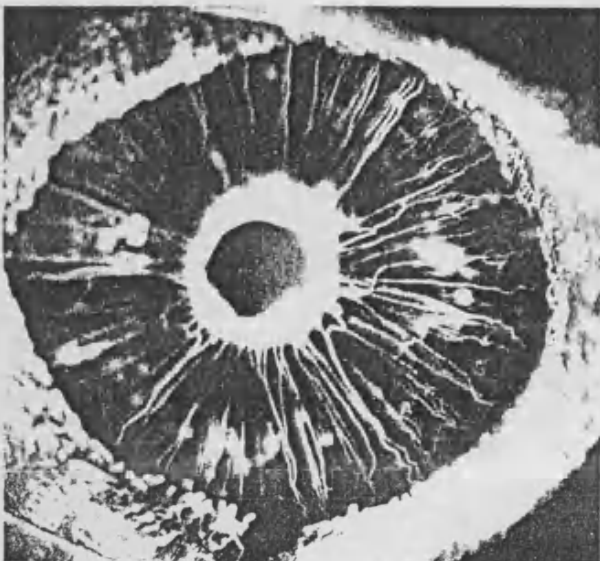


Figure 8. Iris angiogram, 5 months after onset of an acute central retinal vein occlusion, showing leakage from the mid-zone and pupil margin.



Figure 9. Angiogram of a haemangioma of the conjunctiva.

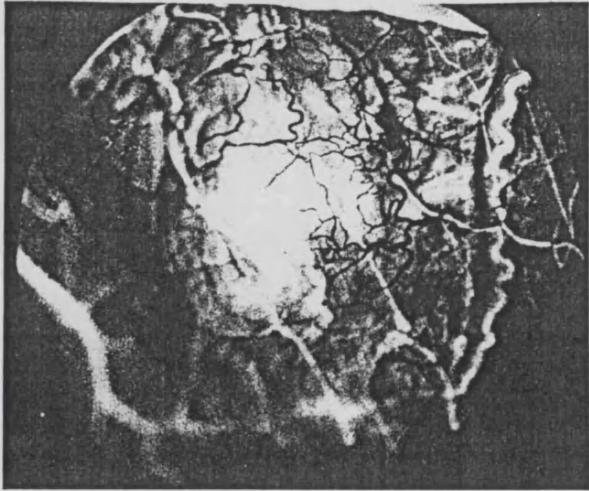


Figure 10. Corneal angiogram of nodular episcleritis showing slow filling and abnormal dilation of vessels.

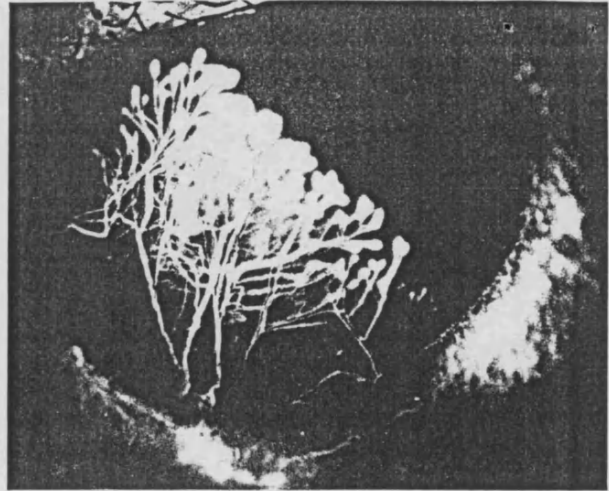


Figure 11. Corneal angiogram of disciform-type lipid keratopathy.

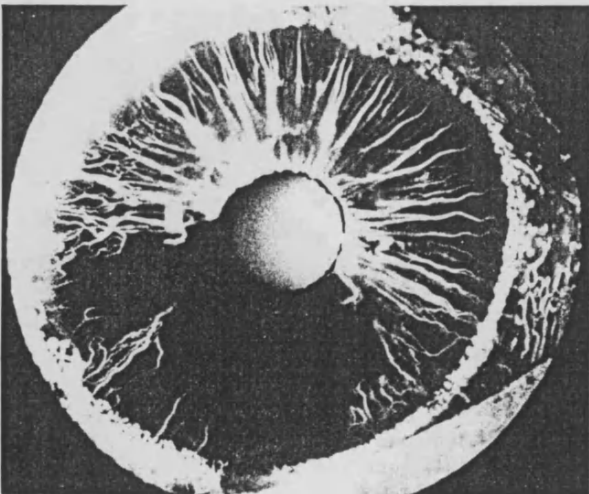


Figure 12. Iris angiogram showing severe impairment of filling below, 2 days after recession of the inferior rectus muscle, in a patient with dysthyroid ophthalmoplegia.

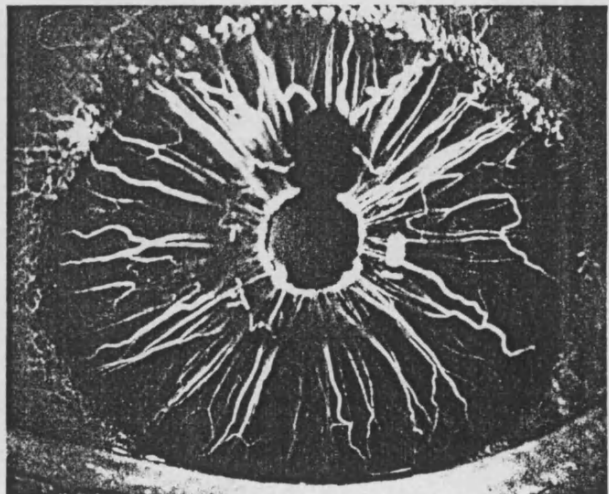


Figure 13. Angiogram of a benign iris melanoma showing masking of vessels.

patients are photophobic, it is difficult for them to keep their eyes open as the halogen light is extremely bright.

Video recording

We have also developed a technique for video recording (Marsh and Ford, 1978). The cine camera is replaced by a CCTV (HV-625K) miniature television camera and all settings are identical to those used for the cine photography. We view the angiogram on a Hitachi 75-square inch (484 cm²) video monitor (VM-126AK) and record on a U-matic video cassette

recorder (JVC CR-8200E). It is especially useful for studying the vascular pattern of a lipid keratopathy before laser treatment.

Conclusions

We found that cine photography gave good single frame analysis of the vascular pattern and the best definition to date. The major disadvantage was the slow speed of projection required which limited us to an analytical cine projector, although there was also the possibility of double printing each frame of the film. We found cine film expensive and there was a delay

in developing and printing. Video recording on the other hand can be viewed immediately, conveniently and repeatedly, during and after recording, but as yet the definition is not as good. In the near future with the introduction of low light level charge couple device (CCD) television cameras, computer-enhanced video images and a system that is capable of providing high enough resolution to show the fine capillary network of the iris and offer single frame analysis, cine photography will be superseded. Surprisingly we found patients remarkably good at tolerating the bright illumination necessarily produced by this system.

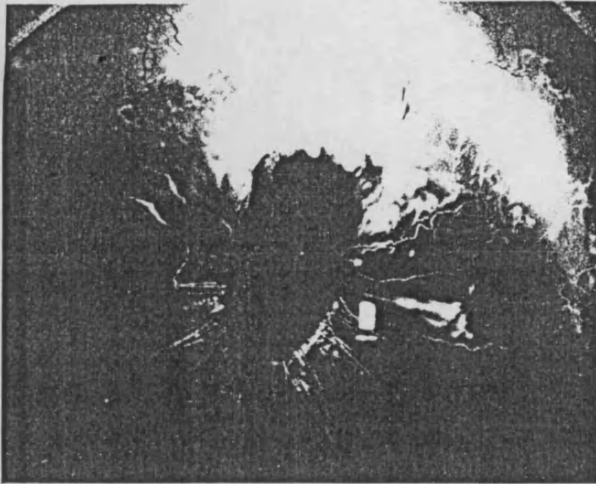


Figure 14. Iris angiogram of a sclerotic malignant melanoma showing distortion of the pupil and a vascular pattern appearing through the masking.

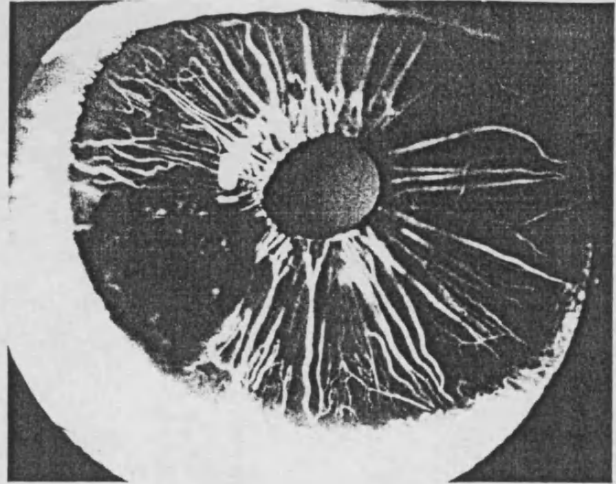
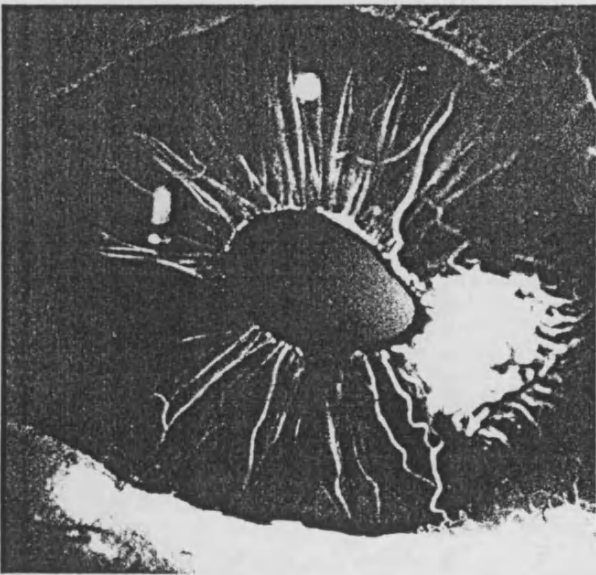
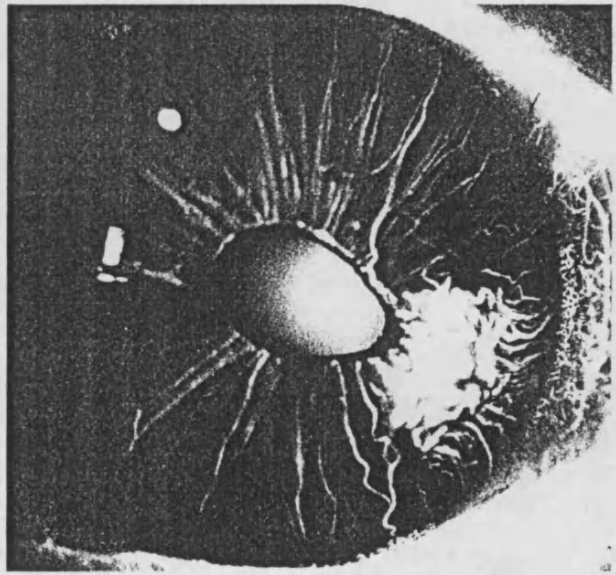


Figure 15. Iris angiogram of a malignant melanoma showing distortion of the pupil and a vascular circulation within the tumour.

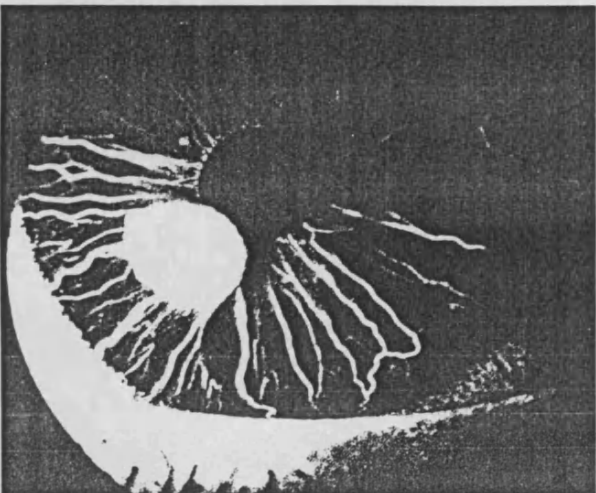


a

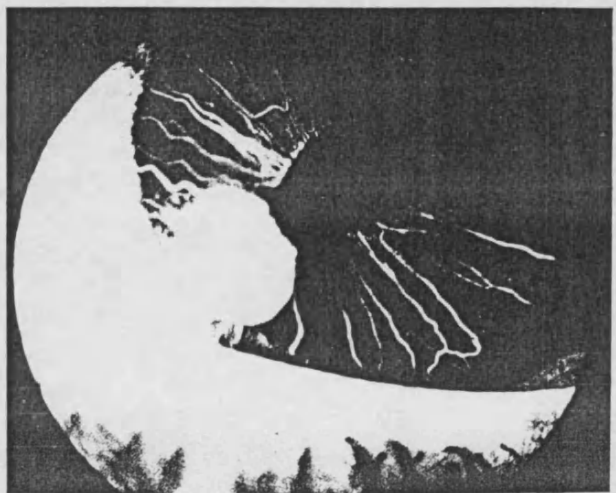


b

Figure 16a and b. a Early iris angiogram of malignant melanoma distorting the pupil and leaking early on. b Two years later, there is no change in the size and fluorescein appearance.



a



b

Figure 17a and b. a Early iris angiogram of a well-differentiated vascular tumour. b Three years later, showing an increase in size of the tumour and distortion of the pupil.

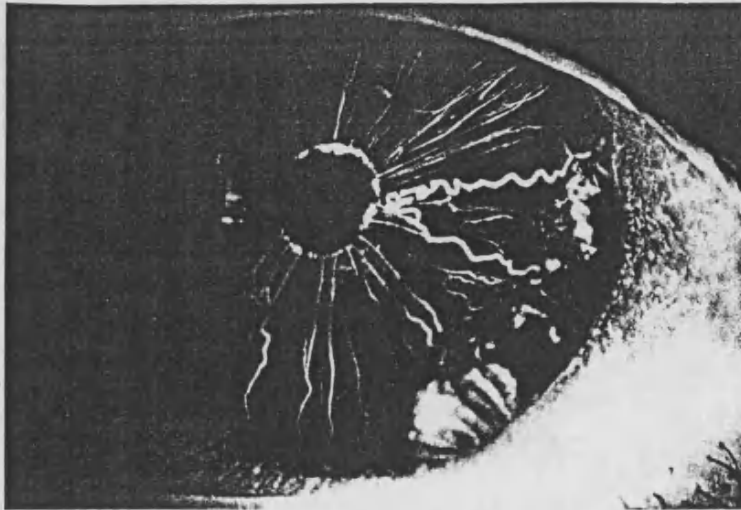


Figure 18. Iris angiogram of a ciliary body melanoma showing leaking dilated tumour vessels over the surface of the fleshy tumour.

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Corneal Epithelial Lesions in Herpes Zoster

R. J. MARSH

*Department Clinical Ophthalmology,
Moorfields Eye Hospital, London, UK*

Introduction

Over 7% of all herpes zoster affects the ophthalmic division of the Vth nerve (Archard, 1924). The globe is affected in approximately 50% of cases and in about 35%, the cornea (Edgerton, 1945). I have examined 900 cases of ophthalmic zoster at Moorfields Eye Hospital under the supervision of Professor Barrie Jones for the past 8 years and some of the disease patterns in the cornea were readily apparent but many continue to remain a total mystery. Most patients were seen within the first week of appearance of the rash and then followed for at least 1 year. The eye was carefully examined on the slit-lamp and corneal sensation was assessed and recorded with the aesthesiometer of Luneau and Coffignon. If corneal lesions were present they were stained with solutions of 1% rose bengal, sodium fluorescein and in a few cases 1% alcian blue, and detailed corneal drawings were made.

Results

Herpes zoster epithelial lesions fall into four groups, based on natural history, biomicroscopic appearance, staining characteristics, corneal sensitivity, cytology, culture results and response to therapy. Three are well defined. These are acute epithelial dendritic, chronic corneal mucous plaque (Marsh, 1973; Marsh *et al.*, 1976) and neuroparalytic keratitis. The fourth is a strange type of chronic exposure keratitis.

Acute epithelial keratitis

This is characterized by small fine multiple dendritic or stellate lesions. On the slit-lamp they appear slightly raised but are only intraepithelial. They are located generally in the peripheral part of the cornea and occasionally small plaques of opaque desquamated epithelium and mucus overlie them. These epithelial lesions stain

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moderately well with rose bengal and fluorescein but only minimally with alcian blue. They are self-limiting, appearing within a few days of the rash onset, resolving within 4–6 days and are always associated with catarrhal conjunctivitis. These dendritic lesions may or may not be followed by an underlying superficial stromal infiltrate (Marsh *et al.*, 1976). Varicella zoster virus has been cultured from them (Pavan-Langston and McCulley, 1973).

Corneal mucous plaque keratitis

The typical lesion is a whitish-grey plaque with sharp margins that lies on the surface of the epithelium and is linear or branching (dendriform) in shape. These plaques are usually multiple, are variable in size and shape and may appear anywhere on the cornea. Indeed, they may change in configuration, number and size from day to day. Application of Acetylcysteine drops usually dissolves them. Fluorescein stains the lesions moderately whilst rose bengal stains the whole lesion vividly. Alcian blue stains the lesions and associated mucous debris in the tear film (Marsh *et al.*, 1976). Corneal mucous plaques appear as early as 7 days and as late as 10 months after the onset of zoster rash (44 cases were seen in this series of 900). A histogram (Fig. 1) shows the variation in time of onset. They are ushered in by ciliary injection, mild

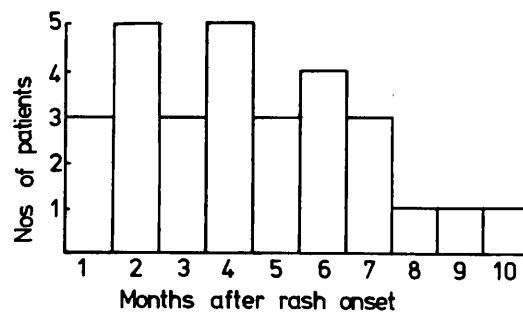


Figure 1. Histogram of the onset of mucous plaque keratitis in 30 cases seen from the start of the rash.

iritis and a profuse deposition of fine keratitic precipitates. Eighty-three are preceded by episcleritis, 80% by disciform keratitis, 6% are associated with severe rash and 56% with iris atrophy. The whole of the corneal epithelium shows bedewing and swelling with an unstable overlying tear film. Frequently rapid formation of corneal dry spots is seen and quite often they take on a dendriform shape. Interestingly, the results of the Schirmer test are usually within normal limits but corneal sensation is always impaired. Slit-lamp examination with retroillumination shows faint superficial stromal haze over most of the cornea. The mucous plaque deposition tends to continue for several months, but eventually the tear film and epithelium usually stabilize leaving a faint stromal haze which may reduce vision by one or two lines on the Snellen chart. Unfortunately in 16% a severe neuroparalytic keratitis supervenes, often leading to ulceration. There may be difficulty distinguishing this lesion and the acute zoster epithelial keratitis from herpes simplex keratitis. The following headings suggest methods of differentiation.

Biomicroscopically

The dendrites of simplex are finer, more lacey, may or may not have end bulbs but are longer and more central than those of acute zoster dendrites.

Staining differences

Rose bengal brilliantly stains the entire mucous plaque and the margins of herpes simplex dendritic ulcers, but only moderately well the acute dendritic zoster lesions. Fluorescein stains the ulcer bed of herpes simplex ulcers intensely, but the zoster lesions are only moderately well stained. Alcian blue stains the corneal mucous plaque well, but the lesions of acute zoster and simplex poorly.

Debridement

The dendritic lesions of simplex and acute zoster can be removed only if corneal epithelium is detached. Since the corneal mucous plaques are on the surface of the epithelium they can be removed easily by gentle scraping with minimal damage to the underlying epithelium.

Response to corticosteroids

Topical corticosteroids do not appear to be detrimental to the acute lesions of zoster since the lesions disappear within about the same time as those that do not receive this drug. They do not have a notable effect on corneal mucous plaques since they vary in size, number, appearance and frequency regardless of whether this medication is used. In fact topically applied corticosteroids seem to provide most of these patients with increased comfort and are necessary in cases with accompanying iritis. However, corticosteroids must be used with great caution when there is total loss of corneal sensation in mucous plaque keratitis because of the risk of neuroparalytic ulceration and rapid perforation of the globe. They can and often do appreciably increase the width of individual branches as well as the overall size of dendritic lesions of epithelial herpes simplex.

Cytology

Scrapings from the margins of herpes simplex and the acute zoster lesions show degenerating and large multinucleated cells with moulding of nuclei and margination of chromatin. The cytology of the corneal mucous plaques shows no viable cells but strong positive staining for mucus (alcian blue and Southgate mucicarmine). Scrapings of the underlying epithelium demonstrate typical large, multinucleated cells similar to the others with swollen and degenerated surrounding epithelium (Marsh *et al.*,

1976). In one patient fluorescent antibody staining of cells underlying a plaque has shown features suggestive of viral infection (Hayashi *et al.*, 1973).

Virology

Herpes simplex virus can be readily isolated from the edges of its ulcer. Varicella zoster is cultured with difficulty from the acute epithelial lesions (Pavan-Langston and McCulley, 1973). We failed to isolate this virus from the mucous plaques (Marsh *et al.*, 1976), as did Piebenga and Laibson (1973) in their cases.

Prior to reports of pure zoster-induced dendritic epithelial lesions there have been several cases of epithelial lesions occurring in the course of zoster attributed to herpes simplex superinfection (Acers and Vaile, 1967; Giles, 1969; Sugar, 1971). A review of my 900 cases showed only four cases of ophthalmic zoster with true complicating herpes simplex corneal epithelial disease. It seems to me, therefore, that coincident corneal epithelial infection with the two viruses is an extremely rare event and that epithelial keratitis with typical ophthalmic zoster rash on the involved side is caused by zoster until proved otherwise.

Neuroparalytic keratitis

This is characterized by generalized corneal epithelial bedewing, and punctate epithelial erosions with or without frank interpalpebral epithelial ulceration. The epithelium stains moderately well in a punctate fashion with fluorescein and rose bengal. The ulcers tend to be oval in shape with opaque water-logged epithelial edges, and the base stains brilliantly with fluorescein and moderately well with rose bengal, but alcian blue should not be used because of the risk of long-term stromal staining. There is accompanying bulbar and tarsal conjunctival injection. The keratitis may be of acute or late onset. Acute cases occur as early as 7 days and as late as 2 years after the first signs of cutaneous zoster. The aesthesiometer shows total loss of corneal and conjunctival sensation with frequent loss at the lid margin too. There is great risk of the punctate keratitis going on to ulcer formation and 16% of our mucous plaques did so after an average period of 9 months. Viscous drops and protective spectacles may be successful in preventing this, but tarsorrhaphy is the surest method. Neglected ulcers grow rapidly with excavation and opacification of the stromal base with a distinct risk of severe secondary bacterial infection. Two of our cases perforated; four developed severe stromal scarring with a subepithelial formation of a dense inspissated mucous deposit. Topical corticosteroids are strictly contraindicated here as they tend to encourage rapid excavation and growth of the ulcer; similarly bandage lenses have proved unsatisfactory with four of my cases developing a corneal abscess and hypopyon. Tarsorrhaphy, preferably central, has proved by far the most effective therapy. Histology of the ulcers shows degenerative changes in the epithelium and extensive necrosis in the stroma (Duke-Elder, 1965).

"Exposure" keratitis

Under this heading comes an ill-defined group of patients who show generalized corneal epithelial swelling. Biomicroscopy shows a grossly oedematous epithelium

with frequent formation of white raised ridges horizontally in the interpalpebral area. Rose bengal and fluorescein give diffuse punctate staining with moderate linear stain along the white lines. There is generally accompanying hyperaemia of the bulbar and tarsal conjunctiva and always an extremely unstable precorneal tear film. The Schirmer test and tear production tend to be normal but plugs of mucus are often seen in the tear film. The corneal sensation is partially depressed only and the lid margins are generally healthy with good blinking. The onset is usually shortly after development of the rash but can be delayed and runs a very long course where topical viscous agents are only partially effective. Severe chronic cases can go on to develop permanent superficial stromal haze formation. The only therapy which appears to stabilize the epithelium consistently is tarsorrhaphy. The aetiology of this keratitis is very obscure.

Conclusion

Ophthalmic zoster is responsible for at least four types of epithelial keratitis. All but the acute epithelial dendrites have an obscure aetiology, tend to be chronic and if incorrectly handled, lead to corneal scarring, secondary bacterial ocular infection and perforation of the globe. Thus, it is important that these lesions are regularly examined and given careful long-term follow-up. It is essential to differentiate the dendriform keratitis of zoster and simplex remembering that the topical treatment of the two diseases is quite different. Corticosteroids on the one hand aggravate herpes simplex ulcers and topical IDU on the other hand adversely affects herpes zoster keratitis.

Acknowledgements

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Herpes zoster ophthalmicus: a medical review

SUSAN LIGHTMAN, R. J. MARSH, AND DAVID POWELL

From the Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD

SUMMARY Patients with herpes zoster undergo extensive screening to detect underlying malignant disease which is compromising their immunity. In a retrospective survey of 1000 patients with herpes zoster ophthalmicus 12 patients had malignant disease which was known on presentation. No new cases were detected or discovered on follow-up. Three patients developed a disseminated rash, but none of these had an underlying malignant disease.

For many years it has been suggested that patients contracting herpes zoster have compromised immunity¹⁻⁴ and the zoster infection is symptomatic of an underlying immunosuppressive process. However, zoster occurs widely in the community, especially in the elderly, and it was our impression that most of the patients we saw with herpes zoster ophthalmicus (which constitutes 7% of all zoster infection)⁵ had good general health prior to contracting it.

We therefore decided to carry out a retrospective study on our patients to see if this impression was correct and to see if the infection and ocular complications were more severe in those patients with underlying disease.

Patients and methods

Our study was based on patients attending the Zoster Clinic at Moorfields Eye Hospital over the past 9 years. The vast majority of the patients were referred directly to the Casualty Department from their general practitioner within the first 10 days of onset of the rash. The diagnosis was confirmed in the Casualty Department and preliminary treatment started. Within the next few days the patients were seen in the Zoster Clinic, which is part of the External Diseases Group of Clinics under the auspices of the Professorial Unit at Moorfields. Apart from the ocular examination all patients had a medical history taken and underwent the following tests: a full blood count, differential white blood count and film, erythrocyte sedimentation rate (ESR), liver function tests, electrophoretic strip, blood sugar, and chest x-ray. The patients were also

asked about previous zoster infections and whether they were on systemic steroids. Regular follow-up appointments were then made until the eye was quiet or they defaulted.

Those patients whose blood tests were abnormal (abnormal being taken as anything outside the normal range in biochemistry, and differing from a normal differential white blood count) were looked at in detail and multivariate analysis was undertaken with age, sex, haematological results, biochemical results, and type of eye problem as variants. Probabilities were then computed by means of the Fisher exact probability test.

Results

One thousand patients have attended the Zoster Clinic in the last 9 years. A small proportion of the patients had no ocular involvement—the infection being confined to the skin. Thirty-six patients reported previous zoster infections. These had usually been thoracic or lumbar, but 1 patient had suffered ophthalmic zoster on the other side 18 years previously and had visible pitting and depigmentation in the skin on that side. Three patients developed a disseminated rash—with more than 5 spots in places other than those which could have been produced by auto-inoculation. None of these 3 patients had malignant disease or developed it during the period of follow-up.

Five patients were on steroids for unrelated problems including chronic chest disease, eczema, and nephrotic syndrome. Associated diseases included 4 with diabetes, 3 postgastrectomy patients (benign gastric ulcers), 1 patient with discoid lupus erythematosus, 1 with sarcoid, and 3 with ulcerative colitis. None of these were on steroids or had been

for at least 4 months. Two patients developed transient hemiplegias on the opposite side to their zoster ophthalmicus. One episode was 6 weeks after the onset of the zoster and the other 5 months.

No previously undiagnosed malignancies were found or developed during the period of follow-up. Six patients had carcinoma of the breast, diagnosed between one and 21 years previously. Three had carcinoma of the colon; 1 patient was on chemotherapy and the other 2 had been diagnosed 2 and 6 years previously. There was 1 patient with Hodgkin's disease on chemotherapy, 1 with carcinoma of the lung diagnosed 10 years before, and 1 with a 'brain tumour' diagnosed in 1952.

Of the 1000 patients screened 364 had abnormal blood results of any sort, of which 72 patients had no ocular involvement. Table 1 shows the haematology results in this group. 176 were male and 188 were female. The commonest age range was 50–70 years, with the youngest being 18 years and the eldest 91. The average period of follow-up was 2 years with the range being less than 1 year to 8 years. Most patients were followed up until their eye was quiet and they were discharged, with a very small proportion defaulting before this time.

The commonest eye problems which developed were iritis/iris atrophy, episcleritis, and superficial stromal scarring. The age and sex of the patient were irrelevant to the type of eye problem which developed, and there were no correlations with abnormal biochemical results. There were no prognostic indicators in the blood results. The outcome of the ocular disease was not affected by the presence or absence of a lymphocytosis, raised gamma globulins or any other blood factors. There was a significant association between the presence of an abnormal haematological result (as opposed to a normal result) and mucus plaque keratitis ($p < 0.0005$), but when the abnormal results were looked at no specific abnormality was more common.

When the different eye problems in the 364 patients were analysed, several significant associates emerged. Patients with iritis/iris atrophy had a higher incidence of keratitis ($p < 0.001$) and episcleritis ($p < 0.01$) than did the others. Similarly patients

with mucus plaque keratitis had a higher incidence of neuroparalytic ulcer ($p < 0.01$) and cataract ($p < 0.001$).

Discussion

Only 12 of our patients, who were from a general rather than a hospital population, had malignant disease, and no new malignancies were discovered on screening or developed during the follow-up period. This confirmed our clinical impression that we are dealing with a predominantly healthy population. Dissemination of the rash occurred in only 3 patients, and none of these had malignant disease. A previous study of 175 patients with herpes zoster had 17 patients who developed widespread vesicular lesions during the course of typical localised herpes zoster. Eleven of these 17 patients had serious underlying diseases.⁶ The difference in our results probably reflects the selection of patients, ours coming from the general population not from a hospital population.

Second attacks of zoster are thought to be rare. Head and Campbell found 4 patients in a survey of 400 patients,⁷ whereas 36 of our patients had suffered previous attacks. None of these patients had underlying disease nor a history suggestive of reinfection, so it is difficult to explain how they developed the disease.

The associates of eye complications are interesting. Both episcleritis and iritis involve an occlusive vasculitis and hence would be expected to be associated. Mucus plaque keratitis tends to be a chronic diffuse keratitis with progressive loss of corneal sensation, so it is not surprising that neuroparalytic ulceration occurs more commonly in this group. The high incidence of cataract in this group poses a problem in aetiology, since severe anterior segment ischaemia can lead to cataracts, as can intensive local steroid therapy.

This study has shown that the great majority of patients contracting herpes zoster ophthalmicus are healthy and therefore do not have diminished immunity. The trigger factors for this disease remain a puzzle and require further investigation.

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Table 1 Haematology results in 364 patients

Result	No. of patients
Normal	225
Lymphocytosis	64
Neutrophilia	19
Monocytosis	19
Leucopenia	14
Lymphopenia	13
Eosinophilia	10

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Treatment of lipid keratopathy with the argon laser

R. J. MARSH AND J. MARSHALL

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**LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, WC1H 9JR**

Treatment of lipid keratopathy with the argon laser

R. J. MARSH AND J. MARSHALL

From the Western Ophthalmic Hospital and the Institute of Ophthalmology, London

SUMMARY Twenty-two patients with lipid keratopathy were treated with argon laser photocoagulation to the feeder vessels. Two were grafted just over a week after treatment and the corneal discs examined histologically. The remainder of the patients were followed up for at least a year. In 6 cases the visual acuity improved, in 3 deteriorated, and in 10 did not change. The density and extent of the lipid deposition were diminished in 50% of cases. The commonest complications were bleeding into the lipid keratopathy and iris damage. The only serious problem was a disciform type of lipid keratopathy that flared up after treatment. Suggestions are made on improvements in the technique of laser application.

Many patients with chronic corneal inflammatory disease are left with a vascularised scar and secondary lipid deposition. Not only is this unsightly, but it may spread across the pupil, diminishing vision and causing troublesome photophobia. Treatment may be considered under 2 main headings: primary preventive and secondary measures to deal with established disease. Primary measures include adequate early treatment of keratitis to prevent infiltration and vascularisation—for example, adequate long-term topical steroid administration in herpes simplex and zoster keratitis (with suitable antiviral cover in the former)—and the investigation and treatment of any systemic lipid anomaly. Established lipid keratopathy is more of a problem. Direct removal of superficial deposits may be attempted by keratectomy, but, when they are deeper, lamellar or penetrating corneal grafting is necessary.

Obviously the results of grafting are particularly poor in a vascularised host. Much attention has been concentrated in the past on the occlusion of these new vessels in the hope that further lipid deposition may be prevented, some resorption occur, and the host made safer for grafting. The methods have included peritomy, severing or cautery of the vessels at the limbus,¹ β radiation,²⁻⁶ thiotepa,^{7,8} and cryotherapy.⁹ All these methods were assessed by Ey *et al.*¹ in the inhibition of induced vascularisation in rabbits, and they found the most effective were β radiation, thiotepa, and topical steroid. The latter is known to reduce cellular infiltration, diminish fibroplastic

repair and postinflammatory vascularisation, and reduce capillary permeability associated with inflammation of the cornea.¹⁰⁻¹² More recently, renewed attempts have been made to occlude the new vessels unresponsive to steroid with the argon laser.¹³⁻¹⁵ Cherry *et al.*¹³ treated 4 patients with lipid keratopathy and had a short-term success in closure of new vessels in all cases, but regrowth occurred in 3 patients after 6 months. We felt that by modifying the technique used for closure of small new vessels in diabetic retinopathy¹⁶ we might have something useful for early cases of keratopathy, further lipid deposits being prevented and existing lipid absorbed by macrophages passing into adjacent corneal lymphatics. However, in the more advanced cases we recognised that major irreversible structural changes had occurred in the cornea and that full recovery would be impossible.

We proposed to give due consideration to possible dangers to iris, lens, and retina during the trial. We decided to try to obtain the discs from patients grafted soon after corneal lasering.

Materials and methods

Patients with all degrees of lipid keratopathy were drawn on a voluntary basis from those attending the Western Ophthalmic Hospital and Moorfields Eye Hospital. A history and full examination were carried out and the following recorded: history and aetiology of keratitis, drug treatment, visual acuity, the extent, density, and vascularisation of lipid deposits, iris appearance, and lens clarity. They were reassessed every 3-6 months, and most patients were screened for any systemic lipid anomalies.

Correspondence to R. J. Marsh, FRCS, Western Ophthalmic Hospital, Marylebone Road, London NW1.

Colour photographs were taken on the photo slit-lamp every 6 months at $\times 2$ magnification with identical settings, lighting conditions, and film. A careful grading was made on the density and extent of lipid deposits. Density was recorded as mild, moderate, or severe, and the extent was expressed as a fraction of the total area of the cornea. Corneal fluorescein angiography was carried out on all patients prior to treatment and thereafter every 6 months to 1 year. Vascularisation was scored as mild, moderate, or severe and a note added on the size of the stem. Earlier patients were recorded at $\times 1$ magnification on 35 mm film but later at $\times 2$ magnification on film and videotape by the technique described by Marsh and Ford.¹⁷ The videotape was particularly useful because it could be immediately and repeatedly replayed to identify vascular filling pattern and closure.

Prior to treatment with a coherent radiation 900 argon laser 1% amethocaine was instilled; the patient was cautioned to be very still and stare constantly at the fixation light. To a certain extent the instrument settings and technique varied and underwent evolution as we progressed. The aperture setting varied from 50 μm to 100 μm depending on the size of the vessels to be treated, but it was important to have the machine checked regularly for correct focusing of the beam. The intensity necessary to occlude the blood column varied from 0.2 to 0.8 watts and again depended on the state of repair of the machine, although we found it better to start at a low level and slowly increase. We used 0.1 s exposures, the slowest speed possible consistent with comfort. The illumination of the slit was kept as low as possible and the delivery system angled to the cornea so that rays were directed away from the pupil to the periphery of the iris. It was best to constrict the pupil prior to treatment.

We preferred to begin treatment just behind the limbus, occluding all the main feeder tracks seen on the angiograms (this tended to 'trap' blood columns in the cornea). Next we occluded the main veins, just corneal to the limbus, which expanded and darkened these columns, facilitating further photocoagulation. They were progressively closed or blackened towards the centre of the cornea. After we closed the large veins we returned to the larger arteries in which flow had been considerably slowed. Smaller aperture settings and more power were necessary to close them all along their course. We next tackled any remaining small vessels and found it best to treat them initially at 'cross-over' points and then fill in intermediate sections.

All treatments were recorded. We found it best to arrange 3 treatment sessions in a day owing to the tendency of anastomotic channels to open up $\frac{1}{2}$ –1 hour after initial laser treatment. So we started early in the morning, and applied the second at midday and

the last in the late afternoon. In cases of profuse vascularisation patients were initially brought back for treatment every 2 weeks. As successful closure was achieved patients returned approximately every 3 months for assessment, including repeat of angiography and further treatment as necessary.

Efficacy of treatment was judged by improvement in visual acuity, a reduction in density and extent of the lipid, and by disappearance of vascularisation. Thus, these details were carefully recorded at each visit and photographed. In 2 cases histology was obtained after laser application.

Case 1 was a 27-year-old man with a history of keratitis and dense vascularised central lipid keratopathy. Photographs and angiogram were taken and laser was applied to the vessels. Ten days later a corneal penetrating graft was carried out with immediate transfer of the disc to fixative.

Case 2 was a 30-year-old man with a history of keratitis and dense vascularised central lipid keratopathy. Photographs and angiogram were taken and laser was applied to the vessels. Eleven days later a penetrating graft was carried out with immediate transfer of the disc to refrigerated fixative.

Both discs were fixed for at least 1 hour in 2.5% glutaraldehyde buffered in 0.1 M sodium cacodylate containing 10 mg/ml calcium chloride and with a final pH 7.4. After initial fixation each disc was briefly washed in cacodylate buffer containing 7.5% sucrose, and the areas exposed to laser irradiation were then isolated under a dissecting microscope. Samples of irradiated and unirradiated areas of both discs were postfixed for 1 hour in 2% osmium tetroxide in 0.2 M sodium cacodylate, dehydrated through a graded series of ethanol concentrations in water, and then embedded in Epon via epoxypropane. Semithin sections (0.75–1 μm thick) were cut on glass knives and stained with alcoholic toluidine blue.

Results

Twenty-two patients were treated with laser and of them 19 were followed up for a minimal period of a year. One patient failed follow-up after 3 months and 2 received corneal transplants 1 week after treatment.

The keratopathies could be broadly classified by morphology into several types: (a) central; (b) eccentric disciform; (c) marginal; (d) diffuse interstitial; and (e) diffuse deep. Table 1 shows the distribution of patients to these groups and their aetiology.

Table 2 shows the results of treatment in the 19 patients with minimum follow-up of 1 year. It can be seen that there was improvement in visual acuity in 6 cases, deterioration in 3, but no change in 10. The density of the lipid was reduced in 9 cases, increased

Table 1 Distribution of keratopathy

Aetiology	Central disciform	Eccentric disciform	Marginal	Diffuse interstitial	Diffuse deep
HS	4	5	2	1	
HZ	1	1			
Rosacea	0	1			
Trauma	0	1			
Idiopathic	0	1			2

HS=herpes simplex. HZ=herpes zoster.

in 3, but remained the same in 7. The extent of the lipid was reduced in 11, increased in 1, and there was no change in 7. Recurrence of vessels was troublesome in 7, easily handled in 4, and not a problem in 8.

COMPLICATIONS

During lasering 6 patients developed peaking of the pupil and 7 bled into the area of keratopathy. Both of these complications had usually resolved after 2 weeks and seemed not to lead to any serious long-term problems. Most patients tolerated the treatment very well, though some found fixating difficult. Occasion-

ally, when a large vessel near the surface was treated, a hole was punched out of the overlying cornea, through which blood found its way to the surface. However, these lesions healed very well over the following days. Great care was taken to avoid hitting the iris, but it was impossible to achieve this at all times. When it was hit several reactions occurred depending on the strength and siting of the shot. Firstly, nothing appeared to happen; secondly, a sudden spurt of cells and debris appeared in the adjacent aqueous drifting upwards, often accompanied by the production of an air bubble on the iris and a faint popping sound. If a major radial artery to the sphincter was hit peaking occurred.

The commonest late complication occurring in nearly all cases was iris atrophy. This obviously lay under the treated area and was chiefly stromal. The pigment epithelium was visibly breached in a few cases only. In 2 the pupil was permanently peaked. These complications rarely gave rise to a visual or cosmetic problem. There was no biomicroscopically observable lens defect as a result of treatment in any of the cases (the longest follow-up period being 5 years). So far as we are aware, the retina was not

Table 2 Results of laser therapy in 19 cases of lipid keratopathy

Case	Distribution of lipid	Density	Extent of cornea	Vascularity	Stem	Amounts of laser (sittings)	Density	Extent	Visual acuity (Snellen's)	Vascularity
1	Marginal	Mild	1/9	Mild	Several	114 (2)	Less	Less	Same	A little recurrence
2	Marginal graft host junction	Moderate	1/10	Moderate	Narrow	1154 (3)	Much less	Much less	Same	No recurrence (Fig. 1)
3	Graft host junction	Moderate	1/8	Moderate	Narrow	868 (3)	Less	Same	Same	Minimal recurrence
4	Eccentric disciform	Severe	1/3	Moderate	Several	4023 (14)	Less	Less	Same	Constant recurrence
5	Eccentric disciform	Severe	1/2	Moderate	Multiple	2411 (5)	Same	Same	Same	Constant recurrence
6	Failed follow-up at 3 months									
7	Eccentric disciform	Moderate	1/4	Profuse	Broad	891 (1)	Less	Less	Same	Some recurrence
8	Eccentric disciform	Moderate	1/6	Mild	Narrow	68 (2)	Much less	Much less	Improved	Minimal recurrence (Fig. 2)
9	Eccentric disciform	Moderate	1/2	Moderate	Narrow	859 (3)	Much less	Much less	Improved	Minimal recurrence
10	Eccentric disciform	Severe	1/4	Moderate	Narrow	577 (2)	Same	Same	Same	Some recurrence
11	Eccentric disciform	Severe	1/4	Moderate	Several	2562 (4)	Same	Less	Slightly improved	Minimal recurrence
12	Eccentric disciform	Severe	1/3	Moderate	Several	2180 (4)	Slightly less	Less	Same	Minimal recurrence
13	Central disciform	Moderate	1/4	Moderate	Multiple	9417 (14)	Worse	Worse	Worse	Constant recurrence
14	Central disciform	Severe	1/4	Moderate	Narrow	331 (2)	Worse	Same	Same	Constant recurrence
15	Central disciform	Severe	1/6	Moderate	Several	1865 (3)	Same	Less	Same	Minimal recurrence
16	Central disciform	Severe	1/3	Profuse	Narrow	2592 (5)	Worse	Same	Worse	Constant recurrence
17	Central disciform	Moderate	1/6	Moderate	Multiple	3302 (7)	Same	Less	Worse	Some recurrence
18	Deep diffuse	Mild	1/4	Moderate	Narrow	704 (4)	Same	Same	Better	Some recurrence
19	Deep diffuse	Mild	1/4	Profuse	Narrow	2791 (5)	Same	Same	Better	Some recurrence
20	Superficial diffuse	Severe	1/2	Profuse	Multiple	9889 (13)	Much less	Less	Better	Constant recurrence

struck, though this was difficult to assess in some patients with dense opacities.

Two cases got obviously worse after treatment, and both were severe disciform types. The first, however, lost most of his vascularisation and was successfully grafted after 3 years. The second, unfortunately, developed a very serious disciform keratitis. This was partly accounted for by his failure to take his steroid drops after treatment, and his scarring became very dense.

HISTOPATHOLOGY

Both cases showed a similar distribution of vessels in the peripheral cornea with the anterior two-thirds of the stroma predominantly involved. Also in both patients the stromal lamellae were irregular, and centrally a marked erosion of this layer had occurred, resulting in a total central corneal thickness in case 1 of only 280 μm . Descemet's membrane was abnormally thick for individuals in their late 20s, and in some areas discrete deposits of lipid were observed within this structure close to its anterior surface (Fig. 1e, f). The endothelium in these specimens appeared relatively normal, but macrophages were often observed in contact with its aqueous aspect.

The interpretation of the irradiated areas is complicated by the secondary tissue reactions that have occurred during the postexposure periods. The most significant changes were observed in the more superficial layers of the stroma. The topography of the damage would suggest a highly localised primary damage site associated with limited heat flow from the vessels that absorbed laser irradiation. However, the lamellar structure of the stroma, with vast regions of extracellular collagen, results in an amplification of secondary tissue responses, with tissue displacement through the presence of oedema and macrophages.

Two types of reaction were seen associated with blood vessels in the superficial stroma, namely, haemorrhages (Fig. 2) and blood stasis in areas of capillary closure (Fig. 2). Many areas of haemorrhages were observed, and these were presumably coincident

with certain areas of irradiation. The haemorrhages were of various sizes, and haemolysing red blood cells could often be seen in the abnormally distended spaces between adjacent lamellae. Blood cells were particularly prominent in the region of Bowman's membrane and were often found between this layer and the basal cells of the epithelium. In many areas the disruptive effects of blood cells, macrophages, and oedema had resulted in gross distortions of the regular array of the basal cells such that they resembled those in the limbus (Fig. 3). In other areas the distortion was so gross that islands of epithelial cells were observed deep within the stroma, and some were undergoing division here.

Only 2 areas were found with incompletely healed epithelial erosions, which suggested that significant bleeding to the surface of this cornea was rare and that most sites were repaired within 10 days of exposure.

Vessels showing blood stasis with haemolysing blood cells and areas of capillary closure were usually less superficial and did not have changes in the adjacent tissues that would suggest that they were sites of irradiation. These changes in deeper vessels were probably due to interrupted flow in feeder or drainage systems. Many of these vessels were surrounded by macrophages and were abnormally swollen, both of which reactions caused further distortion of the adjacent lamellae.

In all areas where oedema and macrophages were present, but especially in the superficial layers, active keratocytes were also observed, and most of these had the rounded appearance of embryonic cells.

Discussion

We achieved some success in reducing the extent and density of the keratopathies. As expected, the early milder and marginal cases did best. The very advanced central types were devascularised, however, and made easier for grafting. We were very heartened by the one diffuse dense superficial keratitis which improved considerably. Aside from the small number

Fig. 1a, b Preoperative photograph and angiogram of patient 2 with lipid deposit at graft host junction. c, d Postlaser photograph and angiogram of patient 2 one year later. e, f Light micrograph of central cornea showing erosion of stroma and the presence of both neovascular complexes and lipid deposits. The marker is 100 μm . High-power light micrograph of the posterior cornea in 1e showing lipid deposits within Descemet's membrane and a macrophage in contact with the endothelium. The marker is 10 μm .

Fig. 2a, b Preoperative photograph and angiogram of patient 7 with lipid deposition in eccentric disciform keratitis. c, d Postlaser photograph and angiogram of patient 7 one year later. e Light micrograph of the anterior cornea showing the presence of red blood cells within the stroma resulting from small haemorrhages, and red cell packing in non perfused vessels (arrowed). The marker is 50 μm .

Fig. 3a, b Light micrograph of anterior cornea showing distortion of Bowman's membrane and the presence of numerous red blood cells trapped between the stromal lamellae. Light micrographs of both an occluded (arrowed) and (c) reopened (arrowed) vessel in case 1, both showing the presence of red blood cells between the lamellae of the adjacent stroma. The marker is 25 μm .

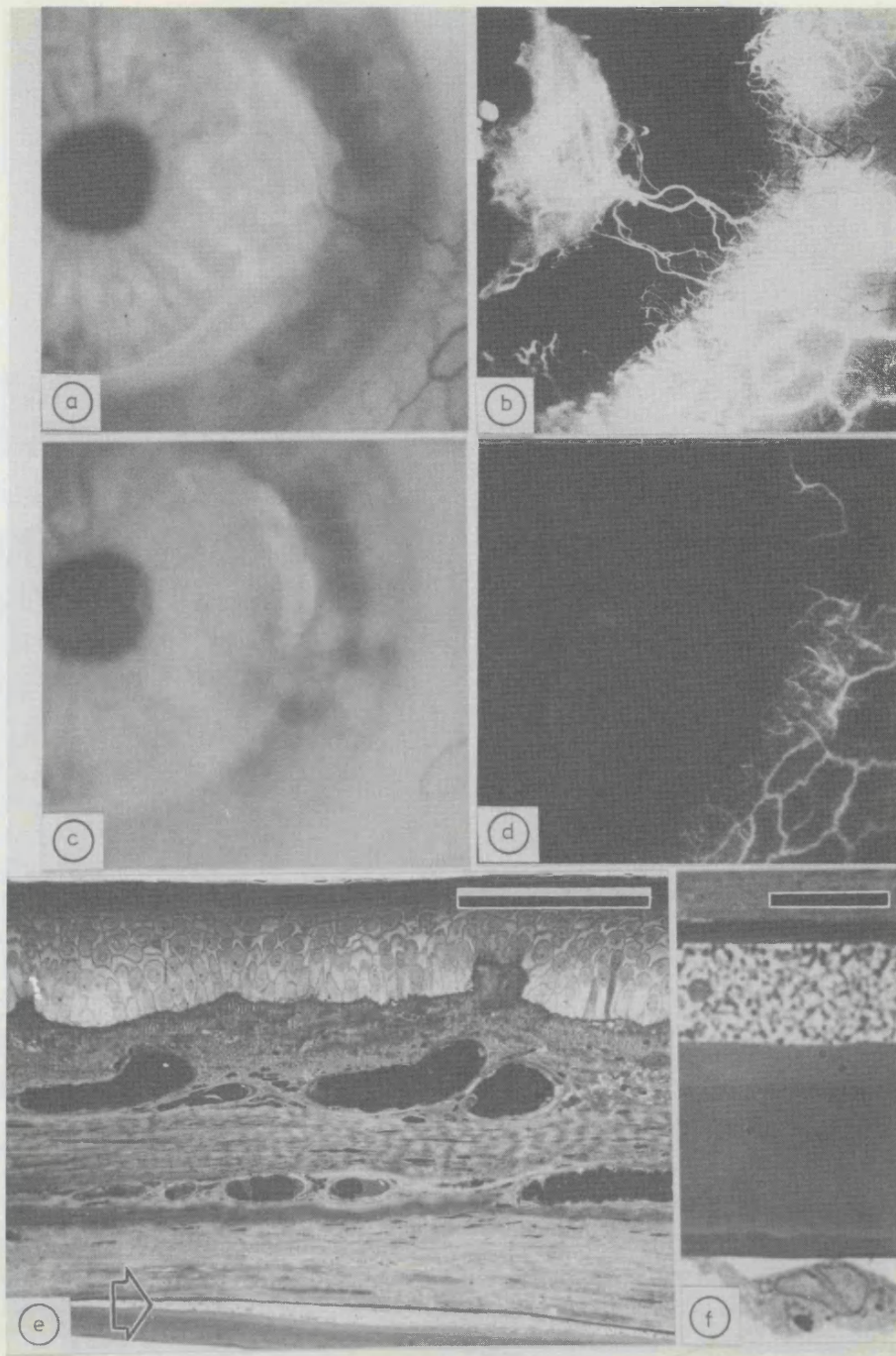


Fig. 1

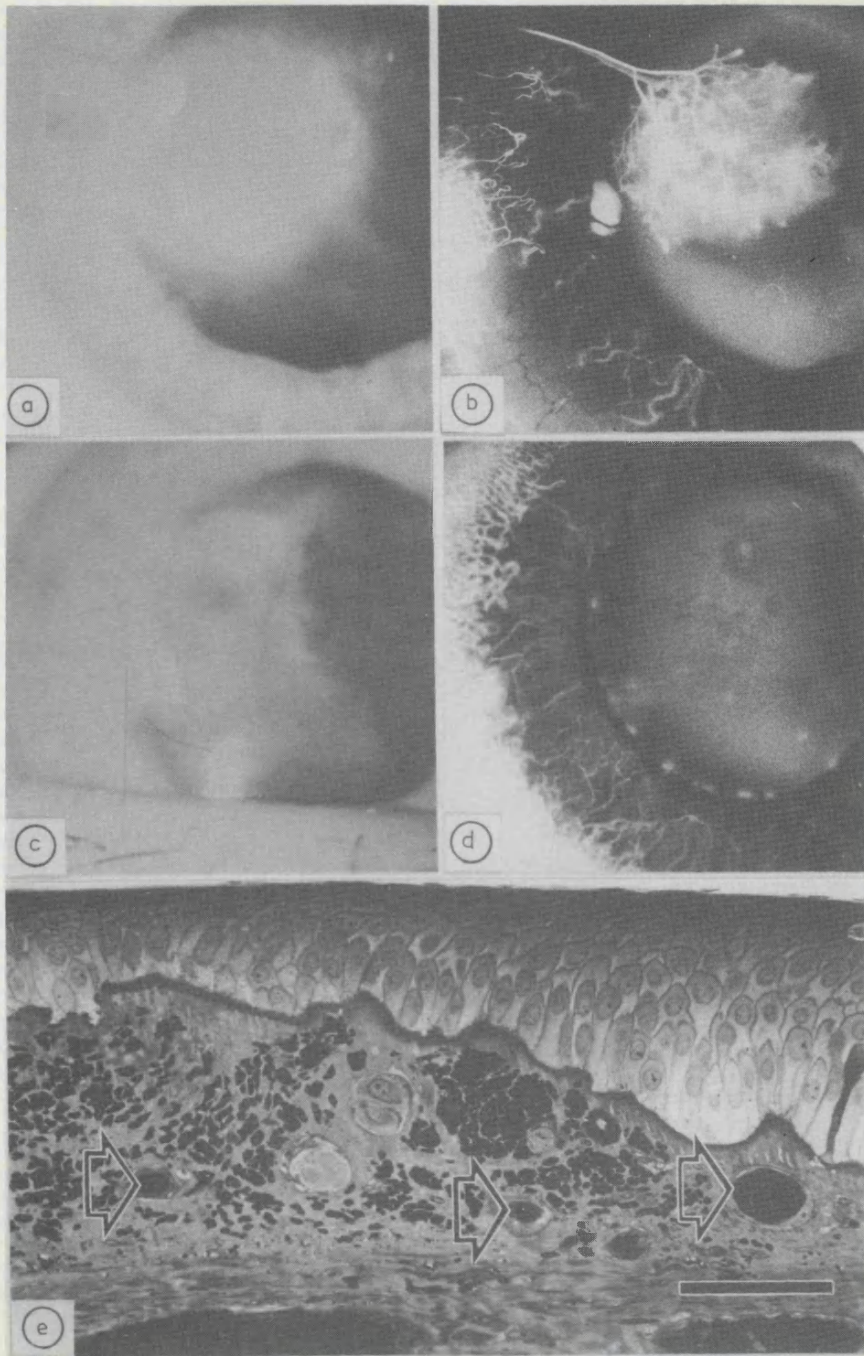


Fig. 2

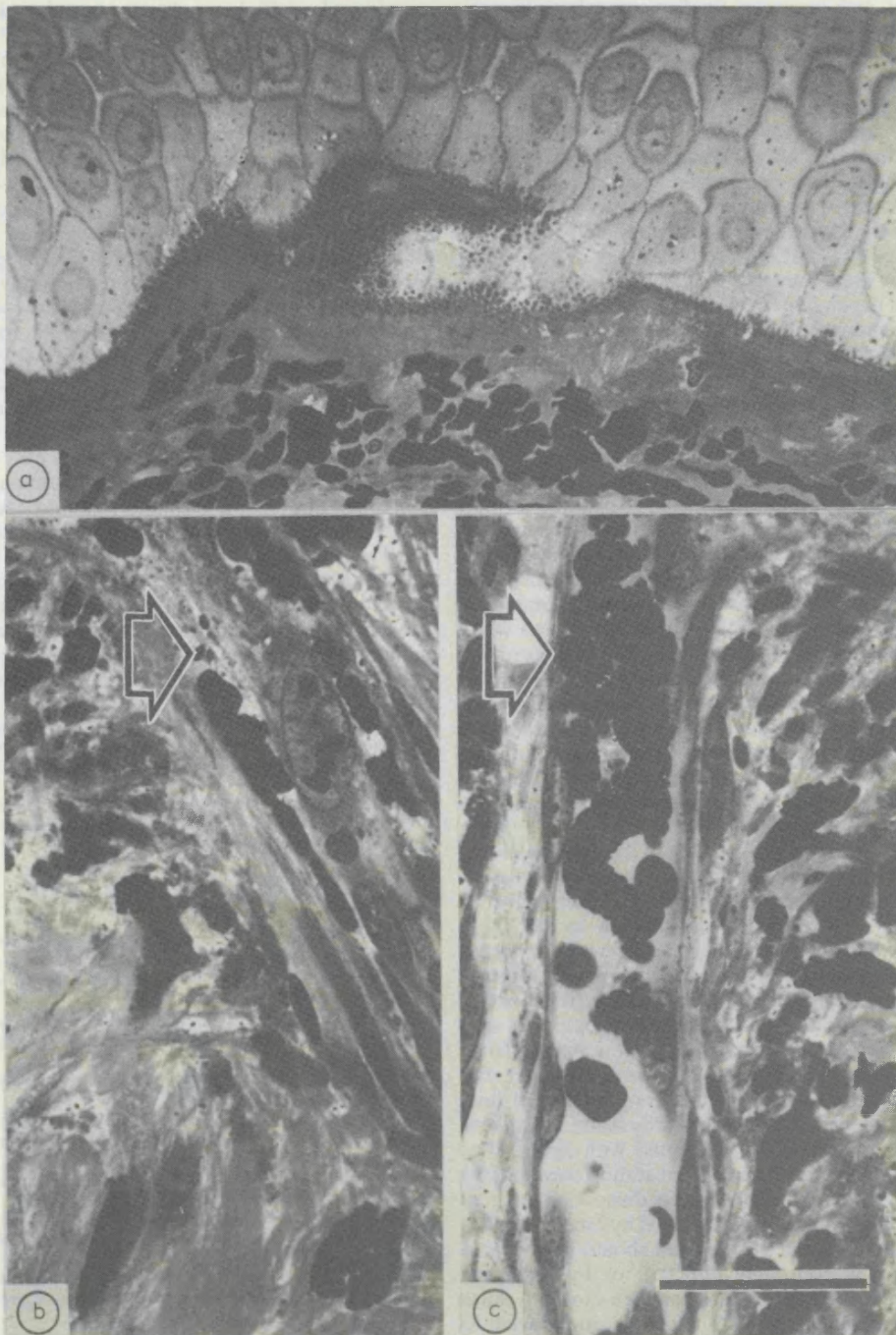


Fig. 3

of cases with improved Snellen's visual acuity many were subjectively better and their symptoms of photophobia improved. It is also notable that a large number failed to progress, contrary to the normal natural history.

The mechanisms of laser-induced vascular occlusion are not fully understood, and elucidation of this problem was not an objective of the present investigation. However, in general our observations support the conclusions drawn from similar studies on argon laser irradiation of retinal vessels.¹⁸ In essence, whatever the secondary mechanisms of vessel closure, they are dependent upon absorption and degradation of laser energy by haemoglobin. The focal irradiance on the vessels must be high to deposit sufficient energy within them to achieve damaging thermal profiles at the vessel wall. Thus attempts to close capillaries with 120 μm spot size exposures were always unsuccessful, because the area absorbing was always too small a portion of the total area irradiated. Once sufficient energy had been deposited within an irradiated vessel to induce temporary blood stasis further coagulation became relatively easier, because the cooling effect of flowing blood was lost. However, we found in our study, as in previous investigations, capillaries remained patent in areas of irradiation even when extensive necrosis of the capillary wall had occurred. Moreover evidence of intracapillary thrombosis and true fibrin deposition was rare, while small haemorrhages were common. Until detailed investigations of thermally induced occlusive processes are undertaken to optimise the required effect such surgical procedures remain empirical and depend upon the experience of the surgeon.

We are clearly concerned about the complications. Corneal transmission of short argon lines of emission is poor; thus dissipation in the cornea may be harmful.¹⁹ The human iris appears to be fairly resilient, and the commonest side effect is a temporary rise in intraocular pressure, with minimal disturbance of the blood/aqueous barrier.²⁰ We found it important to suppress the postlaser inflammatory response with topical steroid and to continue a low maintenance dose to suppress reopening of vessels. However, the iris is so close to the lens that transmission of heat from iris tissue to the lens is readily made.²¹ The lens becomes progressively pigmented with aging; thus there is an increase in absorption at short wavelengths and a greater potential for the dissipation of heat here.²² The retina may be damaged by 2 means: either an accidental direct burn, which should not occur if the beam is accurately directed; or by repetitive exposure to blue light, which has been shown to cause damage in animal eyes.²³ The complications seem to be acceptable in the short-term barring the severe iris damage, but our follow-up had to be carefully super-

vised, and multiple applications and visits were necessary in the very vascular lesions.

We can make suggestions on improvements in the technique so that there is added safety. The first is to make a very short focal length to the treatment beam by introducing a convex lens in front of the mirror of the slit-lamp to cause a widely diverging beam to develop after the point of focus, thereby decreasing the irradiance at deeper tissues. (Recently a new contact lens has become available for better laser of lipid keratopathy. It is an Abraham lens, provided by Coherent Incorporated, UK. It is basically a scleral contact lens with an added strong convex lens cemented to its surface in one quadrant. It has an antireflective coating. The convex lens makes it possible to achieve a more convergent beam and thus avoid excessive iris damage. The contact lens also provides facilities for steadying the eye during treatment. We have found it extremely easy to use.) Secondly, the cornea, lens, iris, and retina absorb more light at short wavelengths; possibly it would be better to use a blue dye for delineating the vessels and a red laser to occlude them.

What is required now is a carefully controlled long-term study. We have started such an investigation with random allocation of cases to 3 groups: (a) has orally administered candicin; (b) has laser treatment only; and (c) has combined candicin and laser treatment.

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LASERING OF LIPID KERATOPATHY

BY

R. J. MARSH

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Lasering of Lipid Keratopathy

R. J. MARSH

Western Ophthalmic Hospital and Department of Clinical Ophthalmology Moorfields Eye Hospital, City Road, London

Summary

A series of 41 patients with varying types and degrees of lipid keratopathy was examined and then treated with the Argon laser. This was done primarily in an attempt to prevent extension of lipid keratopathy, but secondarily to see if any clearing of lipid would occur. The results were encouraging and although the visual acuity was not improved in the majority of patients, the symptoms were alleviated in a significant number. Iris atrophy was very common as a treatment, although the incidence was lowered by the use of the Abraham contact lens. Two cases of severe corneal thinning were encountered 6 months after laser application, but both responded well to corneal grafting.

Lipid keratopathy poses a difficult problem in management for the ophthalmologist. The term was first coined by Cogan for the clinical picture resulting from the appearance of fat in an area of previous corneal vascularization (Cogan, 1960). In most cases vascularization is the legacy of some previous disease and the lipid may occur many years after the original disease or may develop suddenly unassociated with reactivation of the original lesion. Lipid may be deposited as a result of an excess of lipids in the blood, failure in fat metabolism, and a defect in cell processing of lipid within the cornea. Cogan suggested that fat is not usually deposited because the substrates in the blood are usually in a bound form and therefore not available to the corneal cells, but if the blood is overloaded with lipids, free fatty acids may become available for lipogenesis (Cogan, 1960). Like other cells in the body, corneal cells have the ability to form fat when exposed to specific substrates, an enzymic process requiring the presence of serum and suitable fatty acids (Duke-Elder, 1965). The presence of fat in the cornea results in further vascularization stimulated by a foreign body type of reaction. Very rarely fat is deposited in a normal looking cornea with or without normal blood lipids and this is termed a primary fatty degeneration (Conway and Loewenstein, 1943). It is probable that fat is initially intracellular, but when necrosis occurs it becomes extracellular. The main accumulations of fat are in the middle layers of the stroma when the lamellae show necrotic changes and vacuolation with rich deposits of fatty droplets and needle-like crystals in between them (Davidson, 1947). There is also an infiltration of large mononuclear histiocytes undergoing foamy degeneration, the cytoplasm being packed with fatty granules.

Although neutral fat is present, the greater part of the deposition belongs to the cholesterol fatty acid group. The older the lesion the more prominent are the crystalline elements and the fewer the histiocytic cells. In the oldest cases degeneration becomes more complete with the appearance of fibrous tissue and calcification (Duke-Elder, 1965). Morphologically, in the vascularized area, white plaque appears, the nature of which varies with the degree of vascularization and the state of the cornea. Thus, when the vascularization is confined to a localized area in a compact cornea, the deposition tends to adopt a disc-like shape; when the cornea is swollen the deposition takes on a fan-like shape radiating from the ends of the vessels, and in the presence of widespread vascularization the fatty changes are likewise diffuse.

Clearly it would seem logical in the treatment of vascularized lipid keratopathy to attempt to control any increase in blood lipids, the corneal disease precipitating it, and to close the feeder vessels. The first approach has proved disappointing, for despite the possible relationship with fatty change in hypercholesterolaemia there has been no evidence of diet improving the condition. The second approach has been better with the careful treatment of herpes simplex and zoster with steroids and antivirals (the commonest diseases associated with lipid keratopathy). The third approach has been tried by various techniques, including peritomy, severing or cautery of the vessels at the limbus, B-radiation (Lederman, 1952; Michaelson and Schreiber, 1955; Ainslie, Snelling, and Ellis, 1962), thiotepa (Langham, 1960), and cryotherapy (Mayer, 1967). Of all these B-radiation, thiotepa and topical steroids proved the most effective (Ey, Hughes, Bloome, and Tallman, 1968). More recently the laser presented itself as a very accurate instrument for occluding these vessels and some encouraging reports have been made for improving or halting the course of the keratopathy (Cherry, Faulkner, Shaver, Wise and Witter, 1973;

Address for reprints: R. J. Marsh, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1

Read, Fromer, and Klintworth, 1975; Cherry and Garner, 1979; Marsh and Marshall, 1982). The following are my up-to-date findings.

Patients and methods

Patients were referred from several centres to the Western Ophthalmic Hospital. A history was taken and a full ophthalmic examination carried out. The following were recorded: history and aetiology of keratitis, drug treatment, visual acuity, iris appearance, and lens clarity. The extent of density and vascularization of the deposits were drawn in a diagram. All were reassessed every 3 to 6 months and most patients were screened for systemic lipid abnormalities. Colour photographs were taken on the Zeiss photo slit lamp every 6 months at $\times 2$ magnification under identical conditions. A careful grading of these films was made of the density and extent of lipid deposits, density being recorded as mild, moderate, or severe, and extent expressed as a fraction of the total area of the cornea. Corneal fluorescein angiography with video (Marsh and Ford, 1978) was carried out on all patients before treatment and thereafter every 6 months to 1 year if indicated. From these films vascularization was scored as mild, moderate, or severe and a note was added on the size of the stem arising from the limbus. The vessels were drawn on the diagram based on the fluorescein appearance. We found the video tape particularly useful because it could be immediately and repeatedly replayed to identify the vascular filling pattern.

Before treatment with the laser, 1 per cent Amethocaine drops were instilled. An Abraham contact lens was inserted onto the eye which steadied and converged the laser beam more precisely on the corneal vessels. The patient was cautioned to be very still and to stare constantly at a fixation light. The laser used was an Argon Coherent Radiation 900 series. The aperture setting was 50 microns, although it was important to have the focusing of the laser checked at regular intervals so that the beam was properly focused. I used 0.1 sec. exposures which was the slowest speed possible consistent with comfort. I kept the illumination of the slit as low as possible and angled the delivery system so that the beam was directed away from the pupil to the periphery of the iris. In fact it was best to constrict the pupil with pilocarpine before treatment. The intensity necessary to occlude the blood column varied from 0.2 to

0.8 watts and again depended upon the state of repair of the machine. I began treatment by sealing the vessels on the scleral side of the limbus. I started with the veins and then any large arteries that were seen. Occlusion here tended to distend the corneal vessels and slow the blood flow through them. We then occluded the main veins just corneal to the limbus. These darkened and expanded with treatment and showed fragmentation of the blood column. They were progressively closed or blackened towards the centre of the cornea. After this the arterial flow had slowed considerably and they were more accessible to the laser. Treatment was applied until flow stopped altogether. I then tackled any remaining small vessels and found it best to treat them at cross-over points and then to fill in intermediate sections. Clearly I did not occlude vessels that overlay the pupil or where there was a danger of the laser beam causing retinal damage. With new cases I found it best to arrange three treatment sessions in a day because of the tendency of anastomotic channels to open up shortly after laser therapy. I usually started in the early morning, then mid-day, and lastly in mid-afternoon. Where there was profuse vascularization patients were brought back for treatment every 2 weeks, but as successful closure was achieved they returned every 3 months for assessment and if any vessels remained and flow was doubtful in them a repeat angiography was carried out. All treatments were carefully recorded as to the number of burns and their intensity. Efficacy of treatment was judged by improvement in visual acuity, reduction in density and extent of the lipid, disappearance of vascularization, and improvement in photophobia.

Results

41 patients were treated by Argon laser with a minimum follow-up period of 9 months (average 18 months, maximum 7 years). Using my previous morphological classification, the Table shows the distribution of patients by aetiology and shape of lipid deposition.

There was a diminution in the extent or density of the lipid in 14, no change in 5, and an increase in 6. There was a decrease in both modalities in 14 and an increase in 2. There was an improvement in Snellens visual acuity in 15, no change in 18 and a diminution in 8. Six patients showed an improvement of all modalities with more than 2 lines on the Snellen. These cases had a

Table Distribution of Associated aetiology of lipid keratopathy

Aetiology	Central Disciform	Eccentric Disciform	Marginal	Diffuse Interstitial	Diffuse Deep
HS	9	7	3	0	2
HZ	4	6	5	0	0
Rosacea	0	0	1	0	0
Trauma	1	0	0	0	0
Idiopathic	1	0	0	2	0

varying extent of the lipid, but a moderate density only, consisting of two central disciforms and one eccentric disciform due to herpes simplex and a central and eccentric disciform due to herpes Zoster. The last case was a diffuse interstitial keratitis from herpes simplex. There was significant vascular recurrence in 6 patients.

Complications

These could be classified into those occurring during lasering, soon afterwards, and late. During lasering, peaking of the pupil developed in ten patients and sixteen showed bleeding into the area of lipid. Most patients tolerated the treatment well, especially when the Abraham contact lens was used. The incidence of peaking of the pupil was also reduced by using this lens. The early complication that arose was iris atrophy which was present to some degree in all patients; the more laser was applied the more atrophy occurred. I found that the Abraham lens reduced significantly the amount of iris atrophy. Late complications included reactivation of keratitis and corneal thinning. All cases of reactivation responded well to a dose of Predsol drops three times a day with the exception of one patient who failed to take his therapy or to attend for regular follow-up. One patient developed very dense lipid deposition but had a very successful corneal graft. Two cases of dense central disciform keratopathy due to herpes zoster showed an initially good response to therapy, but 6 months later developed severe thinning in the very centre of the keratopathy leading to the formation of a descemetocoele. Both cases have been successfully grafted. Four cases of eccentric disciform keratitis due to herpes simplex showed excellent clearing of lipid at 6 months but marked thinning at the centre of the treated area. There was biomicroscopically no observable lens defect in any case (including one heavily treated case with a 6-year follow-up). Neither, as far as I am aware, was the retina damaged in any case, although it was difficult in some patients with dense opacities to obtain an adequate view of the fundus.

Discussion

The results of my earlier paper were confirmed in that I achieved some degree of success in reducing the extent and density of the keratopathies. Generally speaking the moderate and milder cases did best, although there were the odd surprises. Once again, apart from the small number of cases with improved visual acuity, many were subjectively better and symptoms of photophobia improved. It is also notable that a large number failed to progress contrary to the normal natural history, I was much impressed by the Abraham lens which was a great improvement on the original technique. Patients preferred the immobilization and protection it gave them. I am clearly concerned about the complications that occurred. With the Abraham lens there was certainly less iris damage although it still occurred. It was vital that close follow-up was made on all patients because reactivity of herpes occurred and patients had to be kept on topical steroids to suppress the inflammatory response. Thinning of the cornea may be dangerous. In cases of dense central disciform keratitis prompt corneal grafting was essential before this occurred, but that seen in the moderate eccentric disciforms was more worrying. So far none has formed a descemetocoele or increased in astigmatism but only time will tell. For the future we need better treatment of the precipitating keratitis to prevent development of the keratopathy, and better knowledge of lipid metabolism and the mechanism of local deposition of fat. Finally we need a controlled trial on laser treatment. At Moorfields we are now completing a controlled long-term study of three groups:

- (a) Orally administered Candicidin (a lipid thinning agent);
- (b) Laser treatment only
- (c) Combined candicidin and laser treatment.

I would like to thank Miss C. Smyth for secretarial assistance and Miss. S. Ford for photographic assistance.

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HEADLEY BROTHERS LTD
109 Kingsway London WC2B 6PX
and Ashford Kent

Correspondence

Acyclovir and steroids in herpes zoster keratouveitis

SIR. We read McGill and Chapman's article¹ with much interest. While we agree with them regarding steroid dependency of many of the inflammatory ocular complications of zoster with the attendant difficulty of withdrawal, and that there are significant complications of long term topical steroids, we would not agree to withholding these valuable drugs. In the Zoster Clinic carefully controlled topical steroids have been used successfully in the inflammatory complications of ophthalmic zoster for over 10 years.

During the last year acyclovir alone has been tried in a random selection of cases of varying severity. These were new, acute, and had not had ocular steroid or antiviral therapy prior to their first visit. Twenty-three cases in all were treated from a median of one week after the rash onset with the advocated dosage of acyclovir and followed up at regular and frequent intervals to a mean of 6 months. Twelve patients who did not differ significantly from the group as a whole in their age, follow-up period, or interval before treatment continued with inflammatory changes which necessitated introduction of topical steroid. Seven patients had no response at all in the initial 1-3 weeks of treatment, three having hypertensive uveitis, two episcleritis and raised ocular pressure, one sclerokeratitis, and one corneal oedema and uveitis. The five others deteriorated after three months, one with chronic uveitis and the other four with stromal keratitis and vascularisation. All 13 showed a prompt improvement when changed to steroid therapy (dexamethasone soluble 0.1% at the outset reducing to prednisolone 0.3%).

The literature on zoster before topical steroids were available describes much more severe complications than we see nowadays,² and we would urge ophthalmologists not to withhold steroids in the treatment of inflammatory zoster lesions. Clearly during therapy (1) the intraocular pressure must be monitored frequently; (2) when anaesthetic the cornea must be checked for ulceration; and (3) topical steroid should be withdrawn cautiously.

It remains to be seen if a combination of acyclovir and steroids is more effective than steroids alone, and this will require a properly controlled trial of unselected cases.

The Zoster Clinic,
Department of Clinical Ophthalmology,
Moorfields Eye Hospital,
City Road,
London EC1V 2PD

R. J. MARSH
M. COOPER

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Editorial: Herpes zoster ophthalmicus and AIDS

AIDS is a new disease, first described in 1981,¹ of obscure origin, most likely from Africa, which is rapidly establishing itself throughout the world. It has many parallels with the early days of syphilis in that it has allegedly been imported by travellers from a little-known continent, is mainly spread by sexual promiscuity, and is a multisystem disease that is untreatable, leading inexorably to insanity and death. The causative agent has been identified as a retrovirus now called HIV (formerly HTLV III). It was first described in a small group of young adult American male homosexuals with pneumocystis pneumonia and Kaposi's sarcoma, with a proclivity for opportunistic infections. The ophthalmologist tends to see the disease in its later stages, when the typical retinal changes of the opportunistic infections occur, namely cytomegalovirus, toxoplasmosis, candidiasis, and other fungal infections. Cotton-wool spots are perhaps the commonest manifestation and are probably due to early cytomegalovirus infection.² Sadly most patients die shortly after referral to the ophthalmologist despite vigorous efforts to treat their infections.

The number of patients with positive serology for HIV is expanding considerably in central Africa, and figures as high as 20% have been quoted on random testing.³ There has been some controversy over why this is so. Some say it is due to reusing contaminated needles and syringes in these communities,⁴ but the majority that it is due to heterosexual promiscuity.⁵

The disease has a very long incubation period of four years and more. Furthermore, many patients may show positive ELISA testing and be asymptomatic (pre-AIDS). It is not known what will happen to this group of patients. Some we know go on to persistent generalised lymphadenopathy and florid AIDS, but as for the rest time alone will tell. Very early cases of AIDS have been described as showing herpes simplex, herpes zoster, and tuberculosis.^{6,7}

Herpes zoster on the other hand is an old disease, well known in antiquity, and, although common in Western countries among older people, it has formerly been seen sporadically in Africa. Most herpes zoster occurs in healthy people, though a very small proportion of cases are in younger, immunocompromised patients (systemic zoster).⁸ In these cases the rash will often spread to the rest of the body, the pain and complications tend to be more severe, and the response to intravenous acyclovir is better.⁹

In this issue of the *BJO* a number of cases are reported of young apparently fit patients with herpes zoster ophthalmicus and positive ELISA tests for HIV. A further interesting finding is peripheral retinal perivasculitis and sheathing. Although this is well described pathologically in ophthalmic zoster, it is rarely seen clinically. The rash and ocular complications are described as more severe than usual in this group of patients, though it must be said that the group of patients compared against them were not in any way comparable. It must remain a matter of opinion, but it may be questioned whether the ocular complications were adequately treated with topical steroids.

The position of acyclovir, whether topically, orally, or intravenously in these patients, is rather unsure. It is difficult to achieve adequate safe therapeutic blood levels, and the drug is expensive, especially for routine use in the Third World.

While it is clearly neither practical nor appropriate to check for HIV in every patient with ophthalmic zoster under the age of 40, we must bear it in mind when examining vulnerable groups of patients in this country, namely, promiscuous homosexuals (and now heterosexuals) and intravenous drug abusers.

RJM

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Ophthalmic zoster: mucous plaque keratitis

R J MARSH AND M COOPER

From the Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD

SUMMARY Data taken from 1221 patients attending the Zoster Clinic of Moorfields Eye Hospital over the past 15 years were used to characterise the clinical appearance and behaviour of zoster mucous plaque keratitis (MPK). The typical greyish branching plaques are usually accompanied by a limbitis, stromal keratitis, or decrease in corneal sensation and are commonly associated with cataract, raised intraocular pressure, or corneal ulceration. MPK may begin at any time within two years of onset of the rash, but when it appears after three months there are more complications. Usually MPK settles within one month if appropriate treatment with topical steroids and acetylcysteine drops is given, but surgical intervention is sometimes required to control glaucoma or neuroparalytic keratitis or to remove cataracts. The results of surgery are surprisingly good.

Dendriiform corneal epithelial disturbances have long been recognised in ophthalmic zoster but only relatively recently described in the literature.¹⁻³ The collective term 'pseudodendrite' precludes a satisfactory classification of these disturbances, gives no indication of the nature of the lesion, and is unhelpful in their management.

There are two distinct entities. The first, acute epithelial microdendrites, occurs a few days after the rash and resolves rapidly without complications. Viable virus is recoverable from the lesions.¹ The second, mucous plaque keratitis, by contrast has no clear temporal relationship to the rash and is a chronic disorder which is commonly associated with severe ocular sequelae such as glaucoma, cataract, and neuroparalytic ulcers.^{4,5} Viable virus cannot be identified in the lesions.⁴ The white-grey plaque which characterises the keratitis is adherent to the surface epithelium, has sharply demarcated margins, and may be linear or branched. There are usually several, which vary in size, shape, position, and number day by day, with no preferential corneal site. They stain sparingly with alcian blue, moderately with fluorescein, and brilliantly with rose Bengal (Fig. 1). They are deposited on a diffusely thickened and abnormal epithelium. Their onset varies from one week to two years after the rash. They are usually accompanied by a limbitis, stromal keratitis, diminished corneal sensation, or iritis and may be preceded by an episcleritis, disciform keratitis, or

iritis. Debridement of the plaque leaves an intact but abnormal epithelium.

Mucous plaques also occur with filamentary keratitis, keratoconjunctivitis sicca, superior limbic keratitis, vernal keratitis, varicella keratitis,⁶ and rarely with herpes simplex.⁴ The aim of this study is to define the clinical behaviour of zoster mucous plaque keratitis, to emphasise the difference from herpes simplex keratitis, to plan logical management and to report that the complicating glaucoma, cataract, and neuroparalytic ulcers may be successfully treated surgically.

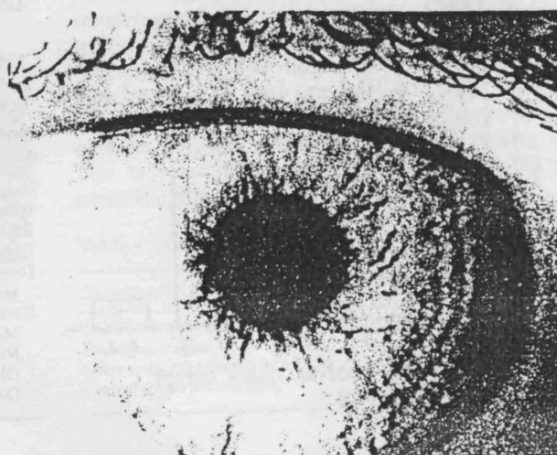


Fig. 1 Mucous plaques stained with rose Bengal.

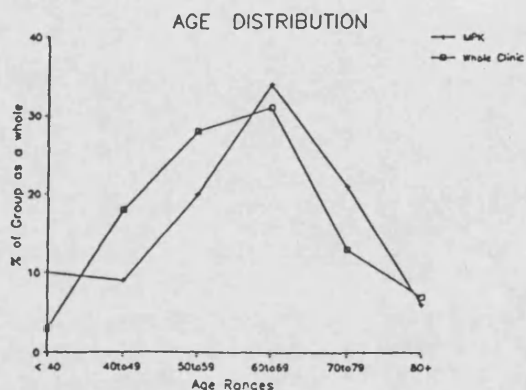


Fig. 2 Age distribution of MPK patients compared with that of the whole clinic.

Patients and methods

The data are derived from patients attending the Zoster Clinic at Moorfields Eye Hospital over the past 10 years, of whom the majority were primary referrals. Their follow-up has been regular and consistent over this period. Corneal sensitivity was measured with the aesthesiometer of Lunau and Coffignon in four peripheral sectors and centrally. The information was put on computer storage. 1030 patients (85%) had follow-up visits at least three-monthly over two years, and these form the study group. We compared the accompanying features of MPK with those of all ophthalmic zoster patients (with similar follow-up).

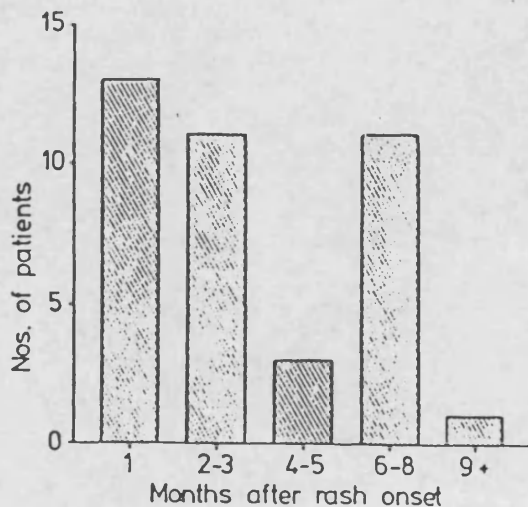


Fig. 3 Time of onset of MPK.

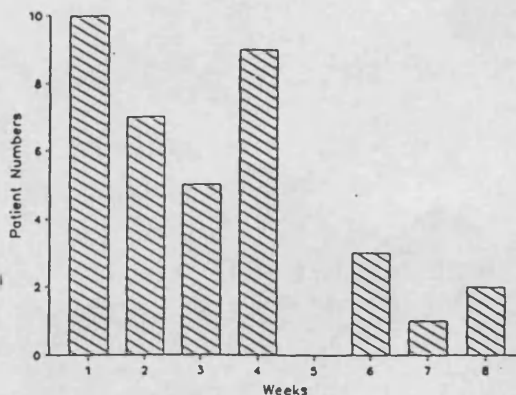


Fig. 4 Duration of MPK.

Results

Forty-seven (4%) cases of mucous plaque keratitis were found, of whom 39 had reliable follow-up data for two to 13 years (mean six years). Compared with the whole clinic population the patients with MPK were on average younger (Fig. 2). Fig. 3 shows the time of plaque onset in relation to the rash, the majority occurring within the first three or between six and seven months. Fig. 4 shows the duration of the plaque, which was usually less than one month.

Associated clinical features may be considered under the following headings: those preceding the onset of the plaque, those associated with it, and those subsequent to it.

There were no preceding features in 28%, but a complication distinguishing them from the rest of the clinic population was an increase in hypertensive iritis (Table 1; $p < 0.05$ by χ^2 test).

MPK is associated with a combination of episcleritis (usually perilimbal), iritis, superficial corneal stromal infiltration, and a decrease in corneal sensation, though none of these taken individually is more

Table 1 Incidence of associated clinical features occurring before and simultaneously with MPK. The incidence of these features in the clinic as a whole is shown in the last column

Category	Previous involvement	Coincident involvement	Overall clinic incidence
Iritis	22 (56%)	20 (51%)	50%
Raised IOP	16 (41%)	9 (23%)	14%
Episcleritis	12 (31%)	22 (56%)	59%
Diminished corneal sensation	14 (36%)	14 (36%)	33%
Keratitis			
Microdendrite	9 (28%)	0	20%
Nummular	13 (33%)	15 (38%)	49%
Disciform	7 (18%)	4 (10%)	12%
Oedema	7 (18%)	?	5%

Table 2 Incidence of clinical features following MPK

Category	Early plaque <3 months	Late plaque 3 months or more	Overall clinic incidence
Corneal stromal haze	16 (67%)	15 (100%)	?
Ulcers	2 (8%)	4 (27%)	4%
Diminished sensation	6 (25%)	9 (60%)	33%
Disciform keratitis	6 (25%)	5 (33%)	12%
Lipid keratopathy	4 (17%)	2 (13%)	5%
Lens opacities	10 (42%)	12 (80%)	12%
Refractory glaucoma	1 (4%)	5 (33%)	3%
Recurrence	6 (25%)	5 (33%)	4%

common in mucous plaque keratitis than in the clinic population as a whole (Table 1).

The sequelae can be split into two groups: one with plaque onset within the first three months and the other after this time. In Table 2 they are compared with the incidence of eye complications in the clinic population as a whole.

Table 2 indicates a generally more severe outcome in plaques of later onset except with respect to lipid keratopathy, disciform reactions, and uveitis. There is a greatly increased tendency to recur, a very frequent occurrence of diffuse anterior stromal haze, diminished corneal sensation, neuroparalytic ulceration, glaucoma, and cataract ($p < 0.05$ by χ^2 test). Only one case had a coincident herpes simplex infection. Two patients rapidly developed large interpalpebral ring-shaped subepithelial plaques with underlying stromal thinning (Fig. 5). These complications often led to visual loss (Table 3). Most of the morbidity was due to cataract and the remainder to various degrees of corneal scarring.

MANAGEMENT

The active keratitis was treated with topical steroid, the dosage being matched to the degree of inflamma-



Fig. 5 Ring-shaped subepithelial plaque.

Table 3 Numbers of patients with decreased Snellen visual acuity (lines)

Lines lost	No of patients
0	11
1	5
2	7
3	3
4	3
5	10

tion (we graded episcleritis, keratitis, and iritis on a scale of 0–6). We started with dexamethasone 0.1% eyedrops four-hourly and, as the condition ameliorated, reduced the frequency over two months by degrees to twice daily. If control was maintained, the drop was changed to betamethasone, but any later recurrence necessitated returning to dexamethasone immediately. Over the next six months we tried to substitute prednisolone 0.3% eyedrops three times a day. Most cases subsided after this period but required a maintenance dose for long term use because there was a pronounced tendency for relapse even after two years, especially on reducing treatment or even on stopping prednisolone drops 0.3% once daily. Acetylcysteine 10% eyedrops dissolved the plaques, and artificial tears helped maintain the precorneal tear film. Timolol eyedrops were successful in most cases in controlling raised intraocular pressure due to iritis and steroids. Topical iodoxuridine, adenine arabinoside, and trifluorothymidine made the epithelial problem worse, and acyclovir had no effect on this keratitis.

Two patients developed severe cataract and glaucoma which required surgical treatment. Neuroparalytic ulcers developed from one month to three years after MPK onset and were always treated with a lateral third tarsorrhaphy. Table 4 depicts the number of cases requiring surgery. In the three cases requiring glaucoma surgery it was successful in controlling intraocular pressure without antiglaucoma therapy, and the acuities of those patients who also had intraocular lens implants were 6/9. All cases required a booster dose of topical steroid over three months postoperatively because of relapsing iritis. The tarsorrhaphies were followed by healing of corneal epithelial ulcers within three days.

Table 4 Cases requiring surgery

Operation	No
Combined trabeculectomy + extraction + implant	2
Trabeculectomy	1
Laser trabeculoplasty	1
Lateral third tarsorrhaphy	5

Discussion

These results indicate that mucous plaque keratitis associated with herpes zoster ophthalmicus has a distinct clinical appearance and evolution. MPK is not difficult to diagnose if an adequate history is obtained. Although the appearance is superficially similar to that of herpes simplex, detailed examination of the morphology and of the staining characteristics will distinguish them. In our experience it is very rare to have coincident zoster and simplex. If there is doubt, a two-day intensive course of topical steroids will usually settle the inflammatory component of mucous plaque keratitis and obviously aggravate simplex dendrites. MPK is a self-limiting condition, but, while the inflammation may soon settle, the epithelium may take much longer to recover, especially if there is loss of corneal sensation or a degree of exposure.

At least two factors are likely to lead to MPK: altered corneal epithelium and disturbance of tear film mucus.⁷ Normal epithelium has mucous receptors primarily involved in the maintenance of the tear film. Alteration of these could reasonably lead to an accumulation of mucus, especially if the mucus derived from goblet cells is less soluble than usual. The entire corneal epithelium appears abnormal,³ as probably is the conjunctival epithelium. This may be due to infection, exposure, inflammatory mediators, and denervation with loss of 'trophic factors', all of which may lead to alterations in cell surface properties. The changing shape, size, and distribution would support the concept of a generalised abnormality that is quite different from the local lesions of acute herpes simplex keratitis, but more akin to those seen in keratoconjunctivitis sicca (although morphologically distinct). The subsequent diffuse stromal haze and decrease in corneal sensation would lend support to this hypothesis.

There are two groups: one with early onset (within the first three months of the rash) and the other with late onset. The latter group of patients have the more severe problems, such as cataract, raised intraocular pressure, and corneal ulceration. The high risk of recurrence may necessitate repeated observations and prolonged topical steroids. Posterior subcapsular lens opacities can arise from both chronic iritis and long-term topical steroid, but steroid is not recog-

nised as giving rise to nuclear sclerosis. Raised intraocular pressure may be due to the necessarily intense and prolonged topical steroid treatment or a trabeculitis accompanying the iritis. An acute hypertensive uveitis will usually settle within a few days on thorough treatment with topical steroids, but if there is steroid-induced glaucoma the prednisolone is replaced by fluoromethalone and timolol eyedrops. With severe refractory glaucoma drainage surgery may be necessary. Continuing denervation of the cornea and conjunctiva leads to neuroparalytic keratitis and ulceration, which is compounded by steroids in the absence of a tarsorrhaphy. The circinate plaque deposits are distinct from those described in corneal infections.⁸

The results of surgery were good in this series. A booster dose of topical steroid is required post-operatively after all intraocular surgery for at least three months. Neuroparalytic ulcers were completely healed within a few days of tarsorrhaphy. Usually a temporal third was sufficient but occasionally a middle third was essential, and it was important to maintain the topical medication. Despite traditional reservations about intraocular surgery in patients with complicated ophthalmic zoster and the relatively small number of cases, we were pleasantly surprised by our encouraging results.

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A Controlled Trial of Intravenous Therapy With Adenine Arabinoside (Ara-A) in Ophthalmic Zoster

R.J. Marsh, R. Laird, A. Atkinson, A. McD. Steele, B.J. Jones, London

Key words. Ophthalmic zoster, ara-A

Schlüsselwörter. Zoster ophthalmicus, ara-A

Summary. A blind trial was carried out on the effect of intravenous Adenine Arabinoside 10 mg per kg for 7 days on ophthalmic zoster. Twenty-four patients were admitted to the study. Its effects were studied on healing of the rash, postherpetic neuralgia and the development of ocular complications. Patients were randomly allocated on three criteria (1) severity of the rash, (2) length of time they had suffered from the rash before treatment and (3) whether ocular complications were apparent at presentation.

More rapid resolution of mucus in the tear film was the only statistically significant finding in favour of Ara A. Clinically there appeared to be faster healing in the rash, quicker resolution of conjunctival hyperaemia, less likelihood of episcleritis and postponement of corneal sensitivity loss in those treated with Ara A. The treatment was well tolerated and no serious adverse effects were recorded.

Zusammenfassung. In einer „Blind-Studie“ untersuchten wir die Wirkung von Adeninarabinosid (10 mg/kg Körpergewicht i.v., Therapiedauer 10 Tage) bei 24 Patienten mit Zoster ophthalmicus. Beurteilungskriterien waren die Abheilung der Hauteffloreszenzen, das Verhalten einer post-zosterischen Neuralgie sowie die Entwicklung oculärer Komplikationen. Die Randomisierung erfolgte unter Berücksichtigung 1) der Ausbildung der Effloreszenzen, 2) der bereits verstrichenen Krankheitsdauer und 3) ob schon oculäre Beteiligung nachgewiesen werden konnte oder nicht.

Die einzige nachweisbare signifikante Wirkung von Ara-A war ein schnelleres Verschwinden des zähen Schleims in der Tränenflüssigkeit. Man hatte auch den Eindruck, daß die Effloreszenzen

schneller abheilten, die Konjunktivitis schneller abklang, eine Episcleritis weniger häufig war und die Reduktion der Hornhautsensibilität nicht ganz so stark ausgeprägt war, wenn Ara-A gegeben wurde. Dies war aber nicht signifikant. Die Behandlung wurde gut vertragen und ernsthafte Nebenwirkungen konnten wir nicht feststellen.

Introduction

Ophthalmic zoster is a viral disease leading to severe neurological and ocular complications, responsible for severe morbidity and persisting debility. About 10% of patients develop, later on in the disease, marked postherpetic neuralgia, corneal scarring or anterior segment necrosis. It would appear that these changes are primed in the acute phase of the disease, and develop fully in the convalescent phase. This being so, it would seem logical that they might be averted by control of the varicella/zoster virus replication at the very onset of the disease. Therefore, a systemic safe effective antiviral agent, easily crossing the blood/ganglion barrier, delivered at this time should be of enormous value in therapy.

Two antiviral agents have been used systemically in the past: Idoxuridine (IDU) and Cytosine arabinoside. The former has proved too toxic for systemic use, and the latter has had mixed reports of success, with the placebo proving more effective in therapy of systemic zoster in the most recent double-blind controlled trial [8]. Recently a new systemic antiviral agent, Adenine arabinoside, has been developed [1, 2] and has been reported to have few side effects [10]. It has proved effective against DNA viruses, including varicella and herpes simplex [3-7] and has favourable reports in the therapy of herpes zoster in the immunosuppressed [9].

In view of the large number of cases of herpes zoster passing through our hands, we decided to set up a clinical trial to decide on the effect of the drug in a presumed immunologically competent group.

Methods

All new patients presenting at Moorfields Eye Hospital, City Road, London, with moderate to severe ophthalmic zoster were invited to participate in the trial. We excluded those patients with a rash duration of over 14 days and those who were pregnant.

The objectives of the study were to assess the effect of intravenously administered Adenine arabinoside (Ara-A) at a dose of 10 mg/kg per day over a seven-day period on the following features of ophthalmic zoster:

1. visual acuity
2. duration of cutaneous ulceration and degree of subsequent scarring
3. duration and intensity of post-herpetic neuralgia
4. scleritis/episcleritis
5. corneal sensation
6. keratitis
7. iritis and iris atrophy
8. glaucoma
9. external ocular motor palsy

The trial was designed as controlled and single-blind. Allocation to treatment groups was by stratified randomisation with the object of making the treated and control groups comparable in terms of the following three variables:

1. time of presentation after onset
 - a. 1-3 days
 - b. 4-7 days
 - c. 8-10 days
 - d. 11-14 days
2. severity of rash
 - a. mild vesicular
 - b. severe vesicular
 - c. haemorrhagic
3. distribution of rash
 - a. ocular involvement
 - b. no ocular involvement

Comparability in respect of other variables, such as age, sex and presence or severity of other clinical features, had to depend on random factors.

We felt the experiment could not be made double-blind because it would have been

ethically not permissible to have administered large volumes of intravenous fluid each day for a week to patients in the control group.

The result of random allocation of treatment was communicated only to the house surgeons (interns) who were to administer it in the mornings. The authors examined the patients in the afternoon when the infusion had been removed. In so far as this device was successful in keeping the authors ignorant of the treatment group, the trial could be called single blind.

On admission to the trial, a full medical and ophthalmic history and examination were carried out. We documented the phase of the rash as vesicular, pustular or crusty. Its severity was scored as nil (0), mild (1), moderate (2), severe with haemorrhages (3), and the oedema as nil (0), mild (1), ipsilateral (2), or bilateral palpebral fissure narrowing (3). Its distribution was noted as nasociliary, lid margin or neither. The degree of pigmentation and pitting with regard to scarring were recorded in four grades from nought to three. Other features were similarly scored at every examination. These included the degree of oedema, the bulbar and tarsal conjunctival hyperaemia, episcleritis/scleritis, corneal tear film mucus, the severity of corneal epithelial stromal lesion and iritis. Other features to be included were the corneal sensitivity (assessed centrally, and in four quadrants, using the aesthesiometer of Cochet and Bonnet). The degree of iris atrophy was marked as absent, small chinks, sphincter atrophy, and massive atrophy. The pupil reaction was recorded and the applanation. The fundi were examined and the external ocular movements assessed. Neuralgia was scored in five degrees as absent, mild, moderate, severe and very severe. Finally, any adverse reactions were recorded. Observations were to be made and recorded three times during the 1st week, twice in the 2nd and once each in the 3rd and 4th weeks, and again during the 3rd and 6th months.

A number of special investigations were carried out including photographs of full face, side face and close-up of the lids, blood analyses, and chest X-ray. To avoid unnecessary repetition, a copy of the check-list is attached.

All patients were treated with Neocortef ointment three times daily to the affected areas of skin, Terra-Cortril spray to the scalp

and Distalgesic tablets to provide analgesia as required. Steroid, mydriatic and antibiotic drops were used as indicated by previous experience with ophthalmic zoster.

The 200 mg/ml drug suspension as supplied was diluted 500-fold in Dextrose saline for intravenous infusion, warmed so as to aid solution and administered once daily intravenously in sufficient volume to provide 10 mg/kg of body weight, i.e. 25 ml/kg. Treatment was continued in the absence of adverse affects for 7 consecutive days.

Each patient was shown a written statement setting out the design and objectives of the trial and invited to participate or not.

Results

Twenty-five patients were initially accepted for the trial on the basis of clinical criteria and allocated to the treatment group according to scheme for stratified randomisation. One patient, however, declined to sign the consent form and was therefore dropped. Another patient, after he had been allocated to a treat-

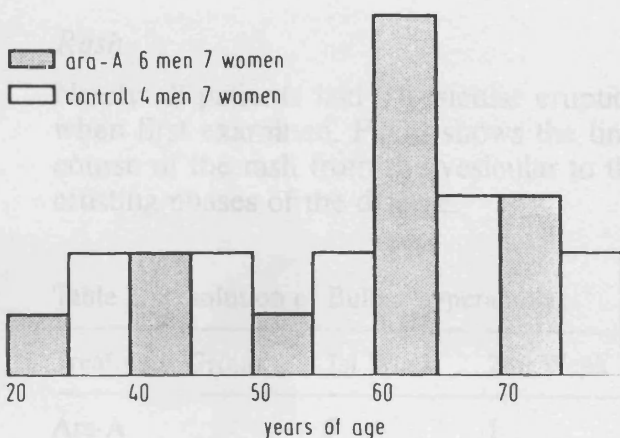
ment group, was found to be suffering from hypertension and left ventricular hypertrophy of sufficient severity to contra-indicate large volumes of intravenous fluid. This patient was therefore relegated to the control group.

Figure 1 shows the distribution of the patients to the treatment and control groups by age.

One patient in the control group had suffered zoster in another part of the body previously, one in the treatment group had suffered Crohn's disease 3 years before and another pulmonary tuberculosis 1 year previously.

Table 1 shows the distribution and severity of the variables upon which the stratification was based at the time of presentation.

This shows that the distribution between groups is as equal as it can be with such small numbers, except in the case of three patients who had mild vesicular zoster without ocular involvement 4 to 7 days before admission to the trial. All three were allocated to the Ara-A treatment group. These three patients were scrutinised to see whether the clinical course was such as to influence the outcome of the trial.



Deviation From the Protocol

Inevitably, dealing with out-patients for a 6 month period, there were some irregular intervals between assessments. Appointments were missed either due to patients forgetting, not wanting to come, or being physically unable to come. There was particularly poor attendance at the second visit during the 2nd week and precisely at the 6th month. The analysis therefore had to be adjusted such that the former was ignored and all observations during the 4th and 5th months were aggregated with month 6. One of the

Table 1. Stratified randomisation of patients to Ara-A and control groups

	Time of presentation				Severity			Ocular involvement	
	1-3 days	4-7 days	8-10 days	11-14 days	mild vesicular	sev. vesicular	haemor-rhagic	present	absent
Ara-A Group	4	9	0	0	8	5	0	10	3
Control Group	2	8	1		5	6	0	10	1

Death was caused by myocardial infarction which the patient had had a previous attack in 1973. The last assessment was carried out on the day of death.

Efficacy was judged on the basis of the following variables: changes in the visual acuity of the affected eye, rash duration, severity and oedema and scarring. Other variables included the incidence severity and duration of conjunctivitis, keratitis, corneal anaesthesia, iritis, glaucoma, optic neuritis, ocular motor palsies and post-herpetic neuralgia. The object of the trial was, of course, to determine the effect of Ara-A and not to record the natural history of the disease. Thus the patients in whom a given feature is absent throughout can provide no useful information, variables that are not influenced by the disease are valueless and similarly variables that are not influenced by the treatment. For these reasons it was unprofitable to pursue the analysis of many of the supposed indices of effect. Consequently, the rash and neuralgia were the key parameters in the sense that they were not only clinically important but likely to be demonstrably influenced by effective therapy.

Visual Acuity in the Affected Eye

No relevant effect was seen here.

Rash

Nearly all patients had a vesicular eruption when first examined. Fig. 2 shows the time course of the rash from the vesicular to the crusting phases of the disease.

pustules later than day 4. The earliest time at which no skin lesions were recorded was day 7. In the control group vesicles persisted in one patient until the fifth day of treatment and pustules in another until the seventh. The earliest time at which no skin lesions were recorded was day 14.

These results do seem to suggest that the rash cleared more quickly in the Ara-A treatment group.

No significant effect was found on the degree of severity of the rash. This may be explained by difficulty in estimating the degree of severity.

Oedema and Scarring

No real difference was found between the two groups.

Conjunctivitis

Tables 2 and 3 show the effect on tarsal and bulbar conjunctivitis. There was a suggestion of more rapid resolution in the Ara-A group: five members of which achieved a sustained zero rating during the first 7 days compared with only one in the control group.

Episcleritis/Scleritis

There was no difference between the two groups.

Cornea

There was less mucus in the tear film in the

Table 2. Resolution of Bulbar hyperaemia

Treatment Group	1st Week	2nd Week	3rd Week	4th Week	5th Week	Over 14
Ara-A	5	1	2	1	0	3
Control	0	3	1	3	1	3

Table 3. Resolution of Tarsal hyperaemia

Treatment Group	1st Week	2nd Week	3rd Week	4th Week	5th Week	6th Week	Over 14
Ara-A	2	3	0	1	0	2	3
Control	0	0	1	4	0	0	5

Table 4. Resolution of precorneal mucus film

Treatment Group	1st Week	2nd Week	3rd Week	4th Week	5th Week	6-14th	Over 14
Ara-A	2	3	0	1	0	2	3
Control	0	0	1	4	0	0	5

Ara-A group and Table 4 shows when a sustained zero rating was reached.

Corneal Sensation

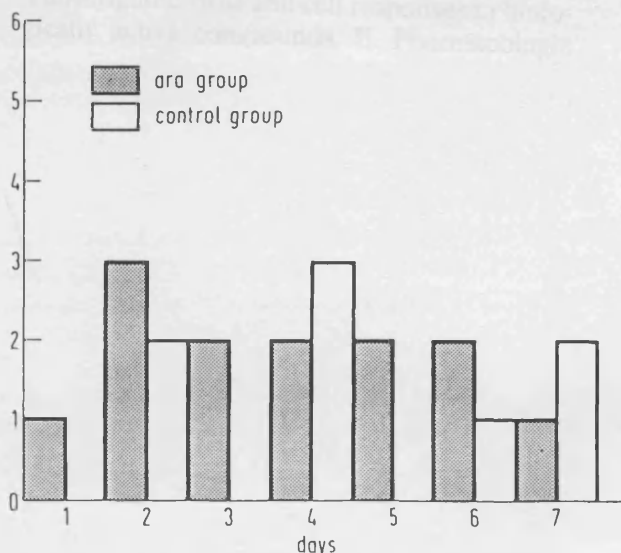
A suggestion that Ara-A can delay the development of sensory loss even though there is no evidence that it can prevent it.

Iritis, Intra-ocular Lesions, Optic Disc, Retina and Neuralgia

There is nothing to suggest an effect of treatment.

Adverse Experiences

Five patients of the Ara-A group and four of the control group experienced adverse symptoms. The symptoms occurring in the former can be divided into those occurring during treatment with Ara-A and those occurring subsequently. The former occurred in four patients including one syncope and emesis of moderate severity on day 1, one moderate left-sided hearing loss on day 3, one headache of unspecified severity on day 4 and one case of mild nausea and vomiting on day 1 followed by mild nausea on day 2. The only severe



“adverse” experience was the nausea and vomiting that affected one patient on days 12 and 13 (5 days after the last administration of Ara-A).

Clinical Laboratory Determinations

Unfortunately a significant number of results were unavailable or wrong, due to difficulties in handling blood samples. So far as they go there was no evidence of drug related toxicity.

Discussion

It was disappointing that neither the severity nor the duration of neuralgia was demonstrably diminished by the administration of Ara-A. This may well mean that intra-neural virus is inaccessible to the drug and that would be consistent with the observation of some other workers: that localised zoster responds less favourably to treatment with Ara-A than varicella and disseminated zoster. The presence of a number of differences between the treated and control groups that seem to suggest a favourable influence of Ara-A without reaching an acceptable level of statistical significance may suggest either that a larger group of patients should be treated or that a larger dose of the drug should be given.

Of the twenty variables analysed only one has shown a statistically significant difference between treated and control groups, i.e. resolution of precorneal mucus. This could easily occur by chance.

The balance of the evidence is in favour of more rapid healing of the rash, quicker resolution of conjunctival hyperaemia, less likelihood of scleritis and episcleritis developing, postponement of corneal sensitivity loss, quicker healing of corneal epithelial lesions and less likelihood of increased intra-ocular pressure.

The treatment was well tolerated and no serious adverse effects were recorded.

Table 5. ARA-A Zoster trial moorfields eye hospital (check sheet)

Name	Hosp. No.										Trial No.	
Day of Observation	Pre Treat	Day 2	4	6	7	9	13	21	28	3 months	6 months	
Date												
History	x											
Ophth. Exam	x	x	x	x	x	x	x	x	x	x	x	
Photos	x	x	x	x		x						
Urinalysis	x	x	x	x	x							
Hb. W.B.Cs. ESR film	x				x						x	
L.F. Ts 'strip												
Enzymes cholestrol	x					x						
Blood sugar												
Adverse effects	x	x	x	x	x	x	x	x	x	x	x	

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A Double-Blind Controlled Trial of Therapy With Levamisole in Ophthalmic Zoster

R.J. Marsh, L. Olsen, R. Weatherhead, B.R. Jones, London

Key words. Ophthalmic zoster, levamisole

Schlüsselwörter. Zoster ophthalmicus, Levamisol

Summary. A double-blind controlled study was carried out to determine the effect on ophthalmic zoster of Levamisole at a dose of 150 mg for 3 days a week over a 6 month period. The same criteria were judged as for the Ara-A trial. Fifty-two patients were admitted to the trial of which 15 had to be excluded from the analysis. The only statistically significant finding in favour of Levamisole was more rapid resolution of mucus in the tear film. There was less rapid healing of the rash in the Levamisole patients than those taking the placebo. A significant number of adverse reactions were noted in both groups.

Zusammenfassung. In einer „Doppelblind-Studie“ untersuchten wir den Einfluß von Levamisol auf den Verlauf eines Zoster ophthalmicus. Die Dosierung war 150 mg an drei Tagen pro Woche über einen Zeitraum von 6 Monaten. Der Beurteilung lagen die gleichen Kriterien zugrunde wie in der Ara-A Studie (S. 449ff). Von 52 initial teilnehmenden Patienten konnten schließlich 37 ausgewertet werden. Die einzige statistisch belegbare Levamisol-Wirkung war das schnellere Verschwinden des zähen Schleims aus der Tränenflüssigkeit. Die Effloreszenzen verschwanden bei den Levamisol-Patienten sogar weniger schnell als bei den Placebo-Behandelten. In beiden Therapiegruppen wurde eine größere Anzahl von „Nebenwirkungen“ festgestellt.

Introduction

For some time there has been a distinct clinical impression that many patients developing

zoster, especially the elderly, have impaired immunity. Certainly patients suffering from zoster with systemic spread of the rash have a high incidence of reticuloses, neoplasms and immunosuppression [3]. Unfortunately proof of impaired immunity is rarely obtained prior to the development of the disease. After the rash resolves many of the ophthalmic zoster patients develop chronic and relapsing ocular complications with features suggestive of defective immunity. However, there seems to be no difference between the neutralising antibody response of these patients and those without ocular complications. The only hint of scientific evidence for defective immunity in uncomplicated zoster is a defect detected in the monocytes during the acute phase of the disease [5]. Assuming a basis of defective delayed immunity it would be worthwhile assessing a drug that would reinforce it. Levamisole presents itself as such a drug [4].

It has been shown to have an immunopotentiating effect following the observation that cows receiving Levamisole developed enhanced immunity for suboptimal brucella vaccine. The effect principally occurs when existing host defence mechanisms are impaired. Levamisole particularly restores T cell and macrophage function (especially to antigen previously encountered), but has little effect on the B cell humoral antibody system. There was a large body of clinical evidence which suggested that the immunopotentiating effect of Levamisole may have been of benefit in chronic persistent infections and a report confirmed this in chronic upper respiratory tract infections in children [6].

Methods

All new patients presenting at Moorfields Eye

We excluded those patients with a rash duration of over 10 days and those who were pregnant.

The objectives of the study were to assess the effect of orally administered Levamisole at a dose of 150 mgm. daily for 3 days a week over a 6 month period on the following features of ophthalmic zoster:

1. Visual acuity
2. Duration of cutaneous ulceration and degree of subsequent scarring
3. Duration and intensity of post herpetic neuralgia
4. Scleritis/episcleritis
5. Corneal sensation
6. Keratitis
7. Iritis and iris atrophy
8. Glaucoma
9. External ocular motor palsy

The trial was designed as controlled and double-blind. Allocation to treatment groups was by stratified randomisation with the object of making the treatment and control groups comparable in terms of the following variables.

1. Time of presentation after onset:
 - a. 1- 3 days
 - b. 4- 7 days
 - c. 8-10 days
2. Severity of rash:
 - a. mild vesicular
 - b. moderate vesicular
 - c. severe vesicular
3. Significant ocular involvement at presentation:
 - a. present
 - b. absent

Comparability in respect of other variables, such as age, sex and presence or severity of other clinical features had to depend on random factors.

The result of random allocation of treatment was revealed to the pharmacist who accordingly dispensed Levamisole or placebo tablets to the patients.

On admission to the trial the same history, examination and documentation were carried out as for the Ara-A trial. Observations were made at the same intervals. The same special investigations were carried out with the addition of blood examinations at weeks 2, 3 & 4 and months 3 & 6. Adverse reactions were carefully recorded.

The Levamisole and placebo tablets were given at a dose of 150 mgm. daily for 3 days a week for 6 months in the absence of adverse affects. Each patient was shown a written statement setting out the design and objectives of the trial and invited to participate or not.

Results

Fifty-two patients presented to the trial. Fifteen patients were excluded from the analysis, 3 of which failed to take their tablets reliably, 3 failed to keep an adequate number of follow-up appointments and 9 had toxic side effects preventing them from completing the trial. This left 37 patients for the analysis. Figure 1 shows the distribution of patients to the treatment and control groups by age. Three patients in the placebo group had suffered general disease including one case of hypertension, one of diabetes mellitus and one had had a rodent ulcer.

Five patients in the Levamisole group had suffered general disease. One had diabetes mellitus, one tuberculosis twenty years previously, two had bronchitis and congestive heart failure and one had thyroid disease.

Table 1 shows the distribution and severity of the variables upon which the stratification was based at the time of presentation. Only global totals are given for stratified randomisation. Eighteen combinations were possible but statistically there were too few patients in the study to merit detailed stratifi-

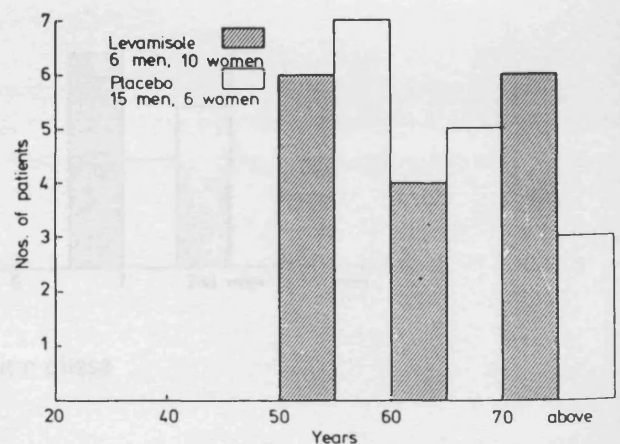


Fig. 1. The distribution of patients to treatment and control groups by age

Table 1. Stratified randomisation

	Time of presentation (in days)			Severity of rash			Ocular involvement	
	1-3	4-7	8-10	Mild	Moderate	Severe	Present	Absent
Levamisole	2	11	3	2	12	2	13	3
Placebo	2	16	3	5	11	4	16	2

cation and this report concerned itself with global totals and not individual strata levels.

Deviations From the Protocol

There were some irregular intervals between assessments as occurred in the Ara-A trial and for precisely the same reasons. However, no serious deviations from the protocol took place. Patient drop-outs and exclusions will be dealt with later on. Efficacy was judged on the same variables as for Ara-A with the same exclusions of clinically unimportant data.

Visual Acuity

No relevant effect was seen here.

Rash

Figure 2 shows the time course of the rash from the vesicular to crusting phases of the disease. This suggests a more rapid resolution

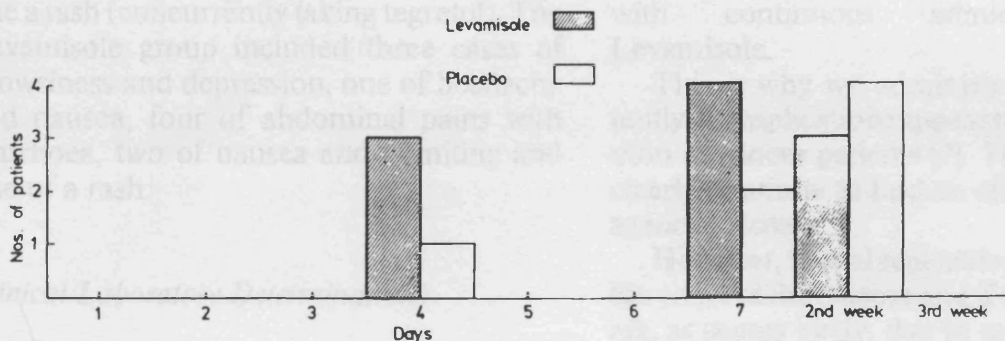
of the rash in the Placebo group than Levamisole. However, the nature of the data does not allow simple hypothesis testing and therefore no statistical significance is attached to speed of resolution.

Oedema and Scarring

No real difference was found between the two groups.

Conjunctivitis

Table 2 records the progress of tarsal hyperaemia and here there is a suggestion of more rapid resolution in the Levamisole group, four members of which achieved a sustained zero rating on or before day 7 compared with none in the Placebo group. There was no difference between the two groups as far as bulbar hyperaemia was concerned.

**Fig. 2.** Time course of rash from vesicular to crusting phase**Table 2.** Resolution of tarsal hyperaemia

Treatment Group	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Over 12
Levamisole	4	1	3	-	2	-	5
Placebo	-	3	3	-	3	1	9

Treatment Group	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Over 12
Levamisole	2	2	1	-	2	-	7
Placebo	-	-	4	2	-	-	7

Precorneal Mucus

Table 3 provides details of the mucus in the tear film. Omitting the patients who scored zero throughout and counting those from each group who achieved a sustained score of zero on or before day 14 a significant difference in favour of Levamisole appears.

Episcleritis/Scleritis, Keratitis, Corneal Sensation, Iritis and Iris Atrophy, Glaucoma and External Ocular Motor Balsy

There were no significant differences between the Levamisole and placebo treatment groups.

Adverse Experiences

The nine patients removed from the trial due to toxic effects included six on Levamisole and three on Placebo. Thirteen patients completing the trial had adverse reactions, five on Levamisole and eight on Placebo. The complications of those taking Placebo were three cases of nausea, three of neutropenia, one of parasthesia in legs and feet, one flu-like illness, one of vomiting, one of body pains and one a rash (concurrently taking tegretol). The Levamisole group included three cases of drowsiness and depression, one of headache and nausea, four of abdominal pains with diarrhoea, two of nausea and vomiting and one of a rash.

Clinical Laboratory Determinations

As mentioned above three patients on the placebo developed neutropenia. These were mild and in two cases sporadic. The third case developed at 1 month and was present at every subsequent month until the tablets were terminated at the 6th. There were no abnormalities in the Levamisole group.

Discussion

It was disappointing to see that Levamisole too had no effect on either the severity or duration of post-herpetic neuralgia. Like Ara-A it had a statistically significant action only on the resolution of mucus in the tear film and a clinically significant action on tarsal hyperaemia. Unlike Ara-A there was a more rapid healing of the rash in the placebo group.

Adverse reactions were of a significant number in both groups. It is difficult to explain all those occurring in the placebo group. Many of them were taking analgesics concurrently and many of the symptoms described may occur during the natural course of convalescent Ophthalmic zoster. The three cases of neutropenia were hard to explain although in severe zoster neutropenia and lymphopenia can occur naturally. The absence of this finding in the Levamisole group, however, might suggest some protective action exerted by this drug. Levamisole has well recognised complications including: nausea, gastric intolerance, central nervous stimulation, nervousness, irritability, insomnia, a 'flu-like syndrome, skin rashes and granulocytopenia [7]. A higher incidence of gastro intestinal discomfort, most pronounced in the first 3 months has been described with continuous administration of Levamisole.

This is why we administered it intermittently. Complications appear to be more common in cancer patients [2]. The search must clearly continue to find an effective antiviral agent in Zoster.

However, if viral replication is confined to the onset of the disease and if the later lesions are, as seems likely, due to immunologically mediated reactions not dependent on the presence of live virus, the results will not prove useful unless the drug is administered at the very onset of the disease [1]. Furthermore an effective anti-anergic drug would be complimentary in the successful treatment of Zoster.

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Ocular Surgery in Ophthalmic Zoster

R. J. MARSH and M. COOPER

London

Summary

Surgical outcome after ophthalmic zoster was analysed with respect to cataract, glaucoma, corneal ulceration and scarring. We used data from the Zoster Clinic and Hospital Activity Analysis (HAA) at Moorfields Eye Hospital and a lipid keratopathy database at the Western Ophthalmic Hospital.

Conventional surgery for cataract, glaucoma and corneal scarring gave good results which were probably no different from experience with routine cases, although there was a tendency for prolonged post-operative inflammation. Lateral and central tarsorrhaphy for neuroparalytic ulceration almost invariably led to rapid healing.

Many ophthalmologists are apprehensive about operating on eyes that have been affected by herpes zoster ophthalmicus because they fear perioperative and post-operative complications associated with inflammation. Therefore elective intraocular surgery tends to be avoided. A survey of the literature is disappointing with only small numbers of cases reported.^{1,2,7} The commonest complications requiring surgery are neuroparalytic ulcers, cataracts, glaucoma and corneal scars.^{1,2} Ulceration occurs in 6-8% of patients with neuroparalytic keratitis and in less than 3% with the chronic exposure type of keratitis.^{3,4} Cataracts may precede, be aggravated or precipitated by zoster and often complicate chronic iritis with iris atrophy. They can also be caused by long term use of potent topical steroids which may be necessary in the indolent ocular inflammations with zoster: They may be posterior subcapsular or nuclear.⁵ Glaucoma, too, may precede zoster but usually complicates disciform and mucous plaque keratitis. Occasionally the picture is complicated by topical steroid-induced

glaucoma.⁶ Corneal scarring follows a small number of nummular, disciform and sclerokeratitis, sometimes forming a vascularised lipid keratopathy⁶ but otherwise complicates neuroparalytic and exposure keratitis. Whilst ulceration or glaucoma may need surgery whatever the underlying causes, cataract or corneal grafts tend to be avoided because the contralateral eye is usually normal. Our data intended to help in evaluating the risks associated with such surgery.

In view of the large number of cases of ophthalmic zoster seen at Moorfields Eye Hospital we felt we had a unique opportunity to see if these fears for surgery were justified.

Patients and Methods

Case-finding was done by reference to the Zoster Clinic, the Hospital Activity Analysis (HAA) at Moorfields, and the lipid keratopathy database at the Western Ophthalmic Hospital. The Zoster Clinic was started in 1968 by Professor Barrie Jones. From 1973 accurate prospective records were kept and in 1985 these and all new patients details were

added to a computer data base. Up to now 1700 patients have been seen and 1243 records of those with regular follow-up computerised. The majority of primary and secondary referrals to Moorfields Eye Hospital pass through the Zoster Clinic. The HAA, the main in-patient diagnostic data base for Moorfields, was searched over the same period as the Zoster Clinic for cataract surgery, glaucoma surgery and corneal grafting associated with zoster. The data base of 85 patients with lipid keratopathy referred to the Western Ophthalmic Hospital, London for corneal angiography was searched for those with zoster who had been subsequently grafted. The records were extracted and scrutinised with relevant cases included in the series.

Tarsorrhaphies were temporal third as first choice and classified as carried out either within the first three months or subsequently. They were tabulated as follows:- the type of corneal problem, early or late tarsorrhaphy, central or temporal, the number of these carried out or expanded on an individual case, time for epithelial healing, late complications and if reopening was successful.

Cataract cases were tabulated according to age, date of zoster onset, acute complications, whether they had prezoster cataract, type of operation, pre- and postoperative visual acuity, length of postoperative follow up and finally a note on late complications.

Glaucoma cases were similarly tabulated with the addition of whether there was prezoster glaucoma, the pre- and postoperative intraocular pressures, and whether the patient was on or off glaucoma medication postoperatively.

Grafts were tabulated on a similar basis with the addition of whether the cornea was vascularised preoperatively and if there had been argon laser therapy to the feeder vessels.

It was not possible to carry out reliable statistical comparisons. We had a relatively small sample of cases and groups for comparison were very heterogeneous and virtually impossible to match. A search of the literature, too, yielded no satisfactory comparable surgical results in otherwise healthy eyes.

Results

Tarsorrhaphy: 45 patients were recorded on the computer of which 40 had adequate follow up. Eleven of these were carried out early and 29 late. Neuroparalytic ulcers were responsible for ten in the former and twenty in the latter, the rest were due to a combination of exposure keratitis, partial loss of sensation and chronic oedema. Thirteen patients had two or more procedures due to disintegration, premature opening and insufficiency of the tarsorrhaphy (six of these were temporals extended centrally). Accurate data on epithelial healing time was available in 29 cases of which 13 recovered within a week, ten within one to two weeks and six were over two weeks. Reopening was successful in five of 12 cases.

Cataracts: (Table I) Eighteen patients had cataract extractions of which eleven were extracapsular with posterior chamber intraocular lenses (one was a triple procedure), two were pure extracapsular and five intracapsular procedures. Accurate follow-up of more than one year was available in 17 cases. Thirteen patients achieved 6/12 or better corrected visual acuity, four did not because of pure corneal scarring in two, macular degeneration in one and a combination of both in one. Topical corticosteroids had to be increased and continued for a prolonged period in three cases because of relapsing iritis.

Glaucoma: (Table II) Twelve patients had glaucoma surgery of which nine were trabeculectomies (one was a triple procedure), one was argon laser trabeculoplasty, and two were peripheral iridectomies for complicating closed angle glaucoma (one occurring after a delay of a year). Accurate follow up for at least a year was achieved in eleven cases. The glaucoma was controlled in nine patients without medical therapy and the remaining two required hypotensive drops. The vision deteriorated in seven patients because of cataract in six and a vitreous haemorrhage in one. The latter occurred unaccountably two weeks postoperatively and had not cleared one year later.

Corneal Grafts: (Table III) Nine patients had corneal grafts of which six were pure perforating keratoplasties, two combined with extracapsular extraction with intraocular lens

Table I *Cataract extractions*

<i>Patient initials</i>	<i>Age</i>	<i>Zoster complications</i>	<i>Pre Zoster cataract?</i>	<i>Type of cataract operation</i>	<i>Post op va</i>	<i>Post op problems</i>
LW	35	disciform & iritis	—	E/C + 1OL	6/9	iritis
IW	83	disciform & iritis	—	E/C + 1OL	6/36	macular degeneration
RJ	41	iritis	—	E/C + 1OL	6/9	iris atrophy
RW	75	iritis	—	E/C + 1OL	6/9	
FM	63	iritis	—	E/C + 1OL	6/12	
JC	54	disciform & iritis	—	E/C + 1OL	6/9	iritis
CC	93	iritis	Yes	E/C + 1OL	6/12	
KL	56	disciform & iritis	—	E/C + 1OL	6/12	lipid keratopathy
IA	66	iritis	Yes	E/C + 1OL	6/6	
GM	73	iritis	Yes	E/C + 1OL	6/9	
CW	45	disciform & iritis MPK	—	Triple Proc	6/6	
AA	64	neuroparalytic keratitis	Yes	E/C	HM	descemetocele
RL	50	disciform & iritis MPK	—	E/C	6/6	iritis
HW	85	disciform & iritis	—	I/C	6/18	macular degeneration
TS	71	sclerokeratitis and iritis	—	I/C	6/24	corneal scar
LC	64	iritis	—	I/C	6/9	corneal scar
AB	65	neuroparalytic keratitis & iritis	—	I/C	6/9	

(equal distribution of sexes)

MPK = Mucous plaque keratitis

E/C = Extracapsular cataract extraction

I/C = Intracapsular cataract extraction

implantation and one was lamellar. Vessels were closed preoperatively with the laser in three cases. Accurate follow up for at least a year was achieved in eight patients. Corrected visual acuities of 6/12 or better were achieved in seven patients. The one neuroparalytic ulcer had perforated and was grafted with a generous lateral third tarsorrhaphy performed at the same time. This functioned well for four years but then decompensated probably due to the poor quality of the donor corneal endothelium.

Discussion

Bearing in mind the severity of the associated ocular disease these results were better than anticipated. Tarsorrhaphy led to rapid corneal epithelial healing, the visual results in the cataract and graft patients were excellent and the postoperative pressure control in the glaucoma cases was also good. Thus, apart from the need to increase topical steroids in a minority of patients for relapsing keratitis and iritis the surgical procedures were straightforward.

The rapid corneal epithelial healing

achieved by tarsorrhaphy facilitated safer topical steroid application for underlying iritis and keratitis and the patient needed to be seen less often. On reflection it may be better to intervene early because there seemed to be less subsequent scarring and fewer outpatient visits. However, our rate of tarsorrhaphies has been declining in the last two years and we felt that this was due to a more aggressive policy of using Blenderm tape to temporarily close the eye and to the use of Botulinu toxin A injection into the levator palpebrae to achieve a temporary complete ptosis.⁸

There were fewer cataract operations than we anticipated and we had the impression that this was due to reticence to operate rather than a lower incidence of cataract in zoster patients. Perhaps, too, many were unilateral cataracts and it appeared unnecessary to operate on most of them. Nevertheless intraocular implantation seemed particularly successful, in our highly selected group.

Along with some relapsing keratitis and iritis, cataract complicated a third of our trabeculectomies. There was a definite reluctance to remove these which we felt was not

Current management of ophthalmic zoster*

R. J. Marsh, FRCS

St Mary's Hospital, London W2 (Western Ophthalmic Hospital), Moorfields Eye Hospital, London

Abstract

Most ophthalmic zoster occurs in healthy people and ocular complications occur in 50%. The mainstay of ocular therapy is topical steroid, but careful follow-up and withdrawal are essential. The place of systemic steroid therapy and acyclovir in immunocompetent patients with zoster is uncertain.

Key words: Acyclovir, D.M.S.O., Flubiprophen, ophthalmic zoster.

Herpes zoster is an acute vesicular eruption caused by reactivation of varicella-zoster virus which is thought to remain latent in the dorsal root ganglion after the original varicella infection. The virus replication causes a slight viraemia but chiefly migrates centrifugally down the sensory nerve to the skin and, in the case of the trigeminal nerve, the eye, where it causes inflammatory changes. The stimulus to reactivation is largely unknown, but rarely it is caused by a local lesion involving the posterior root ganglia or depression of the immune system. The disease may occur at any age but is more common and severe after 50 years of age. The ophthalmic branch of the trigeminal nerve is involved in 7% to 17.5% of all cases of zoster^{1,2} and ocular complications occur in about 50% of cases.¹ It is a variable disease, ranging from trivial to devastating and inadequate management may lead to disastrous neuralgia, scarring, loss of the eye and even suicide.

Systemic involvement

Fortunately the vast majority of patients seen by

ophthalmologists are otherwise healthy, (an exception is those in centres specialising in tumours and immunosuppression); only 12 in 1000 of our cases had malignant disease.³ Thus a small number of patients attending eye clinics develop a systemic vesicular rash and severe illness one to two weeks after the disease onset. Most of these patients turn out to have reticuloses, other malignant tumours, diseases causing immunosuppression such as AIDS or are iatrogenically immunosuppressed.

Ocular complications

These fall primarily into those associated with inflammatory changes, those resulting from nerve damage, and those secondary to tissue scarring. Inflammatory changes may be direct as in dendritic, nummular, and disciform keratitis or indirect as a vasculitis in episcleritis/scleritis, iritis, ischaemic papillitis and orbital vasculitis. Those resulting from nerve damage include neuroparalytic keratitis, ocular motor palsies and neuralgia. Those subsequent to tissue scarring are lid deformities, neuralgia and lipid keratopathy. The course of the ocular disease falls into three phases: acute, chronic and relapsing. Adequate treatment delivered right at the start of the acute phase can significantly reduce severe late and chronic complications. The tendency for eye lesions to relapse even years later is a distinctive feature of the disease.

The objectives of treatment are twofold: to stop viral replication at the earliest opportunity and to control the ensuing inflammatory changes, thus preventing tissue scarring.

Investigations

All patients with systemic rash should be screened

Reprint requests: Mr R. J. Marsh, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD, England.

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by an oncologist or clinical immunologist for malignant disease and immunosuppression. Although most zoster in young patients is unassociated with systemic disease,⁴ if they are from an endemic AIDS community such as intravenous drug abusers⁵ or are from Central Africa⁶ this disease should be considered and HIV antibody testing carried out. Occasionally, the rashes of zoster and simplex can be confused^{7,8} which may lead to problems with the treatment of ocular complications; in such cases serum should be tested for viral antibodies or vesicle fluid should be cultured for virus. Zoster antibodies show an anamnestic rise which may persist for some months after the rash and herpes simplex grows readily in viral culture unlike varicella/zoster.

Systemic therapy

Admission

Patients with the acute disease are frequently elderly, infirm and live alone making it very difficult for them to treat themselves properly. Five-day admission to hospital where bed rest, nursing care, proper diet and administration of therapy can be ensured is very successful in obtaining rapid recovery. The patients should be barrier nursed in a side ward during the vesicular stage and people with no previous infection by varicella should be kept away until all vesicles have gone. After this they are no longer infective. Adequate home nursing must be provided if it is impossible to admit the patient to hospital.

Anti-inflammatory steroids

Although some physicians use systemic steroids routinely, claiming less zoster complications,⁹⁻¹¹ others stress the increased risk of systemic spread of the disease with high doses.^{12,13} I feel that systemic corticosteroids are indicated very early in patients with: large haemorrhagic skin bullae; progressive proptosis with total ophthalmoplegia; optic neuritis; and cerebral angiitis. These conditions are due to an occlusive vasculitis. Untreated, the first leads to severe skin scarring and neuralgia, the second to continuing diplopia, the third to severe optic atrophy and the fourth to hemiplegia. An initial oral dosage of 80 mg prednisone should be given, and this may be rapidly reduced by 10 mg per day to a 5 mg maintenance dose.

Non-steroidal anti-inflammatories

Flubiprophen 50 mg three times daily by mouth is

useful in cases of episcleritis, scleritis and sclerokeratitis. Although this drug alone is usually sufficient to control an episcleritis, with the latter two complications it must be used in combination with potent doses of topical ophthalmic steroids. The anti-inflammatory property of some analgesics is a useful adjunct.

Antivirals

Many antivirals have been tried in zoster, but most have been found ineffective or too toxic. Cytosine arabinoside proved less effective than placebo in a double-blind trial,¹⁴ and adenine arabinoside too insoluble to introduce intravenously in an effective dose without fluid overloading.¹⁵ Amantadine has been anecdotally claimed as effective,¹⁶ but there have been no adequate controlled studies to confirm this. Acyclovir, although not as effective in vitro against varicella/zoster as herpes simplex virus, has been extensively used and has proved effective in reducing the rash duration, spread and acute herpetic neuralgia in immunosuppressed patients.¹⁷ It has also been advocated for the treatment of varicella/zoster acute retinal necrosis.¹⁸ The drug is administered intravenously at 10 mg/kg over one hour, repeated every eight hours for seven days, then orally at 800 mg five times per day. The results in immunocompetent patients are controversial; although acute neuralgia and rash healing time are marginally improved,¹⁹⁻²¹ reports of its effects on incidence of postherpetic neuralgia and ocular complications are conflicting.²² Indeed to date there is only one reliable report about it reducing ocular complications.^{23,24} I feel that before large funds are used to finance use of the drug routinely in zoster, more clinical trials are essential.

Antibiotics

I think there is no place for routine antibiotic treatment in zoster. The acute oedema and crusting are due to viral-mediated damage rather than bacterial secondary infection.

Analgesia

Pain is notoriously difficult to treat, tends to be more severe with advancing age, and, in the majority of patients, is at its most severe within the first two weeks as acute neuralgia. Therefore, during this phase particularly, patients should be given sufficient drugs to suppress it. It is best to start with mild analgesics and build up to stronger as necessary. Table I displays useful analgesics arranged in ascending order of potency. Buprenor-

TABLE 1. Current management of ophthalmic zoster

Drug	Aspirin	Paracetamol	Distalgesic	DF118	Temgesic
			Paracetamol and Dextropropoxyphene Hydrochloride	Dihydrocodeine	Buprenorphine
Total dose per day	4 mg	4 mg	4 mg and 0.4 gm	120 mgm	0.6 mgm

(These doses are based on normal bodyweight; when outside normal limits, check the dose as regards to weight.)

phine tends to make patients feel drowsy and disorientated and is therefore best used at night only in the elderly, although if effective it can be tried as a half tablet during the daytime. I have found carbamazine 100 mg twice a day disappointing in the tic douloureux type of postherpetic neuralgia, but piriton 4 mg three times a day or chlorpromazine 25 mg three times a day have proved useful with severe irritational paraesthesia.

Antidepressants

Post-viral depression often occurs during the acute phase of zoster and may also be an important component of postherpetic neuralgia. It is important to treat it promptly and the tricyclic antidepressants such as amitriptyline (50 mg twice a day) are particularly useful.

Supportive therapy

Patients in the acute phase should be reassured that tissue swelling will rapidly subside and, in most cases, the pain improve. They should be warned that a long convalescence may be necessary. Those with severe chronic PHN should be offered counselling in an attempt to help them live with the pain.

Chickenpox vaccine

Two attenuated strains of varicella are undergoing clinical trials for vaccination.^{25,26} Their impact on the development and the course of zoster is conjectural; they may prevent patients developing zoster or a milder zoster may occur.

Skin treatment

Antivirals

Iodoxyuridine is soluble in dimethyl sulphoxide; preparations are available from 5% to 40% solutions (Iduridin or herpid). These can be applied as a paint or presoaked dressings during the acute vesicular phase and have been claimed to speed the onset of crusting, prevent secondary cropping and reduce acute and postherpetic neuralgia.²⁷⁻²⁹ Acyclovir 5%

ointment supplied three times a day has also had similar claims of efficacy.³⁰

Anti-inflammatories

Steroid creams and ointment are effective when the vesicular phase has passed. We use ung. neocortef, a combination of cortisone and neomycin, applying it three times a day to the skin and lids; the antibiotic is useful for preventing secondary infection in the crusts. The greasy nature of the preparation prevents aggregation of crusts and aids their separation. Patients presenting late with large crusts should have them bathed with warm sterile saline washes followed by ointment. Subcuticular injections of steroids, e.g. triamcinolone, have been tried in the acute and late phases of the neuralgia with mixed results.³¹

Massage

Energetic massage of the affected skin area using a vehicle of lanolin or vaseline can be most effective for neuralgia after crust separation. It is based on the gate theory of sensory neural conduction: stimulation of the large afferent nerves with touch inhibits the smaller pain fibre transmissions. More recently Capsaicin has been reported as an effective vehicle but the results are anecdotal^{32,33} and it is very irritant if it contacts the eye.

Management of postherpetic neuralgia

Postherpetic neuralgia has been defined as pain developing after the crusts separate; variously described as starting at four weeks, six weeks, two months and six months.³⁴ Like acute neuralgia it is worse in older patients. There is a vast spectrum of treatment for postherpetic neuralgia (many anecdotal and rather dubious) ranging from posterior pituitary extract to snake venom, clearly demonstrating the overall failure of treatments for this condition. The use of analgesics has already been described but it should be emphasised that the pain and paraesthesia of postherpetic neuralgia generally tend to be worse at night and are aggravated by heat and cold, wind and touch. These

provocations should be avoided where possible; failing that extra analgesia may be needed at these times. When analgesics and massage fail the following must be considered:

Physiotherapy can provide transcutaneous electrical nerve stimulation, short-wave diathermy and ultrasound which may help some patients.³⁴⁻³⁶

Pain clinics have an important part to play in refractory PHN. They can offer various treatments including subcutaneous injections of anaesthetics³⁷ and steroids, stellate ganglion block which is said to be most effective very early on.³⁸ They can provide the supportive counselling which helps patients live with their pain. Surgery is not recommended because it is often unsuccessful and may introduce other problems such as neurotrophic ulcer formation.

Ocular therapy

Antivirals

I feel that antivirals alone have no place in the treatment of the ocular complications of zoster, even though virus shedding occurs into the tear film and the corneal epithelium during acute keratoconjunctivitis. Despite early reports that acyclovir ointment controlled and prevented later ocular complications,³⁹ we have been unable to confirm this.⁴⁰ In fact, we have found that the early conjunctivitis and microdendritic keratitis are self-limiting and placebo drops seem to show the same result as acyclovir. Furthermore, in cases of chronic keratitis with unstable corneal epithelium most antivirals will further compromise it.

Antibiotics

Drops such as chloramphenicol may be used to prevent secondary infection during the acute stage when lid vesicles are discharging and forming crusts or a mucopurulent conjunctivitis is present. Tetracycline ointment should be applied twice daily to scarred or inflamed lid margins, since they become a focus for staphylococcal secondary infections.

Anti-inflammatories

The bulwark of therapy for the ocular complications of herpes zoster is corticosteroid which has to be used for most inflammatory lesions and is essential for: all scleritis; sclerokeratitis; disciform and mucous plaque keratitis; diffuse corneal oedema; significant iritis; and hypertensive iritis. At the first evidence of these 0.1% dexamethasone drops should be instilled every four hours. Prompt treatment at the start of inflammation cuts down the ischaemic

and fibrotic scarring that usually develops. Once control is achieved, the potency and frequency of administration can be reduced. The dose of topical steroids should be titrated against the degree of disease activity in the eye.⁴¹ This is a slow, cautious process and may extend over a period of years. As well as reducing the frequency of administration of the drug, serial logarithmic dilutions or a change to another weaker steroid may be made (e.g. from dexamethasone to betamethasone to prednisolone). Many of the more intelligent patients can titrate their own dose, which may be reduced to as little as 0.03% prednisolone once a day to maintain control.⁴¹

Precautions with topical steroid

The important essentials of steroid management are careful follow-up and examination to detect toxic side effects. Patients using topical steroids may develop glaucoma, cataract, secondary infections, mydriasis and ptosis. They also tend to develop a dependency on them and withdrawal may be difficult without causing a recurrence of ocular inflammation.⁴² Clearly if glaucoma is detected the dose of steroid must be reduced or substituted by clobetasone and fluoromethalone drops. However, in some patients it may be difficult to differentiate a steroid glaucoma from hypertensive iritis, particularly in mucous plaque keratitis, and a helpful technique is to increase the dose of steroid and review in two days. If the pressure decreases the steroid dose must be maintained at a higher level. Potent doses of steroid should be reduced as soon as possible to avoid inducing lens opacities, although in some cases it is impossible to know whether to attribute them to the chronic iritis. They must be used with great caution in patients with neurotrophic keratitis because of the risk of secondary infections. A mydriasis and ptosis can also be caused by zoster alone. Regular slit lamp examination and applanation are therefore essential when using steroids.

Artificial tears, wetting agents and mucolytics

These are used on unstable corneal epithelium in an attempt to stabilise the surface and prevent mucous deposition. We have found it best to try the different artificial tears empirically to find the most satisfactory and to add Lacrilube ointment. Ten per cent acetylcysteine may be used to dissolve mucous deposits and prevent further deposition particularly in mucous plaque keratitis. Lastly, it should not be forgotten that long-term drop administration can lead to toxic changes to the

epithelium from the preservatives which they contain. It is then essential to switch to preservative-free drops.

Special problems in ocular management

Acute microdendritic keratitis

This is transient and self-limiting, requiring no specific topical treatment.

Nummular keratitis

This varies in behaviour: it may be self-limiting and will recover without treatment, or chronic with oedema and infiltrate leading to corneal scarring. This is characterised either by primary lipid deposition associated with facet formation or a secondary lipid keratopathy with vascularisation. The chronic inflammation should be treated with long-term topical steroid to control the inflammation and vascularisation so as to prevent scarring and lipid deposition.

Disciform keratitis

This may be central or eccentric. It usually starts at three weeks and should be treated with intensive topical steroid, but unlike herpes simplex it does not require cover with an antiviral.⁴³ When treated at an early stage it responds rapidly to steroid, but when this is delayed may be refractory for a month or more.

Mucous plaque keratitis

This can develop insidiously in the first three months or precipitously after that. The aetiology is obscure but a preceding disciform or nummular keratitis that has been treated with topical steroid is common and may indeed prime the condition. Topical steroids are necessary to control the inflammatory features and mucolytics such as acetylcysteine 10% to dissolve the mucous plaques. A common error is to misdiagnose these lesions as herpes simplex dendrites and treat them with topical antivirals and stop the steroid which aggravate the keratitis.⁴³ When the condition remains indolent secondary glaucoma is common.

Acute corneal oedema

This is rare and tends to occur at the start of the disease. It is characterised by very fine deposits on the endothelial layer. Like disciform keratitis, it may take some time to clear when intensive topical steroids are given late.

Iritis

This frequently causes elevation of intraocular pressure; this is true even with low-grade anterior uveitis. Fortunately steroid therapy alone usually controls this within a few days. Although this complication generally occurs at the onset of the disease, it may constitute a late relapsing phenomenon years after the acute attack.

Hypertensive iritis and steroid glaucoma

A major problem arises when there is steroid glaucoma accompanied by a severe steroid controlled inflammation. When pressure remains raised despite adjusting steroid dosage, standard glaucoma drops such as timolol must be used. When they fail it is advisable to use acetazolamide only in the short term while glaucoma surgery is prepared.

Neuroparalytic keratitis and ulceration

A fairly common ocular complication in herpes zoster is loss of corneal sensitivity and damage to the mechanisms maintaining a stable precorneal tear film. A combination of artificial tears and mucolytics will help to stabilise the tear film and improve the health of the corneal epithelium. When ulceration occurs treatment must be prompt. Initially we tape the eye closed with dermalon. When that fails we use botulinum toxin induced ptosis or tarsorrhaphy. It is important over this period to treat any underlying iritis with adequate topical steroid and to use prophylactic antibiotic drops. Bandage lenses are best avoided in all keratitis where there is a loss of corneal sensation because of the risk of hypopyon ulcer formation.

Exposure keratitis

The origin of this is obscure and despite a degree of corneal sensation being present there is a great problem in corneal wetting and horizontal ridges of swollen epithelium develop interpalpebrally. On the whole treatment is very unsatisfactory; wetting agents only help marginally, intermittent taping may be of some use, even a tarsorrhaphy may be necessary. Unfortunately, later on large mucous plaques tend to develop and become partially covered by epithelium. The only effective treatment for this is a formal superficial keratectomy.

Surgery

Lids

Corrective lid surgery may be needed for lid margin deformities (e.g. ectropion and trichiasis) arising

from scarring. It is urgently required when there is full thickness loss of the lid margin. A lateral half tarsorrhaphy should be carried out early on in all cases of neurotrophic ulceration that have failed to respond to medical treatment and it may also be necessary in cases of chronic exposure and neuroparalytic keratitis. It can be difficult to persuade patients to accept this treatment, but it provides rapid healing, security and dramatically reduces outpatient visits. Lastly, if the problem persists after a lateral tarsorrhaphy, a middle third tarsorrhaphy must be carried out.

Intraocular surgery

Cataract extraction. The extracapsular technique with posterior chamber implant is surprisingly straightforward when undertaken in a quiescent phase. The main problem is postoperative inflammation which may persist for more than a year, but always seems to be controllable with a low dose of topical steroid.

Glaucoma surgery Trabeculectomy is similarly straightforward and postoperative inflammation is a problem. There is a high incidence of cataract formation later on.⁴⁴ I have little experience of laser trabeculoplasty but it may be a worthwhile short-term solution.

Corneal surgery. Very rarely an urgent corneal graft has to be done in patients with neurotrophic ulceration and perforation. The prognosis is not good as considerable difficulty may be encountered in establishing a stable corneal epithelium over the graft and because of this it is best to carry out a tarsorrhaphy at the same time. Neglected disciform keratitis or sclerokeratitis frequently gives rise to dense scarring and lipid deposits in the central cornea. A perforating corneal graft tends to be successful in these patients, provided that the corneal sensation is preserved and it is not too vascularised or the vessels have been closed by argon laser treatment.⁴⁵ Keratectomy is sometimes necessary for band-shaped keratopathy and mucous plaques.

Comment

One of the most important aspects of the ocular complications in herpes zoster is their tendency to recur, even years after the rash. It should be remembered that some relapses may occur when the original attack of herpes zoster has either been forgotten or was so mild as to pass unnoticed. The stimulus for the relapse is often unknown, although the precipitate withdrawal of topical steroids is a potent cause (even if small doses are being used).

Therefore, follow-up must be long and thorough in those with ocular involvement and topical steroid must be slowly and cautiously withdrawn (over years if necessary).

The search for future effective antiviral agents will not necessarily provide the therapeutic answer to herpes zoster. It seems likely that the viral activity occurs very early in the disease (during the prodromal phase) and is transitory, priming the more obvious inflammatory changes which do not rely on the continuing presence of the virus. Thus, to be effective, they must be administered very early and must cross the blood-neurone barrier. Unfortunately, most cases present two days and more after the onset of the rash when viral replication is declining or finished, leaving anti-inflammatory agents as the mainstay of treatment.

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Double-masked trial of topical acyclovir and steroids in the treatment of herpes zoster ocular inflammation

R J Marsh, M Cooper

Abstract

Ninety seven new patients with ophthalmic zoster were randomly allocated to three topical treatment groups: acyclovir (ACV) ointment and placebo drops (AP), placebo ointment with steroid drops (PS), and acyclovir ointment with steroid drops (AS). The dosage administered was determined by the score of the ocular inflammation. Follow-up was for at least one year. The results showed that topical ACV alone is insufficient for severe ocular inflammation but is not inclined to lead to recurrences in milder cases. Topical steroid alone is effective but tends to necessitate prolonged treatment. Combined steroid and ACV is questionably better than steroid alone and causes marginally fewer rebound inflammations.

Ophthalmic zoster has been said to give rise to ocular complications in 50% of patients.¹ These are chiefly inflammatory and range from being mild, such as episcleritis, to severe, such as sclerokeratitis and hypertensive iritis. The mechanisms of these complications are poorly understood but clearly involve replication of the varicella/zoster virus in the early stages and then the inflammatory response. The latter is conventionally treated with topical steroid,² which, though usually effective, may have to be continued for long periods, as inflammation tends to reappear during or shortly after withdrawal.

On the other hand, viral replication may be limited early on by acycloguanosine (acyclovir or ACV), a potent and selective inhibitor of viruses of the herpes group, in particular herpes simplex virus types 1 and 2 and to a less extent varicella-zoster virus (VZV).^{3,4} The intraocular penetration of topical ACV is superior to that of other antiviral agents⁵ and would therefore make it the rational choice. An open study of topical acyclovir on 18 patients with a short follow-up⁶ showed it controlled keratoconjunctivitis in 15 of the patients without topical steroid, and there was no recurrence on stopping treatment. A further study comparing topical ACV and steroid reported ACV to be superior to steroid in terms of the median healing time of corneal epithelial ulcers, but there was no significant difference for stromal lesions, uveitis, or scleritis.⁷ Of the patients on steroid 63% had a recurrence of ocular inflammation during or after withdrawal of therapy, making the mean treatment time in the steroid treated group significantly longer than in the ACV group.

These results did not correspond with our experience of ACV at Moorfields,⁸ where half of our patients, despite being treated early with it, developed very serious ocular inflammation

necessitating and responding well to topical steroids (admittedly with attendant liability to relapse). Moreover, in our experience mild disease such as corneal microdendritic ulcers, some nummular keratitis, and most cases of episcleritis are self-limiting and do not require any treatment. Therefore we consider that ACV does not have any effect in these cases and steroid could be positively harmful.

The mechanisms by which rebounds in ocular disease may follow steroid withdrawal are still uncertain. Steroids can enhance viral replication⁹ by the suppression of some of the inflammatory responses. It is not known whether the chronic or relapsing ocular lesions in zoster are dependent on viral replication or the presence of some sort of antigen. Perhaps it is significant that, although replicating virus is present in the acute epithelial lesions of zoster,¹⁰ so far as we know replicating virus has not been identified or cultured in pathological specimens from chronic cases. It would therefore seem logical to try an antiviral during the acute phases of the disease but less certainly in the later phases.

The use of ACV and steroids, separately or in combination, compared with placebo in the treatment of herpes zoster ocular inflammation has not previously been examined in a controlled clinical trial. We considered the large number of patients we see and the doubts raised by our observations justified such a three-armed double blind trial.

Patients and methods

New patients presenting at Moorfields Eye Hospital with ophthalmic zoster were offered inclusion in the trial. Patients excluded were those who did not give their consent, were unwilling or unable to attend regularly for clinical assessment, were under 18 years, had received antivirals or steroid by any route, had other significant ocular pathology, had no eye disease at all, and had had the onset of the rash over 3 weeks previously.

Patients willing to take part were informed of the nature of the trial and gave their written consent.

The trial was double masked and randomised. Patients eligible for entry were randomly allocated to receive either acyclovir ophthalmic ointment and placebo eye drops (AP), placebo ointment and steroid eye drops (PS), or acyclovir ophthalmic ointment and steroid eye drops (AS).

On admission to the trial the following details were recorded: time from onset of rash, preceding ocular therapy, other eye disease, previous glaucoma or family history of glaucoma, and whether eye involvement was mild, moderate, or severe.

Department of Clinical
Ophthalmology,
Moorfields Eye Hospital,
City Road, London
EC1V 2PD
R J Marsh
M Cooper

Correspondence to:
R J Marsh, FRCS.

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Table 1 Score card for recording inflammatory index

Visit (weeks)	1st	2nd	3rd	4th	8th	12th	16th	20th	26th	52nd
Date										
conjunctivitis (0 1 2 3)										
episcleritis (0 2 4 6)										
(sectors 1 2 3)										
scleritis (0 4 8 12)										
(sectors 1 2 3)										
nummular keratitis (0 2 4 6)										
(sectors 1 2 3)										
disciform (0 2 4 6)										
(sectors 1 2 3)										
sclerokeratitis (0 2 4 6)										
(sectors 1 2 3)										
mucous plaque (0 2 4 6)										
(sectors 1 2 3)										
corneal oedema (0 4 8 12)										
iritis (0 2 4 6)										
visual acuity										
applantation										
Score										
Potency										

A scoring system of the degree of inflammation of the eye was devised in order to calculate the intensity of treatment to be used. In essence each inflammatory lesion was scored as follows: no lesion (0), mild (1), moderate (2), and severe (3), and all scores were added together to reach a total. However, we considered from clinical experience that this basic scoring system was inadequate alone to indicate appropriate intensity of treatment, particularly with reference to steroids. This is because lesions are often multifocal in several sectors, and certain inflammatory conditions require high doses of topical steroid to control them. For instance, conjunctivitis is a very mild and transient condition responding readily to a low dose of steroid, whereas scleritis and corneal oedema are severe and require intensive topical steroid to control them. There are other conditions of intermediate severity such as episcleritis and nummular keratitis. We therefore modified the scoring to bring it into line with the most appropriate intensity of treatment and thus quadrupled the score of scleritis and doubled that of the intermediate group. We also added a score of 1 for one sector, 2 for two sectors, and 3 for more than two sectors. Table 1 shows the inflammatory score sheet where the inflammatory indices of the ocular complications were recorded and totalled.

Table 2 gives the therapeutic regimen based on these different scores. All patients with scores over 16 had the most intensive treatment possible, and at each visit the scores were reassessed and the dosage adjusted accordingly. When the score fell below 5 ointment was stopped. This was because Wellcome considered that ACV became relatively ineffective at doses less than three times a day. The drops, however, were continued because even minute doses of steroid appear to have a therapeutic effect. Once signs of active ocular inflammation had ceased, treatment was continued at the minimum dose for at least three months and halved after that for a

Table 2 Dosage regimen

Log dilution of drop	Ointment frequency	Score	Potency
0.1% x6/day	x5	13+	1
0.1% x4/day	x4	11-12	2
0.1% x3/day	x3	9-10	3
0.03% x3/day	x3	7-8	4
0.01% x3/day	x3	5-6	5
0.01% x2/day	Nil	3-4	6
0.01% x1/day	Nil	1-2	7

further two months to cover any rebound phenomenon.

A 1 cm ribbon of 3% acyclovir ointment or placebo was administered on to the lower tarsal conjunctiva. Dilutions of dexamethasone drops at 0.1%, 0.03%, and 0.01% were prepared with matching placebo. One drop was instilled at a time. ACV ointment and matching placebo were packaged and labelled by Wellcome. The placebo consisted of the same ingredients as the drug formulation, without the ACV. Steroid eye drops and matching placebo were prepared and labelled by the pharmacy at Moorfields Eye Hospital. The placebo consisted of the diluent used in the preparation of the steroid drops and was labelled 0.1%, 0.03%, and 0.01%.

Patients were seen as often as clinically necessary but at least twice in the first week of presentation, weekly thereafter until the end of the first month, and then at monthly intervals until the end of therapy. The clinical proformas and score sheets were completed on each occasion, the total inflammatory score calculated, and the appropriate treatment administered. Any adverse symptoms or signs potentially attributable to the therapy were carefully documented in the adverse reactions chart. Final assessments were made at six and 12 months following resolution of active ocular involvement.

Patients were withdrawn from the trial if signs of toxicity or side effects developed, if they deviated seriously from the protocol, or if their ocular complications progressed despite full therapy (potency 1). The last was taken as when the ocular inflammatory score continued to rise over a three-day period or more on full therapy. Then the patient was placed on full strength dexamethasone at least six times a day to prevent any scarring of the eye. We continued to monitor all patients withdrawn from the trial.

Any recurrence of ocular complications

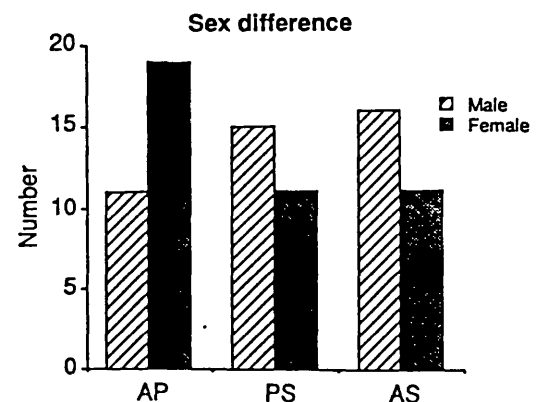


Figure 1 Sex distribution of the patients in the three groups.

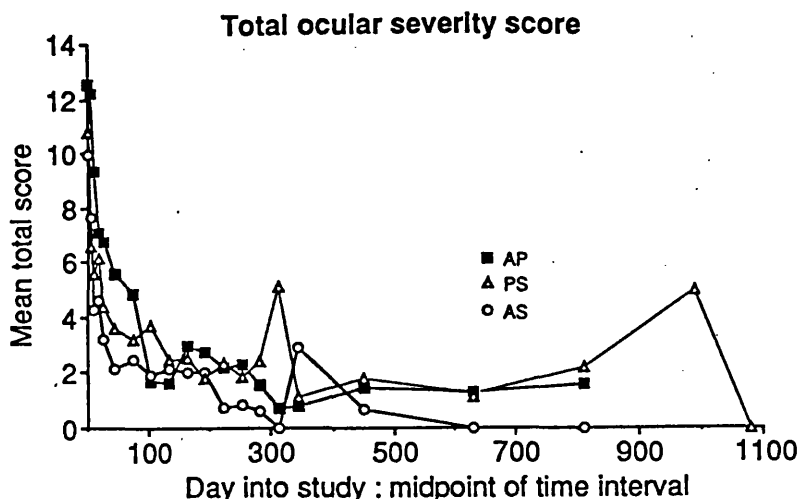


Figure 2 Severity of ocular inflammation plotted against time in the three groups.

during the period in which the frequency of administration of the treatment was being reduced was treated in accordance with the inflammatory scoring and the drug dosage appropriately increased. Any recurrence that occurred after the end of therapy was treated similarly.

Results

The original intention was to recruit 120 patients, but this proved impracticable. The main reason was that in the later stages of the trial a large proportion of patients presenting to the Accident and Emergency Department had already been started on some form of ACV by their general practitioners. This made recruitment increasingly slow and those recruited increasingly unrepresentative. It was therefore decided to limit the numbers to 97. Of these, 14 sets of results could not be used because of inadequate documentation or follow-up; 30 patients remained in the ACV/placebo (AP)

Table 4 Time in days to resolution of ocular inflammation in those patients who healed (expressed as a mean)

	AP ACV/placebo	PS Placebo/steroid	AS ACV/steroid
Conjunctivitis	23.9 (24.4)*	26.2 (33.4)	20.5 (24.6)
Episcleritis	127 (94.8)	85.9 (101.3)	67.9 (74.9)
Keratitis nummular	153 (199.7)	136.5 (24.8)	66.6 (72.8)
disciform	14.0 (0)	63.0 (0)	18 (0)
sclero	7 (0)	6 (0)	124.5 (150.6)
mucous plaque	6 (1.4)	0 (0)	7 (0)
oedema	6.5 (2.3)	35.2 (68.7)	7 (4)
Iritis	91.9 (99.5)	55.5 (72.6)	42.5 (62.1)

*SD in parentheses.

group, 26 in the steroid/placebo (PS) group, and 27 in the ACV/steroid (AS) group.

The sex distribution was significantly different between the groups (Fig 1), but we did not consider this had any relevance to the trial. A significant difference in severity of initial disease was noted, with the rounded mean initial clinical scores for the AP, PS, and AS groups being 13, 11, and 10 respectively (Fig 2). Analysis shows that these scores were not strictly random. There was a bias towards more severe initial disease in the AP group because of a higher preponderance of severe uveitis and corneal oedema and towards less severe complications in the AS one.

There were no significant differences between the groups in terms of distribution of ocular complications (Table 3). For the more infrequent problems there would have been insufficient numbers.

Rates of healing are shown in Table 4. The rate was significantly poorer for episcleritis in group AP, whereas group AS showed faster resolution of inflammation overall, though the rate of severe complications was too low for any differences to be detected.

Table 5 gives the overall resolution of ocular inflammation. Treatment failure, that is where the full intensity of trial drug combinations failed to control inflammation, occurred in 12 out of 30 AP, two out of 26 PS, and three out of 27 AS (χ^2 test, $p < 0.01$). In those patients whose condition failed to settle down it responded to intensive topical steroid and did not present any significant management problems.

Recurrences, either during tail-off or after stopping treatment, occurred in 3/16 AP, 7/24 PS, and 9/26 AS. The denominator is those who did not fail to respond to treatment (χ^2 test $p > 0.05$). Treatment duration was over one year in 3/16 AP, 8/24 AS, and 3/24 AS. However, it should be noted that as 12 of the AP group were withdrawn because of treatment failure the

Table 3 Ocular inflammatory complications in patients with ophthalmic zoster treated with topical acyclovir and placebo, topical steroid and placebo, topical steroid and acyclovir

	AP ACV/placebo (30 patients)	PS Placebo/steroid (26 patients)	AS ACV/steroid (27 patients)
Conjunctivitis			
present at entry	27	24	26
mean baseline score	1.7	1.5	1.5
Episcleritis			
present at entry	29	26	27
mean baseline score	3.2	2.9	2.9
mean no. of sectors	2.7	2.5	2.3
Nummular keratitis			
present at entry	7	5	6
mean baseline score	0.7	0.5	0.3
mean no. of sectors	0.4	0.2	0.3
Disciform keratitis			
present at entry	1	1	1
mean baseline score	0.1	0.2	0.1
mean no. of sectors	0.03	0.1	0.1
Sclerokeratitis			
present at entry	1	1	2
mean baseline score	0.1	0.1	0.2
mean no. of sectors	0.03	0.1	0.1
Mucous plaque keratitis			
present at entry	2	0	2
mean baseline score	0.1	0	0.1
mean no. of sectors	0.1	0	0.04
Corneal oedema			
present at entry	8	5	3
mean baseline score	1.5	0.9	0.7
Iritis			
present at entry	21	14	11
mean baseline score	1.9	1.7	1.0

Table 5 Overall resolution of ocular inflammation

	AP ACV/placebo	PS Placebo/steroid	AS ACV/steroid
Healed	13	21	24
Not healed	17	4	2
Unknown	0	1	1

milder ocular complications tended to remain in this group. Therefore there would be less tendency to relapses among them.

No difficulties were experienced with drop allergies, steroid induced rise of intraocular pressure, or other drug side effects.

Discussion

At their face value these results indicate that topical ACV alone is insufficient for severe ocular inflammation, takes longer to settle milder inflammation, but is not inclined to lead to recurrences in the milder cases. The results of the AP group would suggest that some acute ocular inflammations such as mild episcleritis and nummular keratitis are self limiting. Topical steroid alone is effective but prone to lead to prolonged treatment; whether it worsens ocular complications is not possible to say from these data. The combined ACV and steroid group is questionably better than the steroid alone in the short term and has a reduced number of patients with rebound inflammation, but this is not statistically significant. Interpretation of this trial is made difficult by the obvious initial differences between the groups. However, we have been assured by our statisticians that they do not account for the whole difference, and qualitatively the results are useful.

Having demonstrated the relative ineffectiveness of the topical ACV preparation there remain the systemic preparations which achieve better tissue concentrations. Controlled clinical trials have shown that ACV, given intravenously, significantly shortens the course of acute zoster skin rash, especially in immunosuppressed patients.^{4,11} It is also claimed that given orally at 600 and 800 mg five times a day for 8–10 days at the start of the disease it significantly reduces the occurrence of ocular complications¹² and postherpetic neuralgia.¹³ However, it must be said that the reported reduction of ocular complications is based on one multicentre trial with exclusion of cases with significant ocular inflammation at presentation, and the reduction of postherpetic neuralgia is a contentious issue depending on the definition of postherpetic neuralgia as opposed to acute neuralgia and on the normal incidence of neuralgia.¹⁴ Perhaps the next step is a three-armed clinical trial to decide whether a 10-day course of full dose oral ACV early on is more effective in reducing ocular inflammation than a placebo and systemic steroid. It should of course be borne in mind that the routine use of a systemic course of ACV has financial implications for health services.

It is at first sight surprising that antivirals are not more effective in zoster. The ocular complications of zoster presumably stem from the presence of VZV, which initially is replicating, and the inflammatory response. Treatment can be directed to both components. The main difficulty is with timing and deciding which component is more significant. Another problem is gaining access to patients in the early stages of the disease. Unfortunately, chronic ocular inflammation may continue for years in some cases and is presumably not dependent on the presence of virus as we know it. Perhaps the

virus at its active stage causes an antigenic change in the damaged tissues and remains there not replicating in an altered form, unidentifiable with conventional electron microscopy or culturing. So at a late stage of presentation (often the case) one would not expect conventional antivirals to work. Steroids on the other hand will suppress the inflammatory response causing tissue scarring at any stage and may be necessary in the long term if the antigenic stimulus continues. The latter would explain the difficulty in withdrawing the drug as opposed to steroids promoting survival of live virus in the tissues. The other disadvantages of steroid (glaucoma, cataract, and superinfections) should of course be borne in mind.²

It would be helpful at this stage to compare and contrast HSV and VZV virus. HSV is a more aggressive virus and replication is more significant in producing overall disease events than VZV. HSV can be found replicating in the eye at all stages of the disease, whereas VZV has been cultured only at the beginning. HSV is more sensitive in vitro to ACV than VZV. This would explain the poorer response of zoster to the drug. They both share an inflammatory component in their disease process which is double-edged; modifications by steroid is necessary to prevent scarring and optimise outcome. However, whereas antiviral cover is important with HSV to prevent corneal epithelial loss and stromal thinning, it is not strictly necessary with VZV. At this stage it is not clear whether antiviral cover in chronic HSV corneal stromal disease modifies the inflammation, but the seemingly better results in the AS group in this trial suggest there may be a positive benefit, though not quantifiable in zoster keratitis. It is interesting that chronic stromal keratitis in both conditions may be exquisitely sensitive to topical steroid: even 0.03% prednisolone drops on alternate days can be enough to control a potentially severe inflammation.

The general conclusions relating to management of zoster ocular disease are that mild inflammation does not require any treatment, whereas more severe problems do. In the long term a combination of ACV and steroid in the more severe complications may be appropriate to prevent relapses.

This trial gives only a general indication for treatment and cannot give a recipe, which will depend on individual characteristics. The finer judgments require an extensive knowledge of the natural and unnatural history of viral ocular disease and close observation. There is no single best treatment.

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FIFTY YEARS AGO

Treatment of Mustard Gas Lesions of the Eye

To the Editors of
THE BRITISH JOURNAL OF OPHTHALMOLOGY.

DEAR SIRS—An instruction EMSI 252 (revised) on this subject has been widely distributed to the officers, consultants and hospitals of the Emergency Medical Service. It came before the Medical Board of Moorfields Eye Hospital 'for your information.' The Medical Board considered the instruction and felt that several points in it required comment.

1. The use of albucid solution is advised at First Aid Posts and at Hospitals in cases in which the eyes have been affected by gas vapour or gas splashing. It must be pointed out that the use of sulphanilamide preparations is not directed against gas contamination but only against subsequent infection of the conjunctiva and that opinion as to its efficiency in this latter respect is far from being generally favourable.

2. No mention is made in the instruction of the very diverse lesions which may be produced by gas, most of them slight and very few of them serious.

3. No indication is given of the treatment necessary when the cornea is definitely involved and while water is advised for irrigation of the eye at an incident and at First Aid Posts, no advice is given as to the lotion to be used for the irrigations recommended at Hospital.

It would appear that this instruction is not in fact the 'result of further experience' and should be withdrawn and replaced by a carefully considered and detailed note based on actual experience obtained in the last war and on substantiated experimental evidence.

We are,

Yours faithfully,
F. A. JULER.
MAURICE WHITING

Br J Ophthalmol 1941; 25: 394-5.

OPHTHALMIC HERPES ZOSTER

RONALD J. MARSH and MATTHEW COOPER

London

SUMMARY

A current review of ophthalmic zoster is presented including its virology, immunology, epidemiology and pathogenesis. We give our findings in 1356 patients referred to the Zoster Clinic at Moorfields Eye Hospital, London. The treatment of the disease and its ocular complications is discussed.

Ophthalmic herpes zoster is a disease varying in severity from devastating, threatening life and sight, to so mild that it may pass unnoticed. The ophthalmic division of the fifth cranial nerve is affected in 7–17.5% of herpes zoster patients.^{1–5} Ocular involvement complicates approximately 50% of these cases and very rarely cases of maxillary herpes zoster,¹ affecting many of the tissues of the globe and orbit by highly varied types of lesions.

We felt it would be helpful to report our experience with the disease because the large number of cases we have seen has led us to form slightly different ideas from many previous publications as to the nature of the disease, its complications and management. We gained our experience in the Zoster Clinic which was started at Moorfields Eye Hospital, London, in 1967 by Professor Barrie Jones as part of the External Disease Clinic. Since then the clinic has expanded and chiefly sees patients referred from Casualty. These patients come mainly from the Greater London area and are referred rapidly by their general practitioners after onset of the disease. A relatively small number of patients was referred for second opinion. Since 1971 one of the authors has supervised the clinic continuously. From 1972 to 1988 all new patients were entered into a specially designed database which was continuously upgraded. All those with inadequate details or follow-up of less than a year were removed from the database, leaving 1356 patients. The vast majority of patients received no systemic antiviral or steroid therapy before they saw us and were physically well before the disease started. The figures given throughout this paper on complication incidence are based on this database. However, the series as a whole was slightly biased because those patients with insufficient follow-up were excluded and most of them tended to have very mild zoster.

Correspondence to: R. J. Marsh, MB.BS, FRCS, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD, UK.

Fig. 1 shows the age and sex distribution, which is biased in favour of females and compares with 50.7% males, 49.3% females in another series.⁵ The 1981 census for Greater London recorded 48% males and 52% females.

ONSET

There is a prodromal influenza-like illness of varying duration, with headache, pyrexia, malaise, depression, and sometimes neck stiffness, which may last up to a week before the rash appears. This is shortly followed by localised pain over the distribution of the ophthalmic nerve, lymph node swelling in the corresponding drainage areas and, occasionally, a red eye. The localised pain is well known to precede the rash by several days in some cases. This probably represents the replication and migration phase of the disease and is possibly accompanied by a limited viraemia.

RASH

The rash varies enormously in distribution, density and severity. It commences as macules which rapidly progress to papules, vesicles and pustules. Crusts start to form from about 6 days onwards. All, or just one, of the cutaneous branches of the ophthalmic nerve are affected. The lesions vary from small, discrete, scattered and superficial to large, confluent and deep with haemorrhagic bullae. The latter are probably due to a vasculitis in the dermal papillae leading to severe tissue ischaemia. In our patients the rash was mild in 430, moderate in 743 and severe in 131. The average ages for the different degrees of severity of rash were: 64 years for severe, 61 years for moderate and 56 years for mild.

Oedema is a variable complication, tending to develop after the first 2 or 3 days. It may be so pronounced as to completely close the lids of the affected eye and spread across the midline to involve the other lids (giving the erroneous impression that it is a bilateral disease). Furthermore, oedema is not due to secondary infection in the majority of cases, since it rapidly resolves without any antibiotic therapy.

Differential Diagnosis

The rash can be mimicked by zosteriform herpes simplex

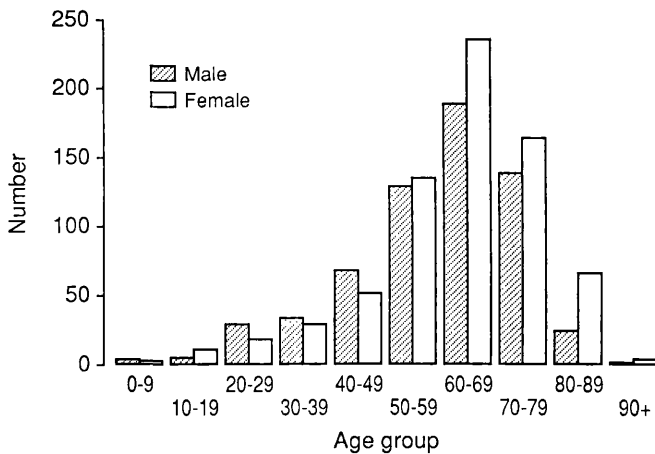


Fig. 1. Age and sex distribution of ophthalmic zoster patients.

which takes on a dermatome distribution.⁶ Herpes simplex vesicles are smaller and frequently recurrent; they do not form the large distinct crusts or the typical punched-out scarring of herpes zoster and are not as painful. The two infections may be differentiated by culturing vesicle fluid and assessing fluorescent antibody membrane antigen (FAMA).⁷ Differentiation from impetigo is usually straightforward because of the lack of dermatome distribution. Very occasionally a brief and mild zosteriform rash appears after trauma to the forehead or eye. It clears in days with no lasting complications. We have no viral cultures on these cases but wonder whether they are caused by a closely related or attenuated strain of varicella/zoster.

SYSTEMIC INVOLVEMENT

Fortunately the vast majority of patients seen by ophthalmologists are otherwise healthy, except for those in centres specialising in tumours and immunosuppression; only 12 in a continuous series of a 1000 of our cases had malignant disease.⁸

A small number of patients attending eye clinics develop a systemic vesicular rash and severe illness 1–2 weeks after the disease onset. Most of these patients turn out to have reticuloses, other malignant tumours,⁹ diseases causing immunosuppression such as AIDS, or are iatrogenically immunosuppressed (symptomatic zoster). Furthermore herpes zoster is more frequent and severe in patients with these diseases. It is interesting that viruses in the same family as varicella/zoster, the so-called latent viruses (herpes simplex virus, cytomegalovirus and Epstein–Barr) produce severe infections under the same circumstances.¹⁰ Recently an increased incidence of ophthalmic zoster has been described in pre-AIDS patients in New York and Africa.^{11,12}

All patients with a systemic rash should therefore be screened by a clinical immunologist or oncologist for malignant disease and immunosuppression. We do not consider it necessary to investigate uncomplicated cases of ophthalmic zoster.^{8,13} There has been a tradition, largely unsubstantiated, that all young children with zoster should be investigated for systemic disease.¹⁴ Our series included 17 patients under 16 years old, none of whom suffered

from or developed serious systemic illness. On the other hand, if a child is from a community in which AIDS is endemic we would agree that screening should be done.

OCULAR INVOLVEMENT

Ocular complications can be categorised primarily into those associated with inflammatory changes, those resulting from nerve damage, and those secondary to tissue scarring. Inflammatory changes may be in the form of dendritic, nummular and disciform keratitis or as a vasculitis in episcleritis/scleritis, iritis, ischaemic papillitis and orbital vasculitis. Changes resulting from nerve damage include neuroparalytic keratitis, some ocular motor palsies and neuralgia. Changes subsequent to tissue scarring are lid deformities, neuralgia and lipid keratopathy.

The course of the ocular disease falls into three phases: acute, chronic and relapsing. Acute lesions of the globe and orbit develop within 3 weeks of the rash. They may resolve rapidly and completely but can lead to a chronic course, especially if untreated, and may linger for years. Alternatively acute lesions may appear to clear but then relapse years after the disease onset – often on suddenly stopping or reducing the topical steroid treatment. Recurrence is a particularly distinctive feature of the disease. Adequate treatment delivered at the start of the acute phase can significantly reduce severe late and chronic complications.

The old rule that cutaneous involvement of the nasociliary nerve heralds ocular complications is a good one (chi-squared $p < 0.01$) but not infallible. We found 6 of our 604 patients with nasociliary nerve involvement had no ocular involvement at all. Vesicles appearing on the lid margins are almost invariably associated with ocular involvement (chi-squared $p < 0.01$), although it must be emphasised that severe ocular complications may occur with a very mild insignificant rash anywhere on the forehead.

Acute Lesions

Eyelids

The lid margin was involved by the rash in 926 cases. Ptosis is common and is usually due to mechanical factors such as inflammation and oedema. Less frequently it is neurological. Haemorrhagic bullae here are a bad sign, heralding severe scarring and all its consequences and post-herpetic neuralgia.

Conjunctivae

Catarrhal conjunctivitis is one of the commonest manifestations of herpes zoster, occurring in 1015 patients, and is nearly always associated with vesicles on the lid margin. It is generally transitory, resolving within a week, and rarely becomes chronic.

Episclera and sclera

Episcleritis and scleritis are common complications, occurring mildly in 545 and moderately in 208 patients (Fig. 2). Sectoral or diffuse episcleritis usually appears at

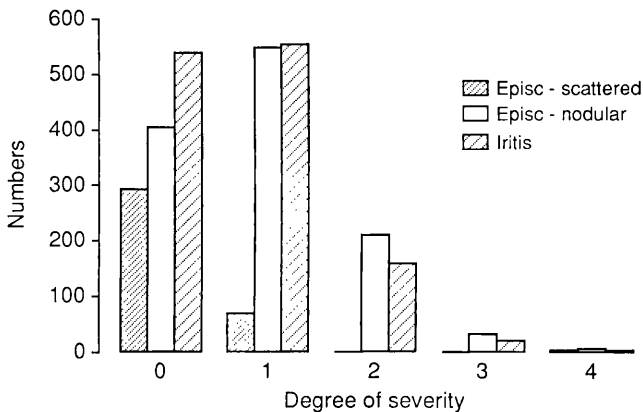


Fig. 2. Numbers of patients with uveoscleral inflammation and its degree of severity.

the onset of the rash when it is frequently concealed by an overlying conjunctivitis. Less commonly, in 37 of our patients, scleritis appeared, usually at the end of the first week. It may be adjacent to the limbus with accompanying corneal stromal infiltrate and swelling, producing sclerokeratitis in 6% of cases.¹⁵ Nodular episcleritis occurred in 70 of our patients, usually starting in the second week of the disease. Fluorescein angiography in these cases demonstrates ischaemia in the centre surrounded by dilated leaking episcleral vessels¹⁶ (Fig. 3a,b) suggesting a vasculitis, but it may be just a lymphocytic response. We have found that mild episcleritis does not require treatment and will slowly resolve without problems.

Cornea (Fig. 4)

Acute epithelial keratitis may occur concurrently with acute conjunctivitis. This is characterised by small, fine, multiple dendritic or stellate lesions which were observed in 253 cases, although the real figure is probably much higher than this because of the difficulty of corneal examination when the patient has swollen lids and the transitory nature of the lesions. On slit lamp examination they appear slightly raised and are intra-epithelial. They are located generally in the peripheral part of the cornea and occasionally small plaques of opaque desquamated epithelium and mucus overlie them (Fig. 5a). These epithelial lesions stain moderately well with Rose Bengal and fluorescein but only minimally with Alcian blue. They are self-limiting, appearing within a few days of the onset of the rash and resolving 4–6 days later, and are always associated with catarrhal conjunctivitis. They may be followed by an underlying superficial stromal infiltrate. Varicella/zoster virus has been cultured from them.¹⁷ Less often a filamentary keratitis occurs which usually lasts only a few days. All these changes may be concealed by lid oedema that prevents proper examination of the cornea during the early period.

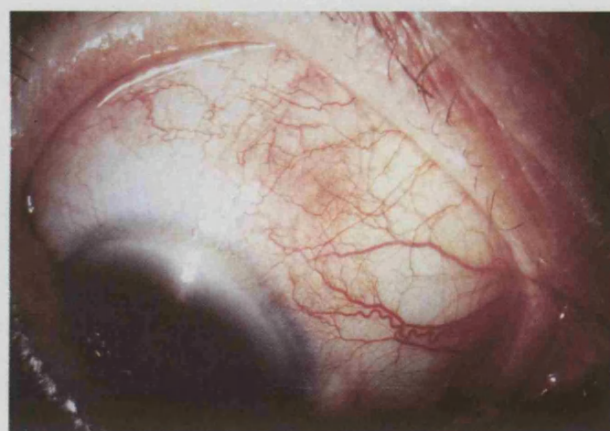
Nummular keratitis is the commonest corneal lesion and was seen in 294 patients in the first month and in 411 after 3 months; 152 patients had combined late and early nummular keratitis. It is characterised by multiple, fine granular deposits in the stroma just beneath Bowman's

membrane which are surrounded by haloes of stromal haze (Fig. 5b). These appear 10 days or so after the onset of the disease and are at first white but later become brown. Sometimes they underlie preceding epithelial lesions, but more often they are seen in close proximity to thickened corneal nerves.¹⁰ The haloes surrounding them vary in size and density, are often very sensitive to topical steroid, but have a strong propensity to become chronic or to relapse. In this they resemble the lesions in adenovirus keratitis. Some patients in whom they fail to clear suffer progressive lipid deposition with facetting, all of which may considerably embarrass vision.

Disciform keratitis developed within 1 month in 61 cases and was seen after 3 months in 51. Early cases present 3–4 weeks after the disease onset. Disciform keratitis is generally situated centrally, but can be eccentric and varies in the degree of stromal oedema and infiltrate (Fig. 3c). It seems to be based on preceding nummular keratitis with new infiltrate appearing in the stroma underlying the corneal granules, and occasionally is surrounded by infiltrate in the shape of one or several immune rings. Commonly there is an associated iritis with fine keratitic precipitates underlying the swollen stroma. When the disciform keratitis is eccentric it often merges into a sclerokeratitis. When the endothelium is examined with the specular microscope it shows spotty loss of endothelial cells and blebs (Fig. 3d).^{18,19} This form of keratitis can be associated with hypertensive iritis and is often followed much later by a mucous plaque keratitis. It tends to become chronic if untreated but rapidly responds to topical steroid, particularly if this is given early on.

Diffuse corneal oedema developed as the presenting feature in 72 of our patients. It would appear to be due to diffuse damage to the endothelium because later, after the oedema has resolved, endothelial microscopy shows more severe changes than the above.^{18,19} Very fine deposits may be visible with the slit lamp on the endothelial surface and there is often raised intraocular pressure with the minimum of signs of iritis. It is equally sensitive to topical steroid, especially early on.

Neurotrophic keratitis. Total loss of corneal sensation occurred at the onset of the disease in 89 patients, 33% of whom developed immediate neuroparalytic keratitis with corneal ulceration; there is usually an accompanying severe rash (chi-squared $p < 0.01$). Neurotrophic keratitis is characterised by generalised corneal epithelial bedewing and punctate epithelial erosions with or without frank interpalpebral epithelial ulceration (Fig. 5c). The epithelium stains moderately well in a punctate fashion with fluorescein and Rose Bengal. It is interesting that in all cases not only is there loss of all corneal sensation but also anaesthesia of the bulbar conjunctiva and lid margins. The ulcers tend to be oval in shape with opaque water-logged edges and the base stains brilliantly with fluorescein and moderately well with Rose Bengal. The keratitis may be of acute or late onset. Acute cases occur as early as 10 days and those of late onset 2 years and more after the first signs of cutaneous zoster. Viscous drops and pro-



(a)



(b)



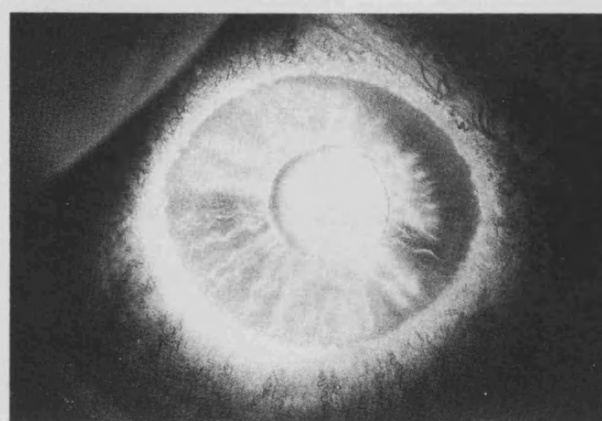
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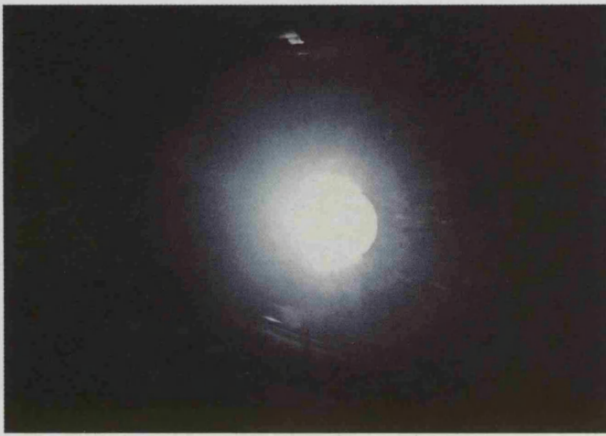


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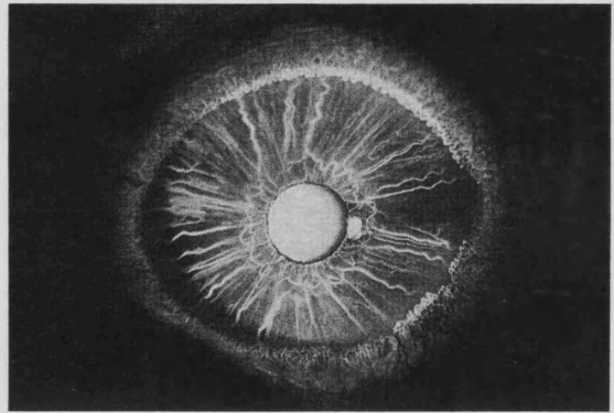


(f)

Fig. 3. (a) Episcleritis. (b) Fluorescein angiogram of episcleritis showing areas of poor vascular filling surrounded by dilated leaking episcleral vessels. (c) Acute disciform keratitis. (d) Specular reflection of corneal endophthalmitis in disciform keratitis. (e) Distorted pupil in acute iritis. (f) Iris fluorescein angiogram of acute iritis. (Continues)



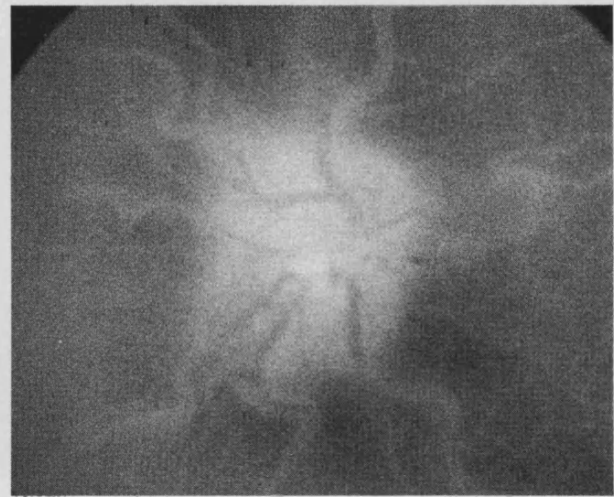
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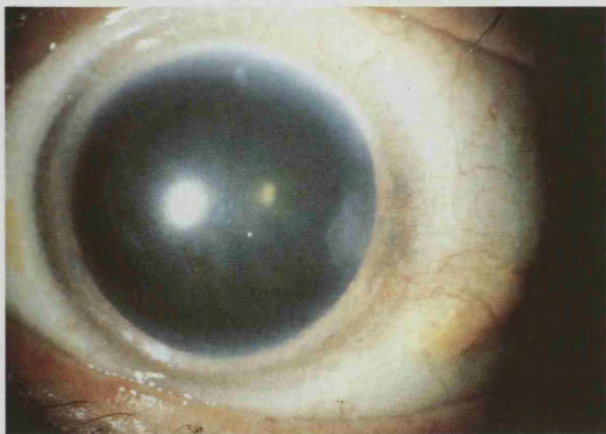
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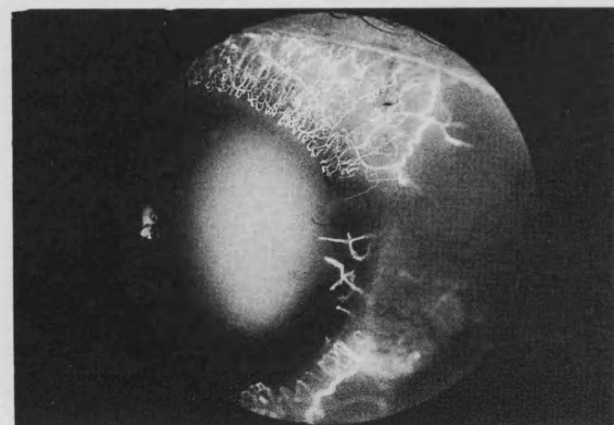
(i)



(j)



(k)



(l)

Fig. 3 (continued). (g) Sectorial iris atrophy (4 weeks after zoster onset). (h) Iris angiogram of Fig. 3g. (i) Acute optic neuritis. (j) Late fluorescein angiogram of Fig. 3i. (k) Vascularised marginal chronic corneal stromal infiltrate. (l) Fluorescein angiogram of Fig. 3k showing poor vascular filling of adjacent episclera

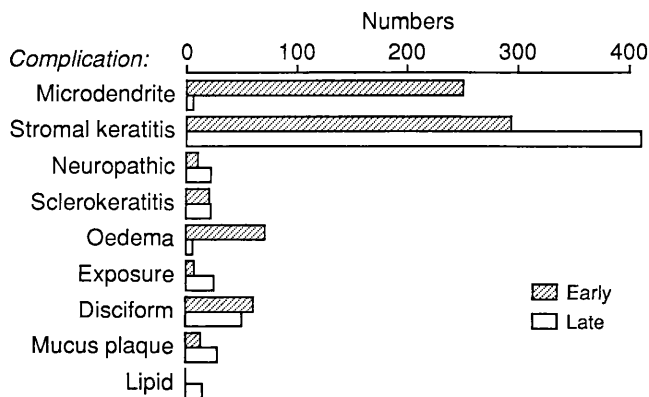


Fig. 4. Number of patients with corneal complications.

tective spectacles may be successful in preventing ulceration but tarsorrhaphy is the surest method. Neglected ulcers grow rapidly, with excavation and opacification of the stromal base and a distinct risk of severe secondary bacterial infection. Topical steroids are strictly contraindicated here as they tend to encourage the rapid excavation and growth of the ulcer; similarly bandage lenses have proved unsatisfactory in our hands, with 4 cases being complicated by corneal abscess and hypopyon formation. Temporary protection may be afforded by taping the eye closed with Blenderm (3M). Tarsorrhaphy, initially lateral third but sometimes subsequently central, has proved by far the most effective therapy, although ptosis induced by botulinum toxin is fast proving an attractive but very expensive alternative.²⁰ Despite prompt treatment many cases heal with the slow formation of severe stromal scarring and large mucous plaque formation.

Sclerokeratitis (Fig. 5d) very rarely occurs (in only 35 of our patients) and may be accompanied by marginal guttering, sometimes called serpinginous keratitis.²¹ It responds well to topical steroid but tends to be indolent and so it is important that the dosage is adequate to control oedema and infiltrate.

Iris

Iritis is another common complication, occurring mildly in 551 patients, moderately in 157 and severely in 20 (Fig. 2). It appears within 2 weeks of the rash.²² It is characterised by very fine deposits on the corneal endothelium, faint flare, and a small to moderate number of cells. Often there is complicating ocular hypertension (possibly caused by an associated trabeculitis) and overlying corneal stromal oedema. All these features respond rapidly to topical steroids. In many cases pupillary distortion occurs 4–5 days after the onset of the iritis and fluorescein angiography reveals widespread dilation and leakage from iris vessels (Fig. 3e,f). A few days later iris atrophy commences, distinguished by sectoral loss of iris pigment epithelium and migration of pigment into the overlying stroma. At this time angiography shows areas of ischaemia coinciding with the areas of atrophy²¹ (Fig. 3g,h), which has been confirmed histologically as an occlusive vasculitis.²³ The atrophy is readily seen by transpupillary transillumination, especially in blue irides, and is distin-

guished by a rather moth-eaten sectorial distribution. In 12% of cases there is permanent iris sphincter damage.²²

Glaucoma

The *glaucoma* observed in the acute phase of herpes zoster is due to hypertensive iritis and is exquisitely sensitive to topical steroid. We recorded 194 cases of glaucoma and an additional 42 cases related to topical steroid usage.

Choroid

Although *choroiditis* has been described,²⁴ we have not seen a case. Neither have we seen *choroidal detachments*.²⁵

Retina

We have seen 1 case of *retinal pigment epithelial degeneration*. It was interesting that although the scarring appeared quite substantial and was centred around the macula there was very little diminution of vision.

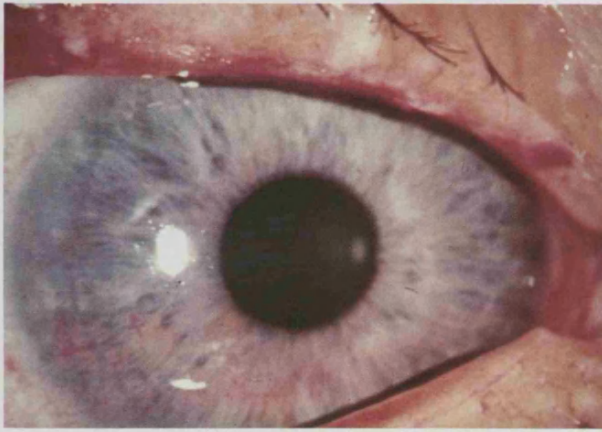
*Retinal vasculitis*²⁶ has been described in both the living and the post-mortem eye. Whilst we have seen the occasional case of branch and central retinal vein occlusion we have not been persuaded by the temporal relationship or numbers that there is any connection with zoster. Earlier reports may, in fact, be referring to acute retinal necrosis.

Acute retinal necrosis has been well described with both ophthalmic zoster and zoster at other sites.²⁷ There seems to be a defined pattern of retinal involvement in AIDS and this consists of a multifocal progressive chorioretinitis^{28,29} which rapidly leads to profound visual loss. The only treatment available is systemic acyclovir, which has a variable influence on the course of the disease.

Neurological Lesions

Optic neuritis is well documented³⁰ and occurred in only 6 of our cases. It is probably ischaemic, is often accompanied by posterior scleritis, and has a poor prognosis for vision. Our fluorescein angiograms showed a close similarity to ischaemic papillitis (Fig. 3i,j).

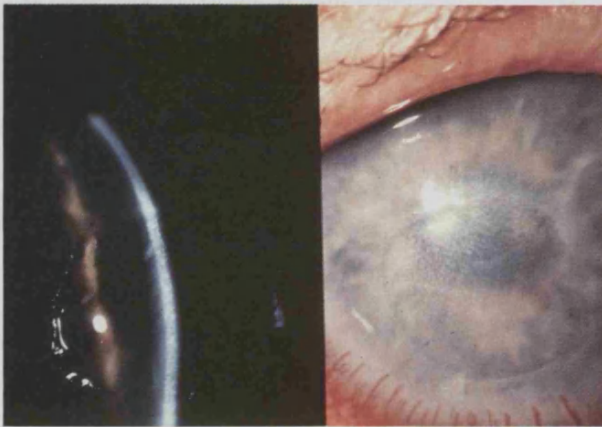
External ocular muscle palsies are common, appearing in 31% of a large series of patients we screened orthoptically at the onset of the disease.³¹ However, only 42 of 58 patients complained symptomatically in our first series and 133 in our present series. All cranial nerves are involved, the IIIrd most commonly then the IVth and VIth. There are highly significant correlations with the severity of the rash, neuralgia and iritis. In 4 of our patients there was a total IIIrd nerve palsy accompanied by proptosis, scleritis and iritis which suggested orbital vasculitis.^{1,32} The majority of palsies recover subjectively within 3 months but an orthoptically detectable lesion remains.³¹ Palsies were ipsilateral in 34 cases, contralateral in 9, ipsilateral becoming contralateral in 6 and bilateral in 5. The sites and aetiology of such lesions are difficult to construe; indeed they may be multicentric and mixed. They include: retrograde spread of virus from the ganglion to the nucleus



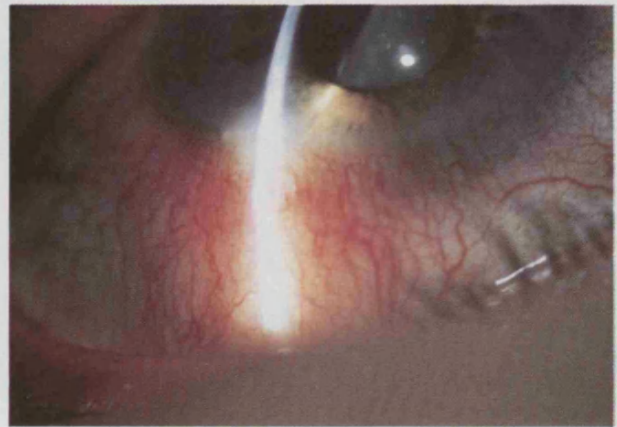
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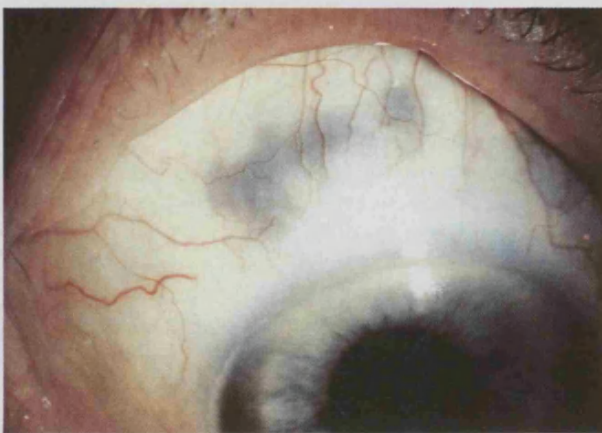
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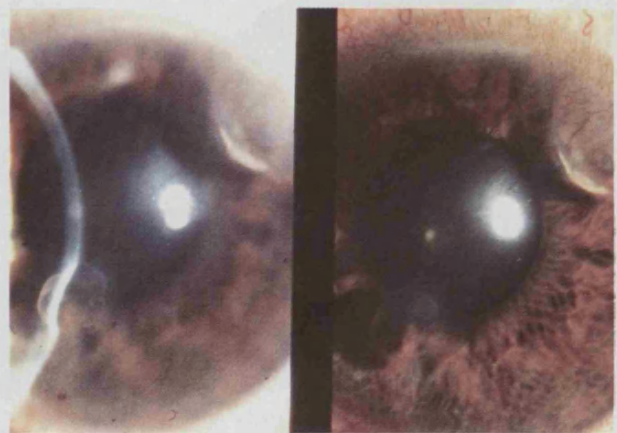
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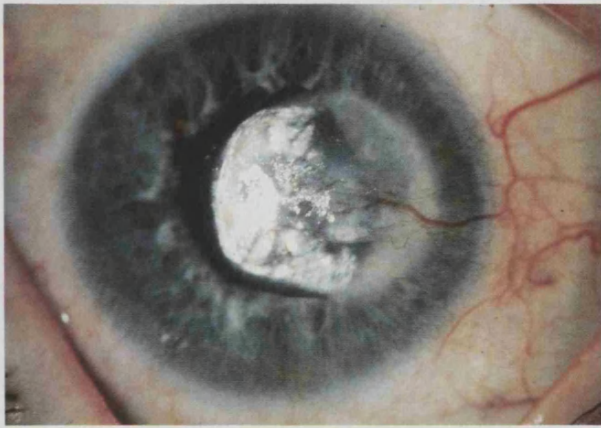


(e)



(f)

Fig. 5. (a) Acute epithelial keratitis stained with Rose Bengal. (b) Acute nummular keratitis: diffuse illuminator and slit view. (c) Acute neurotrophic corneal ulceration. (d) Acute sclerokeratitis. (e) Scleral atrophy in zoster. (f) Corneal facets following stromal infiltrates (diffuse illumination and slit). (Continues.)



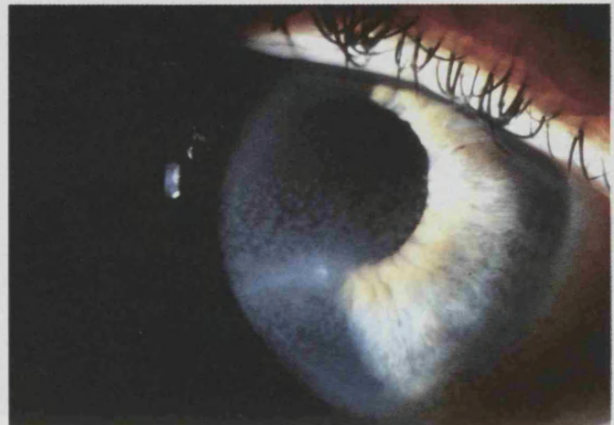
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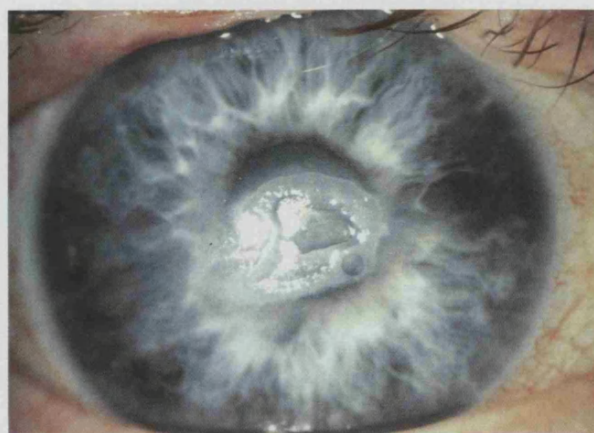
(h)



(i)



(j)



(k)

Fig. 5 (continued). (g) Dense central lipid keratopathy following neglected disciform keratitis. (h) Mucous plaque keratitis stained with Rose Bengal. (i) Mucous plaque keratitis to show interstitial infiltration and keratitic precipitates (slit view). (j) 'Exposure' keratitis showing ridge of swollen epithelium. (k) 'Megaplaque' keratitis in zoster.

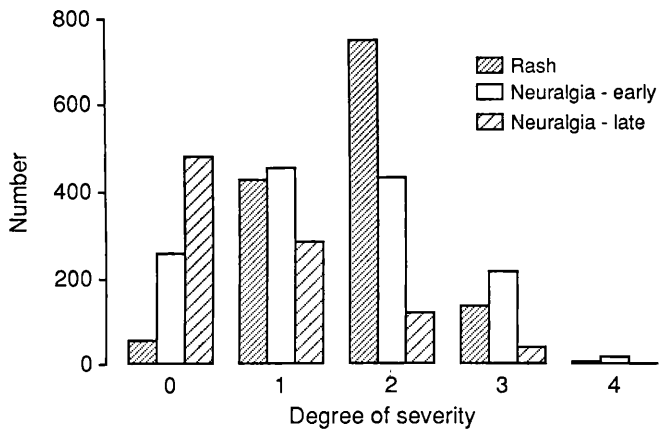


Fig. 6. Comparison of the severity of early and late zoster neuralgia and the severity of the rash. (The degrees of severity are scored as 0 for none, 1 for mild, 2 for moderate, 3 for severe and 4 for very severe.)

in the brain stem, a basal meningoencephalitis, a separate motor neuritis in the brain stem, an occlusive vasculitis involving either the pontine region or cavernous sinus and environs or orbit, and, lastly, possible myositis affecting the external ocular muscles. The latter seemed unlikely to us as the CT scans on 4 cases of total ophthalmoplegia showed no thickening of the muscles. External ocular muscle palsies generally recover subjectively and require no treatment. However, we feel that total third cranial nerve palsies accompanied by proptosis, posterior scleritis and possibly optic neuritis are best treated with systemic steroids in an attempt to prevent ischaemic damage to the optic nerve. We have tried retrobulbar triamcinolone in some of these cases with mixed results.

Rarely an ipsilateral *VIIth nerve palsy* occurs (7 in our series). Very rarely *encephalitis* develops, mainly in severe cases of herpes zoster with systemic spread of virus and a defective reticuloendothelial system: it is usually fatal and we have seen 2 cases. Another rare cerebral complication is *contralateral hemiplegia*, which occurs at about 7 weeks; patients usually recover well.^{33,34} We saw 7 cases. Recent investigations suggest a virus-induced granulomatous angiitis is responsible producing thrombosis of either large vessels such as the middle cerebral artery or small intracerebral vessels.³⁵

At the onset of the disease *neuralgia* is severe and constant in the majority of cases, but tends to remit at the end of the first week. It is localised to the dermatome distribution of the rash and tends to be proportional to the severity of the rash. Of our patients, 252 had no pain, 454 mild transitory pain, 428 moderate pain, 212 severe pain and 11 very severe pain. There was a very close correlation between early neuralgia and rash severity/late neuralgia (chi-squared $p < 0.01$) (Fig. 6). There was also a close correlation between neuralgia and loss of corneal sensation (Fig. 7). In many cases acute neuralgia is accompanied by a post-viral *depression* which comes on a week or two after the rash onset.

Table I compares the incidence of ocular complications in different series

Chronic Lesions

Skin

Varying degrees of *scarring* develop, ranging from undetectable lesions to extensive areas of deep scarring resembling that seen after full-thickness burns, and even to cicatrix production. Generally, the typical punched-out geographical scars appear early with differing amounts of pigmentation or depigmentation, loss of hair, and some acne formation. These lesions frequently fade with time. Occasionally episodes of *hyperaemia* and *recurrent rash* may occur, leading the patient to think there is another attack of zoster. No true vesicles appear, however, and they are probably episodes of neurologically induced hyperaemia with secondary dermatological changes: often they are due to patient-induced skin trauma as a result of the persistent irritation.

Eyelids

Persistent *ptosis* is common and nearly always of mechanical aetiology due to chronic inflammation, oedema and scarring. Chronic *blepharitis* secondary to scarring of the lid margin is less commonly seen. Severe *scarring* of the lids may lead to trichiasis, loss of lashes, abnormal tear film distribution, ectropion, entropion occlusion of lacrimal puncta and notch defects. Extremely rarely full-thickness lid loss occurs.

Conjunctiva

Mucus-producing *conjunctivitis* is a common chronic lesion. This mucus is abnormal and adversely affects the tear film, making it greasy and unstable. Less often, large lipid-filled *granulomas* appear under the subtarsal conjunctiva and severe submucosal scarring similar to that of old trachoma can develop.

Episclera and Sclera

Scleritis and *nodular episcleritis* are particularly chronic

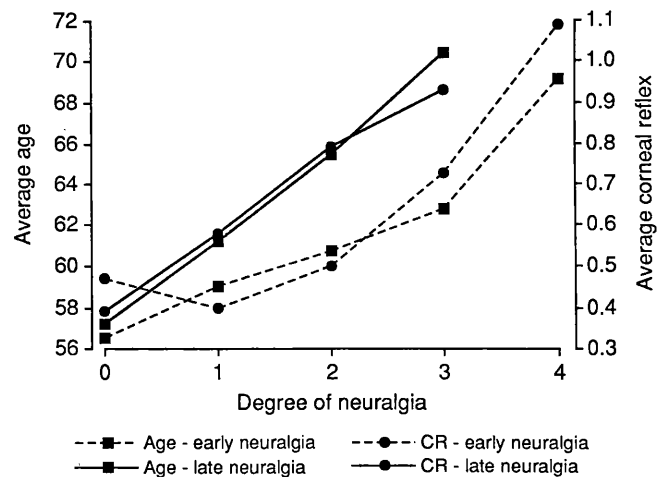


Fig. 7. Severity of acute and post-herpetic neuralgia in relation to the patient's age and corneal sensation. (Neuralgia is scored as 1 for mild, 2 for moderate, 3 for severe and 4 for very severe. The corneal sensation is scored as 0 for total loss, 1 for partial loss and 2 for no loss.)

Table I. Comparisons of the incidence of ocular complications of ophthalmic zoster in different series

	Marsh and Cooper (n=1356)	Burgoon <i>et al.</i> ⁵ (n=36)	Womack and Liesegang ³⁶ (n=94)	Harding ³⁷ (n=71)	Scheie ³⁸ (n=93)
Conjunctivitis (%)	75	7			
Episcleritis (%)	55				
N episcleritis (%)	5				
Scleritis (%)	5				
Keratitis (%)	49	8	61	22	28
Microdendrites (%)	19		51		
Nummular (%)	30		41		
Disciform (%)	5		10	13	
Oedema (%)	5				
Mucous plaque (%)	3				
Neurotrophic (%)	7		25	4	
Exposure (%)	1		11		
Sclerokeratitis (%)	3		1		
Serpiginous (%)			7		
Iritis (%)	54	3	34	3	26
Glaucoma (%)	14			3	12
Muscle palsy (%)	10	3		3	2
Optic atrophy (%)	0.04				1
Neuralgia (%)					
Acute	76	18			
Chronic	21	10			

and frequently leave patches of increased scleral translucency and scleral atrophy (Fig. 5e). *Neglected sclerokeratitis* runs a very chronic course with progressive deposition of infiltrate, vascularisation and lipid in the cornea which may either remain confined to the periphery to form a faceted type of scarring or may migrate across the cornea causing severe visual embarrassment.

Cornea (Fig. 4)

Nummular keratitis or superficial stromal infiltrates can behave like those of adenovirus type 8 in that they fluctuate in density, become chronically active and can diminish visual acuity. They are both exquisitely sensitive to low doses of topical steroid. Peripheral infiltrates if untreated may, over the years, consolidate and form facets (Fig. 5f) which show primary lipid deposition and can later become vascularised with secondary lipid deposition. It is notable that the adjacent episclera is relatively ischaemic (as demonstrated by fluorescein angiography: Fig. 3k,l). We feel in some cases a very small dose of topical steroid may be enough to prevent this scarring occurring. Infiltrates may rarely invade the central region of the cornea, profoundly reducing vision and necessitating corneal grafting.

Disciform keratitis, if untreated with topical steroid, nearly always becomes chronic with progressive accumulation of infiltrate in its centre and immune rings. This is followed by lipid deposition and vascularisation with very dense nebula formation (Fig. 5g), often adversely affecting vision. Here, too, corneal grafting is very successful because the corneal sensation is usually preserved. Unfortunately some cases evolve into a mucous plaque or neuroparalytic keratitis,^{39,40} both of which are unfavourable for grafting.

Neurotrophic keratitis may develop in the later stages of ophthalmic zoster with late loss of corneal sensation or decompensation of a previously quiet anaesthetic cornea

(23 in our series). Total loss of corneal sensation alone does not lead to this type of keratitis. Other factors are required, such as chronic conjunctivitis, lid margin deformities and loss of lid margin and bulbar conjunctival sensation.⁴¹ Chronic corneal epithelial swelling is seen first and leads to punctate epithelial erosions, ulceration in the interpalpebral area and infiltration of the underlying stroma.¹⁵ If untreated, either the ulcer tends to deepen and perforate or the underlying stroma becomes rapidly calcified (dependent on the state of the collagen, glycosaminoglycans, tear calcium and phosphate).

Neurotrophic keratitis is a very difficult management problem and patients must be carefully and frequently reviewed. The precorneal tear film must be stabilised by the use of artificial tears. Any coexisting ulcerative blepharitis should be treated firstly with lid toilet and antibiotic ointment; if this fails tetracycline tablets 250 mg b.d. should be given. Abnormal plugs of mucus in the tear film may be dispersed by mucolytics such as acetylcysteine 10%. In our own experience severe indolent ulceration of the cornea is best treated by a large lateral half tarsorrhaphy at an early stage, although taping of the lids and induction of a temporary ptosis with botulinum toxin may be tried first. We have been very impressed by the latter,²⁰ but this facility is not available in many departments and recovery after tarsorrhaphy is remarkable, with stabilisation of the tear film and rapid healing of ulceration. A year or two after this procedure it may be possible to open the tarsorrhaphy in stages.

Mucous plaque keratitis. A strange form of keratitis developed in 44 of our cases of herpes zoster (13 within the first 6 months and 31 after that). It commences in two time periods: within the first 3 months (early) and after 6 months (late). It is characterised by transitory epithelial lesions followed by permanent stromal haze formation. The onset is sudden, with ciliary injection and the production of mucous plaque deposits on the surface of a dif-

fusely swollen corneal epithelium. The overlying tear film becomes unstable and rapidly forms dry spots, often in dendriform shapes. The plaques look like fragments of white blotting paper and in the branching form often resemble dendritic ulcers. They stain brilliantly with Rose Bengal (Fig. 5h) and moderately well with fluorescein and Alcian blue. The plaques can easily be removed from the surface of the cornea without any damage to the underlying epithelium. They vary in size, shape and number from day to day and are accompanied by diffuse stromal haze in both the superficial and deep layers of the cornea. There is always underlying iritis with formation of small white keratitic precipitates (Fig. 5i). The plaques will usually resolve after treatment with 10% acetylcysteine drops and the underlying inflammation responds well to topical steroids. The keratitis progresses with loss of corneal sensation and increased stromal haze. After 3–4 months the plaques disappear and the tear film stabilises, revealing more clearly the large sheets of stromal haze which lead to a drop in visual acuity. In other cases there is late development of neuroparalytic keratitis or deposition of a ring of white surface plaque with gross reduction of vision. It is important to differentiate these plaques from the dendritic ulcers seen in herpes simplex. The features mentioned above greatly facilitate clinical diagnosis, but culturing of the epithelial lesions for virus clearly identifies herpes simplex from herpes zoster.⁴²

The aetiology of mucous plaque keratitis is obscure. No virus has been cultured from these corneas but there does appear to be a connection with the prior use of topical steroids.⁴³ In our series 11 of the early-onset and 21 of the late-onset patients had received them and disciform keratitis had preceded 6 of the 31 late-onset cases.⁴⁰ However, the only significant correlation (chi-squared $p < 0.01$) with any associated ocular lesions was with absent corneal reflex. It is vital to control the accompanying secondary glaucoma and surgery should not be delayed. Topical steroids treat the underlying iritis, mucolytics frequently clear the plaques, and artificial tears stabilise the tear film.

'Exposure' keratitis covers an ill-defined group of patients who show generalised corneal epithelial bedewing which often advances to grossly oedematous areas of epithelium with the formation of white ridges horizontally in the interpalpebral area. Rose Bengal and fluorescein give diffuse punctate staining with moderate linear staining along the ridges (Fig. 5j). There is generally accompanying hyperaemia of tarsal and bulbar conjunctivae and always an extremely unstable tear film. Schirmer's test and tear production appears to be normal but plugs of mucus are often seen in the tear film. Strangely, corneal sensation is only partially lost, the lid margins may or may not be healthy and there is usually good blinking. The onset is usually just after the start of the rash but can be delayed. This type of keratitis runs a protracted course in which topical viscous agents are only partially effective. Some chronic cases may go on to develop large central white surface deposits and calcification.⁴⁰ neurotrophic keratitis and permanent superficial

stromal haze formation. Attempts can be made to stabilise the epithelium by intermittently taping the eye closed and lid hygiene, but the only therapy which appears consistently to stabilise the epithelium is a temporal third tarsorrhaphy. Dense plaques may have to be removed by superficial keratectomy⁴⁴ (more recently with the excimer laser). We saw 25 cases in all. The aetiology is very obscure.

'Megaplaque' keratitis arises in some cases of mucous plaque and exposure keratitis. The plaques may be disc-shaped or ring-shaped and are attached to the underlying stroma by a narrow neck (Fig. 5k). They profoundly interfere with vision and often there are epithelial defects around their base where secondary infections start. We have been impressed by the results of excimer laser superficial keratectomy in these patients.

Lipid keratopathy complicates severe cases of nummular, disciform and sclerokeratitis, especially when these are inadequately treated with topical steroids. Lipid keratopathy may occur in the absence of demonstrable blood vessels but dense deposits are always vascularised. The vessels may stem from the limbus at a narrow origin of a single artery and vein or from multiple stems all around the limbus. Unless their development is controlled with topical steroid or they are closed by laser the deposits increase.⁴⁵

Iris

Iritis often becomes chronic and, if untreated with steroid in the acute stage, posterior synechiae develop. The iritis may progress in its ischaemic manifestations to massive iris atrophy in 6% of cases.²² It is interesting that the iris changes sometimes seen after cases of acute closed angle glaucoma and following retinal detachment operations are similar and also due to iris vascular closure.

Cataract

Posterior subcapsular lens opacities and nuclear sclerosis often develop in severe and chronic cases of iritis. Rarely a sector of subcapsular lens opacity may underlie a sector of iris atrophy.

Glaucoma

Hypertensive iritis may persist with a minimum of flare and cells. Unfortunately, confusion can occur during the management of this condition when steroid glaucoma also develops and, indeed, was a problem in 42 of our patients. It is always worth considering the diagnosis of zoster in unilateral open angle glaucoma.

Neurological Lesions

Optic atrophy follows optic neuritis with a profound loss of vision: 6/60 and less. Permanent symptomatic external ocular muscle palsies rarely occur despite defects on the Lees screen, and when they do the affected muscle usually lies adjacent to an area of chronic scleritis and iris atrophy.

Post-herpetic neuralgia (PHN) has been defined as pain

developing after the crusts separate – variously described as starting at 4 weeks, 6 weeks, 2 months and 6 months.⁴⁶ Because acute neuralgia usually ameliorates rapidly in the first month and a different type of PHN develops from 3 months, we chose this period for our definition. When measured at 6 months no PHN occurred in 478 of our patients, mild in 269, moderate in 120 and severe in 31 (Fig. 6). It is correlated (chi-squared $p < 0.01$) with rash, ocular involvement, loss of sensation and early neuralgia, but not age. It may take on different forms and can be a chronic constant pain or ache, an intermittent severe stabbing pain (closely resembling tic douloureux) or an intermittent very unpleasant paraesthesia or a sensation of crawling under the skin. The pain is often aggravated by touch, heat, cold winds and is worse at night. The majority of patients improve slowly over 1 year; the proportion who do not usually suffer depression and there may be severe exhaustion and even a danger of suicide.

Recurrent Disease

Perhaps the strangest aspect of ophthalmic herpes zoster is the recurrent nature of the ocular complications. These can reappear as late as 10 years after the onset of the disease and appear to be unrelated to the severity of the initial disease. They are frequently precipitated by the sudden withdrawal or reduction of topical steroid therapy. Episcleritis and scleritis often recur and can cause much resulting scleral atrophy. When nummular or disciform keratitis relapses there is an increase in stromal infiltrate, haze and thickness. Neuroparalytic keratitis is very prone to recur, with repeated disruption of corneal epithelium and ulcer formation. Mucous plaque keratitis also readily reactivates, with further formation of plaques, ciliary injection and iritis. Profuse cream-coloured keratitic precipitates usually accompany relapsing iritis, although hypertensive iritis may show practically no flare, cells or keratitic precipitates; in this it closely resembles Posner-Schlossman syndrome and can even mimic unilateral chronic open angle glaucoma.

It should be borne in mind that all these recurrent lesions may be separated by some time from a previous attack of herpes zoster and, indeed, the original attack may have been forgotten or so mild as to have passed unnoticed. It is therefore worth bearing the diagnosis of herpes zoster in mind when any of the lesions described above are seen in a patient for the first time, especially when old stigmata of zoster are apparent. These include the typical geographic skin scarring, the areas of increased scleral translucency or atrophy and the patchy iris atrophy.

AETIOLOGY

The current theory of aetiology is that, after an initial attack of chickenpox with its attendant viraemia, virus is retained in the posterior root ganglion in a latent form that later reactivates under the influence of unknown trigger factors, replicates, and migrates chiefly centrifugally down the sensory nerves.^{47,48} The virus eventually reaches the skin where it produces the familiar herpes zoster ves-

icles and, in some cases of ophthalmic zoster, the eye (it can be isolated from both sites^{49,50}). It causes a perineuritis and perivasculitis in the affected dermatome and underlying areas leading to varying amounts of direct and indirect tissue damage.

VIROLOGY

Varicella zoster virus (VZV), or as it is now known, human herpes virus 3 (HHV3), is a typical herpes virus containing DNA, an icosahedral nucleocapsid and a glycoprotein-containing outer membrane. Under the electron microscope it is indistinguishable from the rest of the herpes family of viruses. Until recently it had not been possible to acquire enough pure virus to characterise its constituents, but the complete DNA sequence has now been elucidated.⁵¹ Using conventional methods there has only been one VZV strain detectable, but with the advent of restriction endonuclease analysis more are definable: this makes possible the tracing of virus in one host or within a population. Some of the genome is homologous with other herpes viruses⁵² and in a few cases amino acid sequences have been shown to be very similar to those of herpes simplex virus 1 (HSV-1).⁵¹ Most gene functions have not been elucidated as yet, except for the production of glycoproteins which reside in the outer coat and appear in the later stages of viral replication. Comparisons with HSV-1 also suggest evolution from an ancestral genome, so it is very likely that VZV gene products appear in a similar way to those of HSV, with an early phase (concerned with regulatory function), an intermediate phase (concerned with DNA synthesis) and a late phase (concerned with capsid and membrane synthesis).

Laboratory research on VZV has been sketchy, unlike that on HSV, because it is difficult to obtain cell-free virus and no satisfactory animal model has yet been developed. Both viruses are neuro- and epithelio-tropic, tending to cause direct cell damage in the acute stages: this is especially so for HSV. When they establish latency there is little evidence of cellular disruption but HSV seems to establish latency and reactivate more easily. Both viruses have humans as their only reservoir, HSV being more widespread with an endemic pattern, and VZV being more prevalent in urban societies and showing an epidemic pattern. The presence of antibodies as shown by sero-conversion in adult life approaches 70% for HSV and 95% for VZV;^{53,54} implying that virtually the whole population comes into contact with these viruses, although not all get clinical manifestations.

EPIDEMIOLOGY

The classic paper on epidemiology is that by Hope-Simpson,⁴⁸ which covers 192 cases of zoster seen in general practice: he found the incidence of new cases per population block to be 0.074% in those under 10 years of age, a plateau of 0.25% from 20 to 50 years of age, and over 1% over 80 years. In our series of over 1300 patients from the Zoster Clinic at Moorfields⁵⁵ we found a slightly different pattern: a steady exponential rise rather than a

dramatic increase in later life, though the figures are unreliable after 80 years of age. Hope-Simpson's cases came from general practice whilst ours are mostly from referrals to Casualty, so they may not be strictly comparable. We found no consistent changes with season, or with sex.

The weekly returns from the Royal College of General Practitioners (RCGP) give countrywide figures on zoster in general.⁵⁵ Zoster incidence stays steady at 3–4 per 1000 and does not follow the epidemic pattern of chickenpox, thus making it unlikely that zoster is an immediate result of contact with VZV. This is contrary to the old theory of aetiology in which close exposure to the virus was thought to cause a change in immunity resulting in reactivation of virus and an attack of zoster. It is also significant that at the vesicular phase of zoster close contacts who have not suffered from chickenpox risk acquiring the infection. The higher zoster prevalence rates in the older age groups are the opposite to that in chickenpox, but the age intervals provided by the RCGP are not sufficiently narrow to make any comparison with the Moorfields' figures. Females have a slightly lower incidence for chickenpox and a higher one for zoster than males. AIDS, Hodgkin's disease and other conditions causing impaired cell-mediated immunity are associated with a higher incidence and severity of the clinical disease. Varicella in the first year of life leads to a high incidence of a mild variety of zoster within the next year or so.^{14,56} Second attacks of herpes zoster occur in 4% of patients⁸ and two areas of the body can be affected simultaneously.

IMMUNOLOGY

It is often stated that the development of zoster is associated with a temporary depression of immunity and so there have been many studies in zoster.

Humoral immunity

It has been known for many years that there is an anamnestic rise in the level of varicella-neutralising antibody during an attack of herpes zoster, demonstrating that the virus had been encountered previously.⁵⁷ There is typically a rise in immunoglobulins G and A within 2 days of rash onset, reaching a peak in 2–3 weeks, and declining to very low levels at a year.^{58,59} There is an elevation of immunoglobulin reported in some series; this usually indicates a primary infection and suggests that although the antibody pattern of response to zoster has components similar to varicella there are some additional ones which make it distinct.⁶⁰ The outcome of varicella, either as zoster or chickenpox, does not seem to be adversely affected by the absence of serum antibodies,⁶¹ whereas those with Hodgkin's disease, who have normal antibody levels, usually do badly. The consensus is that other, presumed cellular factors are more important. Antibody localisation may, however, be important in causing some of the pathological findings, such as the granulomatous angiitis thought to be associated with orbital involvement, ocular muscle palsies, iritis, episcleritis/scleritis, stroke, ischaemic optic neuropathy and encephalitis: the mechanism may well be a type 2 hypersensitivity.

Cellular Immunity

Cellular responses to VZV have also been studied extensively and reveal a consistent depression of cell-mediated immunity in the first 5 days of the zoster rash as assessed by blastogenesis of peripheral blood cells and reduced delayed-type sensitivity response to skin testing.⁵³ It is possible that this is either a true depression of cell-mediated immunity or is due to recruitment of immunologically competent cells into affected tissues so that they are not available in the circulatory pool. A reversal of T4/T8 subsets in the peripheral blood has been noted⁶² and this could be either due to reduced circulating number of CD4+ T cells or to increased numbers of circulating CD8+ T cells.

Cytotoxic CD8+ T cells are important in destroying virally affected cells. These CD8+ cells can become activated when their receptor recognises viral antigens in combination with class I HLA antigens on the surface of the infected cell. Activation of CD8+ cytotoxic T cells results in target cell death by membrane cell lysis after secretion of substances such as perforin by the activated T cells. CD4+ cells are necessary for the maturation of cytotoxic CD8+ T cells and for the production of specific neutralising antibody by B cells maturing into plasma cells, which occurs as a result of secretion of lymphokines such as interleukin-4.

PATHOGENESIS

Herpes zoster is a reactivation of latent VZV, in a similar way that cold sores are of HSV.

Latency

HSV and VZV are thought to become latent in the primary attack, being transported from the epithelial vesicles along the sensory axons to the neural cell body.^{63,64} This has been demonstrated in animal models for HSV, and in the main depends upon the amount of virus.^{65,66} A similar process has been inferred for VZV, because the frequency of dermatome involvement in zoster parallels that of rash density in chickenpox, being most common on the trunk and head. Latency occurs in only a small fraction of neurones, and involves the incorporation of viral genome into the host one; whether this is in a specific site, randomly, or whether there are several sites in each cell is not known (with HSV it is an extrachromosomal DNA in the circular episome). VZV RNA and DNA have been demonstrated in cadaver trigeminal ganglia, at a rate of 1/1000 neurones.⁶⁷ To date the same strain of virus has been shown to appear in separate sites during zoster⁶⁸ and probably at the primary and recurrent stages.⁶⁹

Reactivation

The mechanisms of reactivation in HS and VZV are likely to be similar and relate to the symbiosis of the virus and host: a disturbance of this causes clinical and possibly sub-clinical disease. Many factors may cause HSV to break out of latency, and it has a much greater inherent potential for

doing this than VZV: this might be related to the position of insertion, quantity of viral genome or proliferative potential. Traditional hypotheses of reactivation involve alterations in the immune system with time, trauma and neural degeneration.

Reduced Immunity

Hope-Simpson⁴⁸ suggested that when the titres of antibody or reactive cells fall below a certain level, the virus somehow escapes and causes clinical damage. There is no good evidence for this in humans for either virus. After the primary infection with VZV, circulating antibody levels fall off over a year and become undetectable.⁵³ Titres do not consistently decrease with age, as is required if this is to be the main determinant of disease, and there is an anamnestic response in the majority of individuals who have zoster, implying that immunity has not faded. Moreover, those who have suffered zoster early in life are not more likely to have a second attack after a lesser interval than others who get their first attack in middle age (as might be expected if the fall in titres was host-dependent). Cell-mediated responses also decrease with age but we are not aware of any research which has demonstrated this for VZV in particular, and the predominantly lymphocytic infiltration into trigeminal ganglia during the acute phase indicates that cells may certainly be induced to respond specifically and with effect.

Trauma

It seems that damage to part of the neurone or iontophoresis of various chemicals reliably lead to reactivation of HSV⁵⁴ and recovery of virus from tissue is difficult unless there has been a certain amount of damage, such as in explantation.⁷⁰ It is interesting that mild and transient attacks of herpes zoster can follow retrobulbar or trigeminal ganglion injections and neurosurgical incisions (so-called symptomatic zoster).⁷¹ Equally exposure to ultraviolet light, nerve section and irradiation are well known to reactivate HSV. Neuronal metabolism in the adult is mostly concerned with maintenance of the cell and there is virtually no proliferative activity: most of the DNA is inactive. If the cell is damaged in some way, such as by sectioning the axon, repair mechanisms start and it is feasible that the viral DNA may be involved in this process, leading to switching on of viral proliferation which may or may not overwhelm the cell and lead to viral shedding. The likelihood of this happening with VZV is small because of the very low frequency of neurone colonisation; VZV's potential for reactivation is also low, but over a lifetime the chances of viral shedding could well be significant. What is difficult to explain is why in typical zoster, unlike in herpes simplex, the neurones are completely destroyed and there is no potential for recurrence. It is perhaps at this stage that the immune system is important: the frequent recurrences of HSV shedding keep the immune response active and control local spread very quickly, but as VZV recurrence is very infrequent, the response is probably delayed allowing more viral spread in the gan-

glion and a more vigorous tissue response when it eventually occurs.

Other Factors

Neurones may be damaged by other factors, for instance HIV infections; clinically HSV is often reactivated by colds, influenza and pneumonia which may have a direct effect on neuronal metabolism, rather than indirectly by a specific immune response. So far there is no evidence that other acute infections precipitate zoster.

Ageing

Most episodes of zoster cannot be related to a precipitant and occur chiefly in older age groups. It is possible that a latently infected cell is involved directly or indirectly by the normal neuronal death rate and so sets off the process of reactivation: an intellectually satisfying idea for which there is as yet no evidence. Against it is the fact that zoster can present at any time of life: the Zoster Clinic incidences, showing a form of exponential rise with age, might, however, be explained by an appropriate statistical model.

Ocular Pathogenesis

There is undoubted viral replication in the acute phase of the disease, as confirmed by the culture of virus from corneal epithelial lesions,⁵⁰ and there may or may not be replication in the stroma, endothelium, iris and retina. Once virus reaches the tissues acute and chronic inflammatory processes attempt to clear virus and viral antigens; the dose and strain of virus, efficacy of immune response, tissue involved and treatment are some of the governing factors. Inability to clear virus and the establishment of a type of chronic, low-grade infection is probably the main feature of the long-term problems (apart from acute damage such as denervation). Whilst we have been unable to grow the virus in chronic keratitis from either corneal epithelial scrapings or scarred corneal discs removed in keratoplasty and submitted to maceration, recently, viral DNA has been found in post-mortem eyes within the neurovascular bundles and corneal buttons.⁷² We feel that during remissions of inflammation VZV is in the latent form and there is a minimal tissue response, but when chronic inflammation occurs there may be an alteration of viral DNA or a sort of autoimmune response by the host (but no viral replication as we know it). In this way it differs from HSV.

PATHOLOGY

There is relatively little in the literature on the pathology of zoster. Perhaps the earliest paper is by Head and Campbell⁷³ describing inflammation, haemorrhage and necrosis of ganglion cells in the dorsal root ganglion followed by scarring. They stressed the marked variation in the severity of the lesions paralleling clinical experience. As far as we know there is a very short phase of viral replication in the nerves and closely related tissues at the onset of the disease. This is followed shortly afterwards by infiltration

with inflammatory cells and then by variable necrosis of cells – principally neurones. There may then be resolution or continuing chronic and relapsing inflammation persisting for many years with continuing damage to the tissues and scarring. The trigeminal ganglion, brain, peripheral nerves, orbit and globe have been examined.

Trigeminal Ganglion

Virus has been isolated in the very early stages;⁷⁴ within 2 weeks there is infiltration with polymorphonuclear granulocytes, plasma cells and predominantly lymphocytes.⁷⁵ The latter suggests that there is already a coordinated cell-mediated response rather than a purely inflammatory one.⁷⁶ The adjacent dural sheath and carotid are involved in the inflammatory process. Early on there is a varying amount of neuronal necrosis; indeed, in some patients practically all the cells may be destroyed.⁷³

Brain

The mesencephalic nucleus may show large nodular collections of microglia with later effacement of structure. There may be a lymphocytic leptomeningitis and lastly the cranial nerves and their nuclei on both sides may show lymphocytic infiltration.⁷⁷

Peripheral Nerves

At the onset there is a perineuritis with an adjacent perivascularitis. About 10 days later there is secondary decay of axons and myelin sheaths followed by fibrosis.

Orbit

There can be extensive vasculitis, haemorrhage, perineuritis and inflammatory cell infiltration of other orbital contents including the extraocular muscles.

Globe

Most pathological reports are of the later stages of the disease when the eye had been enucleated.⁷⁸ The commonest findings are perineuritis and perivascularitis in the scleral channels, in the long and short ciliary nerves and in the arteries. Presumably the virus reaches the eye via the ciliary nerves. The connection between this and subsequent chronic inflammatory reactions has not been clarified.⁷⁸ Although viral replication has not been demonstrated, in late phases of the disease viral DNA has been found. The vasculitis is probably due to immune complexes, with the antigen in the nerve fibre bundle and the antibody in the adjacent blood vessel²² (an Arthus phenomenon). It is interesting that, at times, lesions of different tissues develop in the same sector of the eye,^{79,80} confirming the neurological distribution of the disease in the globe.

TREATMENT

Ophthalmic herpes zoster offers a great challenge in management. Such is the nature of the complications that effective treatment early in the disease can prevent many

intensive at first and in many cases must include a long-term follow-up. The objectives of treatment are twofold: to stop viral replication at the earliest opportunity and to control the ensuing inflammatory changes, thus minimising tissue scarring.

Systemic Therapy

Short-Term Admission

Short-term admission (5 days) is recommended for those with severe disease, the aged, the immunosuppressed, and those with poor social circumstances. If admission is impossible, there should be 1 week's bed-rest at home with good nursing. Proper diet, care and administration of therapy is usually successful in obtaining rapid recovery. The patients should be barrier-nursed in a side ward during the vesicular stage and those with no previous infection by varicella should be kept away until all vesicles have gone. After this they are no longer infective. Patients are often distressed and frightened of the disease and must be reassured that the acute stage is short-lived and recovery usually rapid with the correct management.

Steroidal Anti-inflammatory Drugs

The routine use of systemic steroids in patients with ophthalmic herpes zoster is controversial.⁸¹ Although some physicians use systemic steroids routinely, claiming a lessening of zoster complications, in particular PHN,^{82,83} others stress the increased risk of systemic spread of the disease with high doses.^{84,85} It should be pointed out that most adverse reports of this treatment were in patients previously immunosuppressed. There are, of course, the routine complications caused by systemic steroids in old people such as gastric ulceration, hypertension and psychosis. There is no doubt that the potent anti-inflammatory properties of steroids are very valuable for the vasculitis which occurs in the skin, eye, orbit and brain. It has also been claimed that the incidence and severity of post-herpetic neuralgia are significantly reduced. We therefore feel that systemic corticosteroids are indicated very early in patients with: (1) large haemorrhagic skin bullae, (2) progressive proptosis with total ophthalmoplegia, (3) optic neuritis and (4) cerebral angiitis. Untreated, the first leads to severe skin scarring and neuralgia, the second to continuing diplopia, the third to severe optic atrophy and the fourth to hemiplegia. An initial oral dosage of 80 mg prednisone should be given, which may be rapidly reduced by 10 mg per day to a 5 mg maintenance dose.⁸⁶

Non-steroidal Anti-inflammatory Drugs

Oral Flurbiprofen (Froben, Boots) 50 mg t.d.s. is useful in cases of episcleritis, scleritis and sclerokeratitis. We have been impressed with its use alone in episcleritis, where the dose must be slowly reduced as improvement occurs and there is less likelihood of a recurrence than with topical steroids. However, in cases of scleritis and sclerokeratitis it must be used in combination with potent doses of topical steroids. The anti-inflammatory property of some anal-

Antiviral Drugs

Systemic antivirals have proved rather disappointing in zoster. IDU is far too toxic for systemic use, cytosine arabinoside proved less effective than the control in one clinical trial⁸⁷ and adenine arabinoside too insoluble to introduce intravenously in an effective dose without fluid overloading.⁸⁸ Despite extravagant claims for amantadine⁸⁹ there have been no adequate controlled studies on its effectiveness. Acyclovir, although not as effective *in vitro* against varicella/zoster as against HSV, has been extensively used and has proved effective in reducing the rash duration, spread and acute herpetic neuralgia in immunosuppressed patients.⁹⁰ It has also been used in the treatment of varicella/zoster acute retinal necrosis with mixed results.²⁷ The drug is administered intravenously at 10 mg/kg over 1 hour repeated every 8 hours for 7 days, then orally at 800 mg 5 times a day. The results of oral and intravenous courses of treatment in immunocompetent patients are controversial; although acute neuralgia and rash healing time are marginally improved,⁹¹⁻⁹⁴ reports of its effects on the incidence of post-herpetic neuralgia are conflicting.⁹⁵ There is one large controlled series showing a reduction in ocular complications in patients who were treated within 72 hours of developing the rash, but where all those with ocular complications at presentation were excluded.^{96,97} We feel that before substantial funding is used to finance use of the drug routinely in zoster more clinical trials are essential.

The search must continue for a more effective antiviral agent, but if viral replication is confined to the onset of the disease and if the later lesions are, as seems likely, due to immunologically mediated reactions not dependent on the presence of live virus (as we know it), the outcome will not be improved unless the antiviral is administered at the very onset of the disease.

Antibiotics

In our experience antibiotics have no value in the treatment of acute zoster. The early oedema and crusting are due to viral-mediated damage rather than secondary bacterial infection.

Analgesia

Fortunately, acute neuralgia, although at its most severe within the first 2 weeks, is usually short-lived. Full analgesia should be given in the early stages because there is increasing evidence that when administered at this stage it reduces permanent damage to the nervous pathways. It is best to start with milder analgesics and rapidly build up to stronger ones as necessary: for instance paracetamol by itself or in combination with dextropropoxyphene hydrochloride (co-proxamol), or dihydrocodeine (DF118). In very severe cases pethidine may be necessary. Buprenorphine tends to make patients feel drowsy and disorientated, especially the elderly, and is therefore best initially used at night only, although if very effective it can be tried at a dose of half a tablet during the daytime.

Post-herpetic neuralgia is extremely difficult to treat

and, like acute neuralgia, is more of a problem in older patients. The pain and paraesthesia tend to be worse at night and are aggravated by heat and cold, wind and touch. These provocations should be avoided where possible; failing that extra analgesia may be needed at these times. The remedies recommended in the literature are legion (many anecdotal and rather dubious) and range from posterior pituitary extract to snake venom. The list clearly demonstrates the overall failure of treatments for this condition. Contrary to others we have found carbamazepine 100 mg twice a day disappointing in the tic douloureux type of post-herpetic neuralgia. Chlorpheniramine (Piriton, Allen & Hanburys), 4 mg t.d.s. and chlorpromazine 25 mgm t.d.s. have proved useful with severe irritational paraesthesia. Unfortunately in our experience nothing seems to ameliorate the severe pain.

Antidepressants

Post-viral depression often begins during the acute phase of zoster and may also be an important component of chronic post-herpetic neuralgia. It is important to recognise it and treat promptly with tricyclic antidepressants such as amitriptyline (50 mg twice a day).⁹⁸ Its existence should be explained to patients and they should be reassured that it responds well to treatment and will pass.

Supportive Counselling

Patients in the acute phase should be reassured that tissue swelling will rapidly subside and, in most cases, the pain improve. They should be warned that a long convalescence may be necessary. Those with severe chronic PHN not responding to treatment should be offered counselling in an attempt to help them live with the pain.

Chickenpox Vaccine

Two attenuated strains of varicella are undergoing clinical trials for vaccination.^{53,99} The main advantage in using a vaccine would be to decrease the complications of varicella in children and adults, but it probably would have no action in those who are immunosuppressed. At best, vaccines prevent or ameliorate the development of zoster, but it would be virtually impossible to do a trial to decide this because of the numbers and time course involved.¹⁰⁰

*Specific Treatment**Skin Treatment*

The main objective of treatment is rapid healing without the massive crust formation that so often gives rise to severe scarring.

Antivirals must be used only in the early vesicular stage of the disease when there is marked virus activity. Idoxuridine, although insoluble in water, is highly soluble in dimethylsulphoxide; preparations are available in 5-40% solutions (Iduridin or Herpid). These can be applied as a paint by the patient or as presoaked dressings changed daily for the first 4 days by a nurse; they have been claimed to speed the onset of crusting, prevent secondary cropping

and reduce acute and post-herpetic neuralgia.¹⁰¹⁻¹⁰³ Many patients also prefer the fact that their rash is covered. Acyclovir 5% ointment applied 3 times a day has also had similar claims of efficacy.¹⁰⁴

Anti-inflammatory steroid creams and ointment should be applied when the vesicular phase has passed (usually 10 days after onset). We use a combination of cortisone and neomycin, applying it 3 times a day to the skin and lids; the antibiotic is useful for preventing secondary infection in the crusts. The greasy nature of the preparation prevents aggregation of crusts and aids their separation. Alternatives are Terra-Cortril spray (Pfizer) and Betnovate (Glaxo). Patients presenting late with large crusts, especially those erroneously treated with starch powder and calamine, should have them cleaned off with warm sterile saline washes followed by ointment. Subcuticular injections of steroids such as triamcinolone have been tried in the acute and late phases of the neuralgia with mixed results.¹⁰⁵

Energetic massage of the affected skin area using a vehicle of lanolin or petroleum jelly can be most effective for neuralgia after crust separation and possibly also reduces scarring. It is based on the gate theory of sensory neural conduction: stimulation of the large afferent nerves with massage inhibits the smaller pain fibre transmissions. It is reputed to be best in the 'trigger' type of pain. More recently capsaicin has been reported as an effective vehicle, but the results are anecdotal^{106,107} and it is very irritant if it contacts the eye.

Topical management of post-herpetic neuralgia by the following must be considered when analgesics and massage fail: transcutaneous electrical nerve stimulation, short wave diathermy and ultrasound.^{108,109} Physiotherapy departments can provide these treatments, which may help some patients.

Pain clinics have an important part to play in refractory PHN. They can offer various treatments including subcutaneous injections of anaesthetics¹¹⁰ and steroids, and stellate ganglion block, which is probably most effective when given very early.¹¹¹ They can also provide the supportive counselling which helps patients live with their pain. Neurosurgery is not recommended because it is often unsuccessful and may introduce other problems such as neurotrophic ulcer formation.

Lid Treatment

The same topical agents as described for the skin may be used for the lids. If there is severe scarring of the lids it may be necessary to epilate and electrolyse the trichiasis or to correct lid deformities by plastic surgery. Chronic blepharitis should be treated by lid toilet and the application of antibiotic ointment to the lid margins twice a day.

Ocular Therapy

The objectives of ocular therapy are to minimise scarring, to reduce inflammation and to maintain a stable corneal epithelium and tear film.

Antivirals

Our experience with topical antivirals such as idoxuridine,

adenine arabinoside and trifluorothymidine has been disappointing even though virus shedding occurs into the tear film and the corneal epithelium during acute keratoconjunctivitis.¹⁷ Despite early reports that acyclovir ointment controlled and prevented later ocular complications¹¹² we have been unable to confirm this.^{113,114} In a recent double-masked trial we found that acyclovir alone was inferior to steroid for controlling inflammation but when combined with steroid led to less rebound inflammation on withdrawal of treatment. Moreover we found that the early conjunctivitis and microdendritic keratitis reported to respond so well to acyclovir are self-limiting, and placebo drops seem to show the same result. Furthermore in cases of chronic neurotrophic keratitis most antivirals will further compromise the already unstable corneal epithelium.

Antibiotics

Antibiotic drops such as chloramphenicol may be used to prevent secondary infection during the acute stage when lid vesicles are discharging and forming crusts or a mucopurulent conjunctivitis is present. Tetracycline ointment is very effective for keratoconjunctivitis when applied twice daily to chronically scarred or inflamed lid margins, since they become a focus for staphylococcal secondary infections.

Anti-inflammatory Agents

As scarring of the eye in zoster is the result of inflammation, the mainstay of therapy for the ocular complications of herpes zoster is corticosteroid, which is essential for scleritis, sclerokeratitis, disciform and mucous plaque keratitis, diffuse corneal oedema, significant iritis and hypertensive iritis. At the first evidence of these complications 0.1% dexamethasone drops should be instilled every 4 hours. Prompt treatment at the start of inflammation cuts down the ischaemic and fibrotic scarring that usually develops. Once control is achieved, the potency and frequency of administration can be reduced and the dose of topical steroids titrated against the degree of disease activity in the eye.⁸¹ This is a slow, cautious process and may extend over a period of years. The main problem is the tendency of the inflammation to relapse, particularly with too rapid or abrupt a withdrawal. As well as reducing the frequency of administration of the drug, serial logarithmic dilutions or a change to another weaker steroid may be made (e.g. from dexamethasone to betamethasone to prednisolone). Many of the more intelligent patients can titrate their own dose, which may be reduced to as little as 0.03% prednisolone daily to maintain control.⁸¹

Precautions with topical steroids. The important obligations of steroid management are careful follow-up and examination to detect toxic side effects. Patients on topical steroids may develop glaucoma, cataract, secondary infections, mydriasis and ptosis. They also tend to develop a dependency on them so that withdrawal may be difficult without causing a recurrence of ocular inflammation.⁴³ Clearly, if glaucoma is detected, the dose of steroid must

be reduced and, if persistent, clobetasone or fluorometholone drops must be used. However, in some patients it may be difficult to differentiate a steroid glaucoma from hypertensive iritis, particularly in mucous plaque keratitis, and a helpful technique is to increase the dose of steroid and review in 2 days. If the pressure decreases the steroid dose must be maintained at a higher level; if not it must be reduced and antiglaucoma treatment such as timolol started. When this fails it is advisable to use acetazolamide only in the short term while glaucoma surgery is prepared. Potent doses of steroid should be reduced as soon as possible to avoid inducing lens opacities, but in some cases it is impossible to know whether to attribute these to the chronic iritis. Mydriasis and ptosis can also be caused by zoster alone. Steroids must be used with great caution in patients with neurotrophic keratitis because of the risk of secondary infections. When using steroids regular slit lamp examination and applanation are essential.

Artificial Tears, Wetting Agents and Mucolytics

These are used for unstable corneal epithelium in an attempt to stabilise the surface and prevent mucus deposition. We have found it best to try the different artificial tears empirically to find the most satisfactory and to add Lacri-Lube ointment (Allergan). Acetylcysteine 10% may be used to dissolve mucus deposits and prevent further deposition, particularly in mucous plaque keratitis. Lastly, it should not be forgotten that unfortunately long-term drop administration can lead to toxic changes to the epithelium from the preservatives in the drops. It is then essential to switch to preservative-free drops. Taping the eyelids closed with Blenderm is often useful for rapidly establishing a stable epithelium, but can be a trial if there is significant neuralgia.

Surgery

Lids

Lid margin deformities arising from scarring (e.g. ectropion and trichiasis) are best treated with corrective lid surgery. Full-thickness loss of the lid margin should be treated as a surgical emergency. A lateral half tarsorrhaphy should be carried out promptly in all cases of neurotrophic ulceration that have failed to respond to medical treatment, and may also be necessary in cases of chronic exposure and neuroparalytic keratitis. Many patients are averse to this procedure but must be persuaded that it provides rapid healing, security and dramatically reduces outpatient visits. Lastly, if the problem persists after a lateral tarsorrhaphy a middle third must be carried out.

Intraocular Surgery

Cataract extraction. The extracapsular technique with posterior chamber implant is surprisingly straightforward when undertaken in a quiescent phase. The main problem is post-operative inflammation, which may persist for more than a year but always seems to be controllable with a low dose of topical steroid.

Glaucoma surgery. Trabeculectomy is usually trouble free and post-operative inflammation is the only real problem. Later on there is a high incidence of cataract formation.⁴⁴ We have little experience of laser trabeculoplasty in zoster but it may be a worthwhile short-term solution.

Combined cataract and glaucoma surgery. This may be necessary and we have found it most successful with the same proviso of covering post-operative inflammation.

Corneal surgery. Neglected disciform keratitis or sclerokeratitis frequently give rise to dense scarring and lipid deposits in the central cornea. These patients tend to do well with perforating corneal grafts, provided that the corneal sensation is preserved and there is not too much vascularisation or the vessels have been closed by argon laser treatment.⁴⁵ Very rarely an urgent corneal graft has to be done in patients whose neurotrophic ulceration has perforated. The prognosis is not good as considerable difficulty may be encountered in establishing a stable corneal epithelium over the graft; because of this it is best to carry out a tarsorrhaphy at the same time. Keratectomy is sometimes necessary for band-shaped keratopathy and mucous plaques and our early experience of excimer laser ablation has been encouraging.

Therapeutic Comment

One of the most important aspects of the ocular complications in herpes zoster is their tendency to recur, even years after the rash. It should be remembered that some relapses may occur when the original attack of herpes zoster has either been forgotten or was so mild as to pass unnoticed. The stimulus for the relapse is often unknown, although the precipitate withdrawal of topical steroids is a potent cause (even if small doses are being used). Therefore follow-up must be long and thorough in those with ocular involvement and topical steroid must be slowly and cautiously withdrawn (over years if necessary).

DISCUSSION

What we hope we have presented here is an accurate and useful review of ophthalmic zoster over the last 20 years, before the advent of effective antivirals. The number of cases we have collected has made it possible to make some statistical deductions to support clinical impressions, and perhaps to clarify some of the folklore associated with a relatively uncommon and pleomorphic disease. Overall we feel we have a reasonably unbiased sample of the disease with perhaps a slight tendency for patients with mild ophthalmic zoster and no eye involvement not to present to us. Current treatment is effective in most areas, with notable exceptions: neuralgia, anaesthetic corneas, mucous plaque keratitis and chronicity. Whether acyclovir or newer antivirals will make a significant impact on these is perhaps too early to judge, but experience over the last 5 years suggests that the clinical problems have not altered much in either type or magnitude, except perhaps for the management of disseminated disease in the immunosuppressed.

There is still no satisfactory explanation for the patho-

genesis of zoster, and without that, management will be restricted to minimising the damage which results, rather than preventing it. A large part of what we deal with clinically is a result of the immune response to the virus, and a therapeutic tightrope has to be negotiated when trying to modify this: too effective a suppression may enhance viral persistence and lead to a more chronic course with treatment dependence over many years. By the time zoster is apparent clinically, a lot of virus has already got into the tissues, and antivirals act only to restrict further proliferation: while this may help, all the disease manifestations are still likely to appear.

Herpes zoster seems likely to be with us until either the virus is eradicated or some means of preventing reactivation is found. For the moment, accurate clinical assessment and prompt treatment, where necessary, will help minimise this troublesome disease.

Key words: Iris atrophy, Latency, Megaplaque keratitis, Mucous plaque keratitis, Oculomotor palsies, Reactivation.

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