TRACHOMA IN NATAL AND ZULULAND*

PART V. TRACHOMA AND ITS TREATMENT

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For a present-day understanding of trachoma, the historical background, with the implied and reported high incidence, the deficiencies and triumphs of the centuries of empirical investigations before the aetiological agent was known, and the clarification afforded by recent discoveries by medical science, will need to be briefly discussed. Also, as trachoma is a chronic infection, comparison with the behaviour of other chronic infections, particularly tuberculosis, is illuminating. Finally, as it is much the commonest ocular infection in Natal[1] and in the rest of South Africa[2,3] in all racial and social groups, trachoma (or if preferred, TRIC agent infection) merits attention as an uncomplicated ocular infection and as a very common complicating factor in all external ocular diseases and in eye surgery.

HISTORICAL BACKGROUND AND INCIDENCE

Newton Kugelmass[4] states that man and many of his maladies have not changed appreciably in the last 20,000 years. Trachoma embraces nearly 5 millennia, being known in China in the 27th century BC. It was endemic in the 20th and 19th century BC in Egypt and was common in Greece in the 5th century BC. Celsus described trachoma in AD 14 and a Sicilian, Pedanius Dioscorides,[5] named it for its rough feel in AD 60. Amida described its 4 stages in AD 550 (also delineated by Galen[5] *circa* AD 160). The Ebers papyrus of Thebes, dating from 1500 BC, of which a translation was published in 1875,[6] mentions infections in which the eyes become inflamed, develop granulations and inturned eyelashes, and become purulent.[7] Thygeson[8] mentions the exudative and cicatricial features, and its treatment with copper salts. If it can be assumed that these reports of trachoma in the important centres of the ancient world are true, and considering the lack of knowledge of hygiene and treatment until recent times, the accessibility of the discharges and the long duration of infectivity, it would be not difficult to prove that all, or nearly all, of the rest of the human race were infected long ago. No country or continent can be expected to be free of it.

Fig. 1. Advanced trachoma showing bilateral ptosis and corneal opacity of and discharge from the left eye.

It is not surprising that the clinical picture most commonly evoked is of its most severe form, represented by a bedraggled, dirty individual with red, discharging eyes, inturned eyelashes and opaque corneae, with flies all over the face. He is usually partially or wholly blind (Fig. 1). The picture described is certainly true of severe trachoma where ignorance, deprivation and neglect have allowed it to reach this terrible state, but it ignores the much more common, mild form and its various manifestations in people of all races and stations in life.

Inaccuracies still occur in recent literature, such as 'trachoma does not affect the eyes of Negroes',[8] or 'the aetiological agent, a member of the psittacosis-lymphogranuloma venereum group, that invades the epithelium of the conjunctiva and cornea and no other human structure'.[4] In contrast it is pleasant to applaud the clinical acumen which allowed Galen to delineate 4 stages. Also admired is the percipience of Fordor[9] who, in 1927, considered the epidemic conjunctival affection occurring in large cities as a subacute form of the disease which, when it occurs acutely, is called 'inclusion-body blennorrhoea of the newborn' and, when chronic, 'trachoma'.

Fordor's views do not appear to have had much influence, with the result that 1,800 years after Galen, his 4 stages amplified by MacCallan[8] and the World Health Organization of the United Nations remained the standard clinical assessment.

The inclusion bodies which they named chlamydozoa (mantle bodies) were found by Halberstaedter and Von Prowazek[10] in Java in 1907, at first in experimental trachoma in apes and later in human trachoma. Before 1911 identical inclusion bodies had been found in bacteria-free ophthalmia neonatorum,[11] in female genital epithelium[12] and non-gonococcal urethritis.[13] The disease had been reproduced in the eyes of a monkey and a baboon from genital secretion from a mother whose baby had inclusion blennorrhoea, and inclusion bodies were recovered from the conjunctiva of the baboon.[11]

Lindner[14] had identified his initial bodies as early as 1910, and the complex nature, and variation in site, of trachoma infection had been indicated.

After initial successes by Macchiavello[15] in 1944 and Stewart and Badir[16] in 1950, T'ang *et al.*[17-19] isolated strains of virus from trachoma cases in serial yolk-sac culture, produced follicular conjunctivitis in 7 rhesus monkeys, and recovered typical HP inclusions from one of them. They demonstrated susceptibility to penicillin, tetracycline and chloramphenicol, and insusceptibility to streptomycin, and indicated a toxic factor associated with the elementary bodies. In 1958, Collier and Sowa[20] and Collier *et al.*[21] produced trachoma in the eye of a human volunteer from a strain of trachoma agent isolated in Gambia. This strain had had 8 passages *in ovo*. They also demonstrated complement-fixing antibodies and the presence of a common complement-fixing antigen for the psittacosis-lymphogranuloma venereum group of viruses.

Since then, the virus has been isolated in egg culture from thousands of cases in this country alone. Human conjunctivae have been infected with egg cultures of trachoma virus, with production of papillary hypertrophy, follicles and pannus by Scott *et al.*[22,23] and in similar ex-

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periments in other countries.[24-34] Trachoma in a modified form has been produced in the orang-utan,[30] the chimpanzee,[25] baboons[31,36,37] and some monkeys,[31,38,39] although most laboratory animals are not affected.[36] Complement fixation,[29] dark field agglutination and immunofluorescent[40,41] antibodies have been identified, and serological protection against trachoma has been demonstrated in vaccine experiments.[25,26,33]

A SUGGESTED PRESENT-DAY DESCRIPTION OF TRACHOMA

As stated in Part II, I consider it timely to define trachoma simply as an infection by the TRIC agent.[42] Definition based on only some of the clinical effects is incomplete and misleading, just as consumption is not a complete definition of tuberculosis. As trachoma is a chronic infection, it should have similarities with other chronic infections, and I think that comparative description with, for example, tuberculosis, may serve as an illustration.

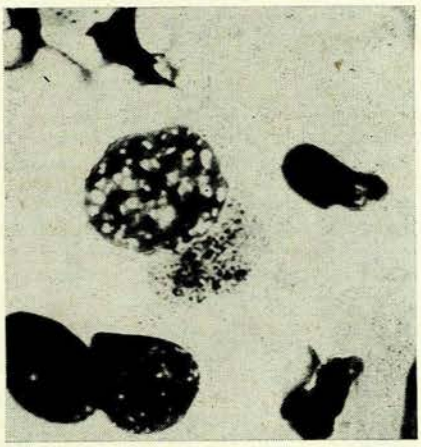

Fig. 2. Inclusion bodies from conjunctival smears stained by Giemsa's stain (oil immersion × 1,000). The smaller dots are elementary bodies and stain red with Giemsa. The larger dots (initial bodies) stain blue. Photographs are by Mr. C. R. Stuart and the preparation by Prof. K. C. Watson of University of Natal Medical School.

The essential lesion of tuberculosis is the presence of tubercle bacilli in the tissues, classically, but by no means always, those of the lung. In response to the presence of the tubercle bacilli and their toxin, there is a host reaction involving lymphocytes and endothelioid and giant cells which comprise the essential tubercle. In addition, there is scar-tissue reaction, to repair or attempt to contain the tubercles. Local necrosis and caseation, and more widespread reactions of delayed hypersensitivity occur. From these elements the great variety of sites and severity of the tuberculosis disease is derived.

In comparison, I see the essential lesion of trachoma as being the presence of virus inclusion bodies in a cell, classically, but by no means always, a conjunctival epithelial cell (Fig. 2). In response to the presence of the trachoma virus and its toxins, there is a host reaction involving lymphocytes, plasma cells and polymorphs which, with epithelial overgrowth, completes the essential lesion of trachoma (Fig. 3). In addition, there is scar-tissue reaction, to repair or attempt to contain the essential lesion; but this is usually 2-dimensional, as the classical site of infection is epithelial (Fig. 4). Local necrosis, usually in the form of ulceration (Fig. 5), and reactions of delayed hypersensitivity occur.

When the biological balance between host and virus is altered to favour the invader, a subacute or even an acute form of the disease occurs. Should a more even biological balance return, the more chronic, and less severe, state of the disease is resumed. It becomes contained, or may be eliminated completely.

After an initial infection, a variable degree of hypersensitivity and of immunity is usual in tuberculosis and to

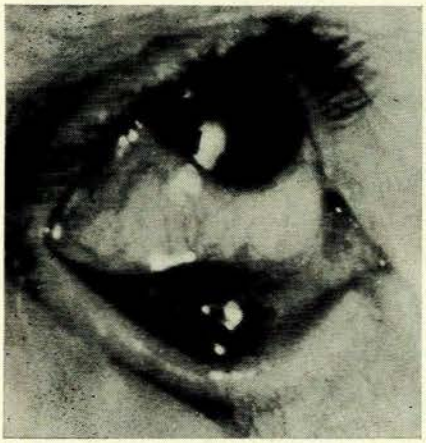

Fig. 3

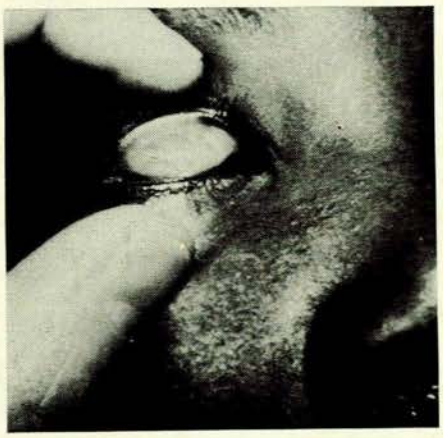

Fig. 4

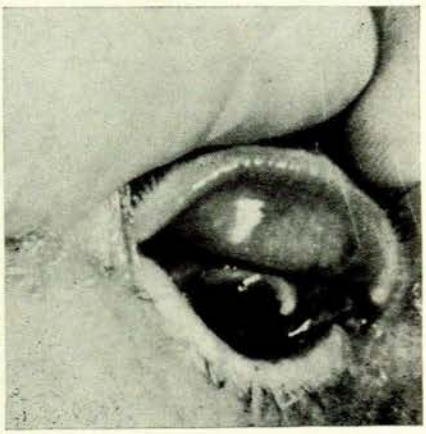

Fig. 5

Fig. 3. An inflamed meibomian cyst, from the conjunctival surface of which TRIC virus was cultured. The rest of the conjunctiva at the canthi, fornices and upper tarsus was not congested, but showed signs of long-standing inactive trachoma. The local inflammation, activated by the associated pathology, is a good example of the congestion, epithelial thickening and papillary hypertrophy comprising the basic lesion of trachoma. *Fig. 4.* Sheets and bands of 2-dimensional scarring. Trachoma III in a Bantu child. *Fig. 5.* Corneal ulcer associated with trachoma in a woman aged 80 years, giving a history of a sore eye for 50 years. The darker areas to the right of the high light on the upper tarsal plate represent a trachoma follicle 3 mm. in diameter which overlies the ulcer when the eye is closed.

a lesser and variable degree in trachoma.[33,42-46] Renna[51] has reported that trachoma antibodies in human milk decrease after the 5th day. These may protect the infant and may explain the rarity of neonatal ocular infection in heavily infected countries such as Egypt, as observed by Thygeson[52] and Maxwell-Lyons.[53] The finding of indirect and fluorescent antibodies to trachoma elementary bodies in conjunctival fluid, sometimes in higher concentration than in the serum,[54,55] suggests that immunity is a local as well as a humoral phenomenon.

The initial infection may find such effective resistance that it is contained or eliminated with a minimal reaction by the host. In tuberculosis, there may be only a very small scar in a lung, and a slightly enlarged and fibrosed related lymph gland. In trachoma, the tissue change may be limited to non-congested papillae, usually along the edge of the upper tarsal plate, which may be visible only with the slit-lamp microscope, and of which the patient is usually unaware. In other cases, the initial infection may find weak defences or be especially virulent, so that in tuberculosis, pyrexia, cough and considerable damage in the lung might follow. In similar circumstances in trachoma, there may be gross swelling and congestion of the conjunctivae, mucous and mucopurulent discharge, enlargement of the related pre-auricular lymph gland, pyrexia and upper respiratory symptoms (Fig. 6). This acute type of reaction has been seen in several adult patients in my practice, usually in visitors to the country and recent immigrants. It might be due to lack of resistance to local virus strains, as enhanced sensitivity to heterologous strains has been reported.[49,56,57] If such virulent infection is not controlled, the result might be death in tuberculosis or blindness in trachoma, after a few months or years (Fig. 7).

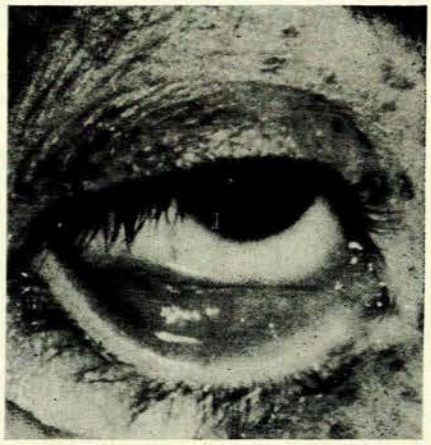

Fig. 6

Fig. 7

Fig. 6. The 6th day of acute trachomatous infection in a woman aged 34 years, showing chemosis and congestion. This was accompanied by an enlarged and tender pre-auricular lymph gland, reduced corneal sensation, mucous discharge from the eye, upper respiratory symptoms and mild pyrexia. *Fig. 7.* An 11-year-old child with a history of trachoma for 6 years. This indicates the potential, though fortunately unusual, seriousness of trachoma even in White patients.

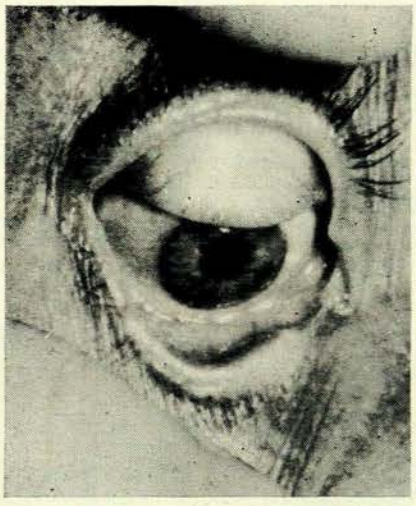

Fig. 8

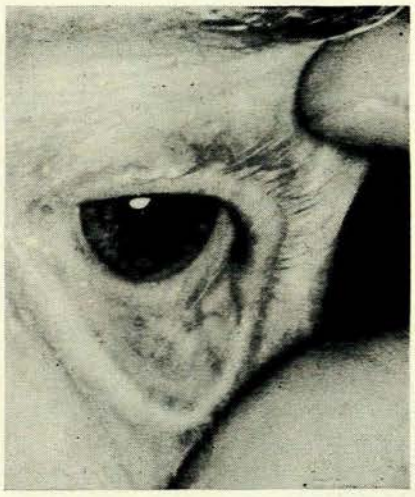

Fig. 9

Fig. 8. Quiet trachoma showing vessels running horizontally on the upper tarsal plate and discrete small follicle remnants. TRIC virus was cultured from the conjunctiva of her husband and son-in-law but not from this patient herself. *Fig. 9.* Symblepharon. Two bands in the outer half of the lower fornix can be seen extending from the bulbar conjunctiva to the lower lid edge. Symptoms date from World War I in Egypt. There were old pannus encroaching onto the pupil and reduction of corrected visual acuity to 6/12, and entropion and trichiasis.

CLINICAL PICTURE

There is an increase in mitosis of the conjunctival epithelium in order to replace lost cells, and the epithelium thickens to 5 or 6 layers instead of 2 or 3 on the tarsal plates. Subconjunctival blood-vessels are seen less distinctly through the thickened epithelium. The epithelium also increases in breadth, so that it is raised into minute papillae (papillary hypertrophy). Blood supply in the submucosa is increased to meet the raised metabolic demands, in response to toxic and viral-particle and protein absorption and to breaches in the epithelial barrier against the external environment. Increasing numbers of lymphocytes, plasma cells and polymorphs gather in the submucosa and in the papillae. Larger clusters may be visible as discrete white, grey or yellow hemispheres, often in or rising above the papillary hypertrophy, on the tarsal plates and in the fornices. These

may be seen only with the slit-lamp microscope or may be up to 2 - 3 mm. in diameter and may become confluent (Fig. 7). These I regard as trachomatous follicles. They resemble minute lymph nodes. The related pre-auricular lymph gland may be involved, with enlargement and tenderness, which may persist for months. To maintain this exuberant inflammation, new blood-vessels grow in horizontally from the ends of the upper tarsal plates and after cure remain as evidence of previous trachoma (Fig. 8). On the cornea there might be multiple superficial erosions or larger ulcers (Fig. 5).

Where the infection has persisted for long enough, and in the case of reinfection, delayed hypersensitivity may be added to a variable degree. The mechanism or mechanisms for the production of pannus may be, or may include, hypersensitivity. This has been suggested by the production of pannus in monkeys and in humans following sensitization by vaccine or by reinfection.[33,46-48,58] In some cases I have found severe pannus associated with mild conjunctival trachoma. In these and in some severe conjunctival cases, good and sometimes striking response to intensive local corticosteroid therapy, always combined with antitrachoma treatment, has suggested that hypersensitivity was an important factor in the pathology.

Where a chronic granulomatous inflammation has been severe enough and of sufficient duration, there is an envelopment and replacement by scar tissue (Fig. 4). This is seen first with the slit-lamp microscope as stellate or arachnoid patterns, usually in the conjunctiva of the lower tarsal plate, and along the upper edge and outer ends of the upper tarsal plates. In time, if the disease continues, the threads of scar tissue thicken and may resemble basket work, and then coalesce to form irregular sheets and bands. Where the inflammatory reaction has affected deeper tissues, there is contracture of the submucosa with bands of symblepharon and ectropion or entropion (Fig. 9). Contracture on the tarsal-plate surface of upper and lower lids leads to retraction of the line of the ostia of the meibomian glands and erosion of the lid edge (Figs. 3, 5 and 8). The upper tarsal plate may be bent convexly forward, along the subtarsal groove, and this, with absorption of the tissues of the tarsal plates, increases entropion and may lead to trichiasis. The irritation of inturned eyelashes usually causes infection to flare up, and there is danger of corneal damage and opacity. Corneal sensation is enhanced or reduced at any stage, and may be abolished. The mechanism might be a neurotoxin or incarceration of the nerves in the inflammation, especially at and near the limbus. The lacrimal ducts may be obstructed by scar tissue, and goblet cells and mucin-secreting glands may be destroyed in the inflammation, so that reduction or abolition of secretions (Fig. 10) is added to the picture which now includes most of the horrible ocular features of classical descriptions, ancient and modern.

Clinical Course

The course of trachoma, like that of tuberculosis, is affected by local, general and environmental factors which alter the resistance of the patient and community.[59]

Just as tuberculosis is not necessarily confined to the lungs, infection by the TRIC agent is not necessarily confined to the conjunctival sac. In 1956 Poleff[60] transmitted trachoma to the lip, with formation of follicles and inclusion bodies, and in recent years TRIC agent has been isolated *in ovo* from the cervix,[3,61-65] urethra,[3,61-66] rectum,[3,62] nose,[3,63] throat,[3,61-66] tonsils,[3] middle ear,[66] joints,[62-64] ulcers in the mouth,[67] and the anterior chamber.[67]

Strains of TRIC agent vary in their tendency to affect tissues other than the eye[47,68-70] and in the frequency with which severe ocular disease is produced.[71] Mann[72] has suggested that strain differences may explain in part the differing clinical pictures found in isolated communities in Australia and neighbouring islands. In my experience, patients who have lived in the Middle East appear to have classical scarring of the upper tarsal plates more often than patients in South Africa, and Scott[3] has commented on the rarity of Arit's line in his White patients.

While these observations may be attributed to differences in the trachoma agent, variations in the environment and other factors may be as or more important.

DIAGNOSIS OF OCULAR TRACHOMA

In examination eversion of the eyelids is essential, and use of magnification, preferably the slit-lamp microscope, is necessary if all the minutiae are to be disclosed.

A high proportion of successful cultures is achieved. A dry throat-swab should be moistened with streptomycin solution and applied to the everted upper tarsal plates, being gently revolved. It is not necessary to use force, as it is mainly the epithelium that is infected, and affected cells are easily caught in the cottonwool. A drop of local anaesthetic such as Novesine 0·4% or Xylocaine 2% is helpful. The end of the wooden stick, including the swab, is broken into a small rubber, screw-capped, bijou bottle containing 1 - 2 ml. of sterile water or saline containing 10 mg. of streptomycin/ml. The bottle should be posted by airmail to the SAIMR Trachoma Unit, P.O. Box 1038, Johannesburg, or any other laboratory able to culture the virus. I have had successful cultures from

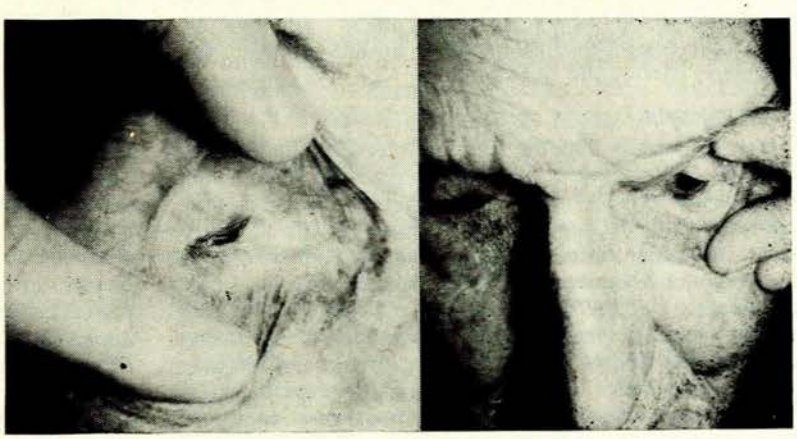

Fig. 10(a) *Fig. 10(b)*

Fig. 10. Keratinized socket of a man aged 83 years. All conjunctival secretion had ceased. The remaining eye had pannus, massive scarring, symblepharon, entropion and trichiasis. A prosthesis had been worn in the socket until a severe illness 7 years earlier. Symptoms dated from World War I in Egypt.

specimens which have been 4 days in transit, but the results are best if they arrive within 24 hours. After the trauma from collection of the swab, gentle as the procedure has been, a flare-up of the infection, occasionally severe, might occur. It is advisable to commence treatment immediately to anticipate this possibility.

Syncope

A note of caution about possible syncope from a sensitive ocular-vagal reflex is advisable. This has occurred in some degree in about 1 out of 500 - 1,000 of my patients, and it can be alarming. The faintness is often felt after 5 - 15 minutes, sometimes some minutes after the examination has been completed. Sudden vomiting may occur. There is usually a quick improvement on loosening the collar and tie and bending the head between the knees, and this is sometimes all that is required. In other cases the improvement is followed by another wave of faintness, with marked bradycardia, and there may be unconsciousness for several minutes. Patients should not be allowed to leave for at least 20 minutes after recovery from a mild attack, in view of the possibility of a second more severe reaction. Injection of atropine might be helpful, but fortunately this has not as yet been necessary in my cases. It is as well to complete the examination of the everted lids quickly, as the mechanism is probably traction on the levator muscles during this part of the investigation. These attacks of faintness have not occurred in mass surveys, when lids are everted for a few seconds only.

TREATMENT OF TRACHOMA

Indications for Treatment

In my experience, at least 3 - 6 months of intensive topical treatment and perhaps a month of systemic sulphonamide therapy is usually the minimum required to achieve clinical cure of trachoma.

Treatment of infected relatives is necessary, to prevent reinfection of a severely afflicted patient. Sometimes treatment of mild trachoma is indicated for its aggravating effect on associated pathologies as discussed in Part III.[59]

Patients with mild trachoma are likely to suffer severely from their own horrifying mental picture of trachoma, and strong reassurance to anticipate and to counter mental distress is part of the treatment.

Problems of Prolonged Topical Therapy

It is important that the highest tolerable concentration of drugs in the conjunctival sac for many of the 24 hours of the day be achieved if their limited efficacy is to be exploited fully. Aqueous drops are usually well tolerated; but their concentration in the conjunctival sac is effective for very few minutes, so that application 10 - 20 times a day is desirable. Effectiveness may be prolonged by adjuvants such as methyl cellulose or polyvinol alcohol, allowing less frequent dosage. An equivalent eye ointment prolongs the effect during sleep. Irritating eyedrops lose some of their efficacy as increased tear secretion hastens their dilution, so that a 10% solution of sulphacetamide may be more effective than one of 30%. Addition of a vasoconstrictor such as adrenaline to sulphacetamide eyedrops may be helpful. Reduction of congestion is soothing, and the cosmetic effect encourages frequent dosage. It is possible that removal of sulphacetamide from the extracellular fluid of the submucosa may be retarded by the vasoconstrictor. These possible advantages are reduced if the adrenaline causes increased irritation.

Eye ointments are tolerated badly by many patients, but are preferred to eyedrops by a few, especially small children. They are convenient for use in mass treatments. The base may do harm to conjunctival epithelial cells and thus weaken their defence against the TRIC agent. This could explain why some patients in clinical trials paradoxically become worse after treatment with eye ointment.[73] Vision is blurred by ointment, but the prolonged effect is useful during hours of sleep. During waking hours the amount applied should be very small. Patients whose tear secretion is reduced find eye ointments particularly irritating, and aqueous drops are preferred by them.

Systemic Treatment

The growing list of non-ocular TRIC infection mentioned earlier, suggests that topical treatment of the conjunctiva may not be enough. I prefer to use the same drug topically and systemically. Some authors favour oral sulphonamide combined with topical antibiotic eye ointment.[74]

With the new long-acting sulphonamides Kelfizine (Farmitalia)[74,75-77] and Fanasil (Roche),[77-81] usually given as weekly doses for 2 - 4 months, the good results reported have been ascribed to persistence of therapeutic levels and a high proportion of 'free' sulphonamide which allowed low dosages. Jawetz *et al.*[82] found that volunteers receiving 1% tetracycline eye ointment for 2 - 3 weeks remained fluorescent-antibody positive, while most of those on sulfisoxazole 1 G *t.i.d.* became negative on the first day. The danger of a Stevens-Johnson syndrome must be borne in mind.[83,84]

CORTICOSTEROIDS AND HYPERSENSITIVITY

That topical corticosteroids may aggravate or activate conjunctival infections by the TRIC agent has been reported since 1952,[5,85-91] so that this form of treatment should be used with care. That hypersensitivity plays an important part in the pathology is also widely reported,[33,43-50] so that treatment to counter this aspect should theoretically be useful. In my experience[92] local corticosteroids have proved invaluable in cases where hypersensitivity to the TRIC agent or to other allergens appears to dominate the clinical picture, and in some cases with excessive corneal involvement. Sulphonamide or appropriate antibiotic treatment should be continued while the local corticosteroid is used. Corticosteroid eyedrops 10 - 15 times a day should be tried on one eye at first. The patient should be examined after 5 days, when adverse effects, if they occur, should be apparent. If its effect is obviously beneficial, the treatment should be extended to the other eye. When no further improvement has occurred, the frequency of dosage of corticosteroid eyedrops should be reduced to the minimum required to maintain the improvement, but the antimicrobial treatment should be maintained at full dosage until clinical cure is achieved.

Other risks associated with topical corticosteroids in the conjunctiva are possible activation of herpes simplex virus infection with potentially disastrous effect on the cornea, and possible induction of glaucoma, especially in elderly patients. It is to be stressed that while local corticosteroids are valuable in treatment of selected cases, they should be used with care.

Influence of Aggravating Factors

Warren[98] has stressed the adverse effect of secondary bacterial infection on trachomatous eyes. This has also been mentioned by others.[45,94-99] On the other hand, Crotty *et al.*[100] found a small blindness-rate in Australian aboriginals who had a remarkably low incidence of pathogenic bacteria in the eyes and nose; and Eiselen and Gear[101] in the Caprivi Strip of South West Africa found few cases of blindness, entropion, trichiasis and other complications, while very few cases showed infection with Kock-Weeks bacilli or pneumococci. Sedan[102] considers superinfection an important complication without which trachoma is a quiet disease as is seen in Japan where trachoma is without secondary infection.

Dust has been shown by various workers to have an important bearing on the production of entropion and trichiasis.[97,103,104] Mann[72] found the disease in Australia and the islands to the north to be worse when use of textiles and poor hygiene coexisted. Good general standards of hygiene are essential.

MEDICATIONS AVAILABLE

Of the more commonly used drugs the sulphonamides, erythromycin, the tetracyclines and the penicillins appear to be most effective against trachoma. Chloramphenicol is not as effective experimentally, but is favoured by some authorities, especially in Russia.[74,105] Hurst[106] reported a synthetic compound ICI 17025 (Nitractin) as having an action comparable with that of the best of the antibiotics *in ovo*, but it has two disadvantages in that secondary bacterial infection is not affected and it has to be administered parenterally. Strains of trachoma agent varied in their susceptibilities to tetracycline and different penicillins[107] and sulphonamides,[108] so that in practice a trial-and-error selection of the best medications may be required.

Drug Resistance Acquired by Trachoma Agents

Resistance to sulphonamides by the trachoma agent *in ovo* was reported by Johnston *et al.*,[109] and Werner[74] has reported a strain which became sulphamethoxypyrazine-dependent. He found that sulphonamide-resistant strains tended to replicate more slowly than others in egg culture, but increased proportionately in the presence of sulphonamide. When the sulphonamide was withdrawn, the proportion of non-resistant strains increased. For this reason I usually limit courses of treatment with sulphonamide to 6 - 8 weeks and interpose a similar course of the tetracyclines or erythromycin between courses of sulphonamide, although patients who have used sulphacetamide eyedrops continuously for several months have often done well.

Considering how common trachomatous infections have been found to be and how often sulphonamides and antibiotics are used in private practice for all sorts of ocular and non-ocular indications, there must be innumerable strains of trachoma agent which have survived exposure to these drugs and which might be better fitted to survive further exposures, including those intended as trachoma treatment. Against this argument Schiao *et al.*[105] found no difference in drug sensitivities between strains isolated in 1958 - 1960 and those isolated in 1963 - 1964, so that poor responses to antibiotic therapy could not be explained by development of resistance between these periods in terms of their experiment. Tarrizzo[110] could not develop strains resistant to erythromycin in at least 10 passages in eggs with increasing amounts of erythromycin.

Trachoma Vaccines

These are still largely experimental and none has yet achieved general acceptance.[111] Bietti *et al.*[112] found benefit for up to 3 years, and Scott,[22] using live vaccine, found some protection for up to a year. Proliferation in the skin, lymph nodes and spleen of baboons[113] and guinea-pigs[114] after injection of live TRIC agent suggests a danger from use of live vaccines.

RESULTS OF TREATMENT OF TRACHOMA IN NATAL AND ZULULAND

The first course of treatment has usually been sulphacetamide 10 - 15% eyedrops with or without methyl cellulose, polyvinol alcohol or adrenaline 1 : 4,000, 8 - 20 times a day for 6 - 8 weeks. Where required, this has been reinforced by oral long-acting sulphonamides for up to 30 days, subject to the approval of the patient's general practitioner. After this a tetracycline eye-ointment *q.i.d.* for 6 - 8 weeks has been given, followed, if necessary, by another 6 - 8 weeks of sulphacetamide or sulfisoxazole eyedrops. Clinical cure is often evident before this routine has ended. Where warranted by the severity, the oral sulphonamide may be repeated with the eyedrops. If the infection is still active, further courses of sulphonamides, tetracycline and erythromycin are given in turn. Courses of penicillin eyedrops 25,000 units/ml. and eye ointment 80,000 units/G for 2 - 3 weeks and perhaps oral penicillins have been helpful. In particularly severe cases oral tetracyclines or erythromycin have been given.

Local corticosteroids have usually been withheld until the infection has been reduced by one or more courses of antimicrobial therapy, or unless there has been no significant improvement. However, where the clinical appearance resembled that of vernal catarrh, and so suggested a considerable allergic component, as noted by Guerra and Vozza,[115] topical corticosteroids have been applied with benefit after only a week or two of antimicrobial therapy.

In some cases initial improvement has been followed by stalemate for months and years. In despair, treatment has sometimes been abandoned, but invariably the disease has become more active, indicating, as the Red Queen told Alice, that one has to run as fast as one can to stay in one place. In order to progress, it has been necessary to enlist most or all of the therapies discussed above. In every case, fortunately, persistence has been rewarded.

Table I refers only to 182 White patients from whose conjunctivae TRIC agent has been isolated in egg culture

TABLE I. RESULTS OF TREATMENT OF 182 WHITE PATIENTS FROM WHOM TRIC AGENT WAS ISOLATED IN EGG CULTURE

Duration of local treatment	*Severity grade*	*Total*	*Receiving systemic treatment*		*Receiving local corticosteroid*		*Clinically cured*		*Uncured*		*Reinfected or relapsed after clinical cure*	
			No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
3–6 months	1	36	7	19·4	0	0	29	80·6	7	19·4	5	17·2
	2	81	28	34·6	2	2·5	65	80·2	16	19·8	12	18·4
	3	27	14	51·9	3	1·1	22	81·5	5	18·4	5	22·8
	4	5	3	60·0	0	0	5	100·0	0	0	1	20·0
	5	2	1	50·0	0	0	2	100·0	0	0	0	0
3–6 months	1–5	151	53	36·1	5	3·3	123	81·5	28	19·5	23	19·5
6–12 months	1	2	1	50·0	0	0	1	50·0	1	50·0	1	100·0
	2	9	2	22·2	0	0	6	66·7	3	33·3	3	50·0
	3	5	3	60·0	0	0	4	80·0	1	20·0	1	25·0
	4	3	2	66·7	0	0	2	66·7	1	33·3	1	50·0
	5	3	2	66·7	1	33·3	3	100·0	0	0	2	66·7
6–12 months	1–5	22	10	45·5	1	4·5	16	72·7	6	27·3	8	50·0
1–3 years	1	0	0	0	0	0	0	0	0	0	0	0
	2	1	1	100·0	0	0	1	100·0	0	0	0	0
	3	4	3	75·0	2	50·0	3	75·0	1	25·0	2	66·7
	4	2	2	100·0	1	50·0	2	100·0	0	0	1	50·0
	5	2	1	50·0	2	100·0	0	0	2	100·0	0	0
Total 1–3 years	1–5	9	7	77·8	5	55·6	6	66·7	3	33·3	3	50·0
0–3 years	1–5	182	70	38·5	11	6·0	145	79·7	37	20·3	34	23·4
Systemic treatment	1–5	70	70	100·0	8	11·4	55	78·6	15	21·4	12	21·8
Corticosteroids	1–5	11	8	72·7	11	100·0	8	72·7	3	27·3	3	27·3
Local treatment alone	1–5	112	0	0	3	2·7	90	80·4	22	19·6	22	23·3

and whose treatment was completed at least 6 months before the time of writing.

Assessment of clinical cure was usually made a month after treatment was stopped. It was arbitrarily based on the significant decline in, or disappearance of, signs of papillary hypertrophy, follicles, pannus, or conjunctival scarring and absence of inflammation. Subjective improvement was not considered, though it usually preceded and exceeded the improvement in physical signs. The relapses or reinfections were mild or asymptomatic. Those severe enough to warrant further treatment usually responded well. Treatment was administered by the patients themselves or their relatives. Its efficiency must have varied greatly, but was generally more carefully executed in the more severe cases. Systemic sulphonamides have been prescribed more often in the past 2 years.

The grading of severity was that used in Part II.[42] The cure rate in grades 3 - 5 (81·1%) was higher than that for the mild cases of grades 1 and 2 (79·1%). This could reflect a greater incentive to achieve a cure in the severer grades, but the difference is not significant. The relapse or reinfection rate for grades 3 - 5 (30·2%) was more significantly higher than for grades 1 and 2 (20·8%), and could be due to the lesser resistance implied by the more severe disease.

Associated pathologies which appeared to have reduced the resistance to trachoma in some degree were recorded in 156 of the 182 patients (85·7%). In 35 of these, elimination of the associated pathology helped the trachoma treatment enormously. In 17 others, trachoma treatment was seriously prejudiced by intractable other pathology. In 18 patients 24 associated conditions were improved after cure of the trachoma. These included corneal opacification in 8 cases, 4 cases with herpetic keratitis, 4 chemical burns, 2 keratoconus cases and one each of episcleritis, old interstitial keratitis, dacryocystitis and endothelial dystrophy. A postnasal drip of 20 years' duration has not recurred for 2 years after cure of trachoma.

The 11 patients of Table I, and others not included in the 182, improved significantly or dramatically on intensive corticosteroid eyedrops. Three had previously deteriorated after topical corticosteroid 4 times a day, but some months later responded well to corticosteroid eyedrops 10 - 20 times a day. The reason for the later good response may have been the increased dosage, or perhaps a reduction in the infecting agent after further treatment. Nine cases had associated pathologies which were improved by topical corticosteroids, including 3 with general allergies, 2 with marked marginal blepharitis and solar sensitivity, and one each with episcleritis, erythema multiforme, postoperative uveitis and keratitis, and a recent chemical burn.

Only 2 patients were considered as clinically cured after less than 3 months' treatment. In each case, elimination of an acute aggravating factor appeared to be responsible. One had a firmly embedded subtarsal foreign body, and the other staphylococcal ulcerative blepharitis. Clinical signs of bacterial infection were rare in this group, so that the benefit from treatment appeared to be from the effect of the drugs on the trachoma agent and from control of associated pathologies, rather than from elimination of superinfection.

The above results of treatment may be compared with results reported elsewhere. Early trials of all the common antitrachoma drugs reported cure rates of usually 75% - 98%.[216] Recent controlled trials have often reported failure or only partial success.[34,73,75-81,136-320] Bietti *et al.*[77] state that practically every case can be cured if the therapy is continued for long enough, and this has also been my experience. Other reported trials have rarely continued therapy for more than 6 continuous weeks and this could explain the disappointing results.

Fortunately, trachoma appears to be becoming less severe and less common in at least 18 countries as testified by 40 references.[121-160] In my experience Natal and Zululand can be added to this list. Part of the improvement may be due to improved living standards.

CONCLUSIONS AND SUMMARY: PARTS I - V

Trachoma was found to be very common in all racial groups in Natal and Zululand (Part I) with severity varying from asymptomatic to the severe classical form of the disease (Part II). Trachomatous infection was found to be influenced by associated pathologies in most White patients, and in some cases treatment resulted in improvement of the associated pathology (Part III). The hypersensitivity and possible toxic aspect were discussed in Part IV.

In Part V the correlation of the variable clinical picture and non-ocular sites of TRIC infection, largely by comparison with the essential pathology of tuberculosis, was attempted in the hope of providing a truer perspective of the infection than has been allowed by classical concepts. Various factors pertaining to treatment have been discussed and results in 182 White private patients have been reported. For success, 3 - 6 months of treatment, and more in refractory cases, is usually required, but in all cases persistence has been rewarded.

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