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T R A C H O M A

WITH SPECIAL REFERENCE TO ITS TREATMENT IN THE NORTHERN TERRITORY OF AUSTRALIA

by

CHARLES M. McLEAN.

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P A R T _ 1.

INTRODUCTION:

Trachoma is a form of kerato-conjunctivitis, with a world wide distribution, and, on account of its potentialities for causing severe visual impairment and even blindness, is generally regarded as the most important ocular disease. It has been recognized as such from earliest times, and discussion as to its causation, pathology, clinical effects and treatment has occupied a large section of ophthalmic literature throughout the ages, but many problems associated with it remain to be elucidated. Recent work has advanced our knowledge of its aetiology (T'ang, Chang, Huang, and Wang,[1] Collier, Duke-Elder, and Jones[2]), but much controversy still exists concerning diagnosis, treatment and control. It is now conceded by most authorities that the causative agent is the Chlamydozoon trachomatis, one of the larger-sized viruses, and now that this has been successfully cultivated in quantity the way may be open to the eventual production of a prophylactic and curative vaccine, but at present our most effective therapeutic agents are the sulphonamides and the antibiotics.

I first became interested in this disease during the Second World War, while serving as an ophthalmologist in North Africa, Italy and India; additional stimulus was provided by experience gained during the past ten years in Africa and Australia, where large numbers of the population are affected. In this latter period, I attempted to assess the role of sulphones in its prevention (McLean[3]), and participated in a successful experiment to isolate the causative organism (Mann, Greer, Perret, and McLean[4]), but my main activities in the field of trachoma research have been concerned with its treatment and control.

Part 11 of this thesis gives a brief historical review of the subject, describes its pathology and bacteriology, discusses various endemiological factors and outlines the differential diagnosis.

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In Part III, trachoma in the Northern Territory of Australia is discussed, and details are given of the results of two forms of treatment in an isolated aboriginal community, of a combined form of therapy in a leprosarium where there was a high incidence of the disease, and of combined treatment in a white and part-coloured population. These results are analyzed statistically in an attempt to arrive at a rational form of routine treatment.

Part IV discusses the importance of trachoma, reiterates the main points in diagnosis, summarizes the clinical effects, presents a scheme of treatment for routine use, and outlines methods for its control.

P A R T _ II

HISTORICAL:

Probably the earliest reference to trachoma is to be found in the Ebers Papyrus, which dates back to about 1650 B.C. There the disease is mentioned, but is not described in detail. However, it is presumed that it originated in Egypt or the neighbouring countries of the Middle East. It was known to the ancient Greek physicians, and Hippocrates included it in the general term "ophthalmia"; in treatment, he advocated rubbing the palpebral conjunctiva with Milesian wool, which had been wound around a spindle of hard wood, until the blood ceased flowing, and then cauterizing the treated surfaces. The Romans also knew the disease, and both Celsus and Galen suggested various forms of treatment. In the Middle Ages, Arab medical treatises dealt with its clinical appearance and treatment, but thereafter little appeared in the literature until the Napoleonic Wars, when large numbers of French and British troops, returning home from the Middle East, suffering from gross visual impairment or blindness, focused attention once more on the disease. It is probable that, in the intervening period, trachoma had spread widely throughout Asia and the countries bordering the Mediterranean, and it seems certain that it was conveyed to North and Central America by the colonizing Spaniards, but it seems to have remained largely unrecognized at that time. The African tribes were probably infected by slave-raiding Arabs in the 18th. and 19th. centuries, and the Australian aborigines may have contracted it from visiting Malays and Indonesians. It also appears likely that the first white inhabitants of Australia, the convicts in the penal settlements, brought the disease with them from Britain. From the beginning of the 19th. Century, when it spread rapidly throughout Europe, it has come to be accepted as the most prevalent eye disease in the world.

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From the era of the ancient Egyptians until the fourth decade of this century, the commonest form of treatment was the vigorous application of crystalline copper sulphate to the conjunctiva of the eyelids and fornices, and this method is still used in some areas. As such treatment is exceedingly painful, and has to be prolonged, it is not surprising that there were numerous defaulters. In effect, a chemical cauterization of the conjunctiva is performed and the formation of scar tissue is hastened; it is interesting to note that some of the severe cicatricial sequelae in old cases of trachoma may have been due to this. The advent of a new and less drastic form of treatment was heralded, in 1937, by the publication by Heinemann[5] of the results of oral administration of sulphonamides, and the development, in the last twenty years, of antibiotic drugs has increased the number of therapeutic agents for use against the disease.

PATHOLOGY AND BACTERIOLOGY:

It has been established by means of experimental inoculation of human subjects with (a) trachomatous material (Kapuscinski[6]), and (b) cultured virus (Collier, Duke-Elder and Jones[2]; Mann, Greer, Perret and McLean[4]), that the incubation period of the disease is five to twelve days. In the experimental disease the onset is usually acute, with marked discomfort in the eyes, conjunctival injection, muco-purulent discharge, and enlargement of the pre-auricular lymph nodes, but in the naturally occurring form these signs are much less common and the onset in these cases is usually insidious.

MacCallan[7] divided the course of the disease into four main stages:-

stage I, the stage of infiltration;
stage II, the stage of active inflammation;
stage III, the stage of scarring;
stage IV, the healed stage.

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This classification is extremely useful for giving a general description of the disease, and will be adhered to in this section, but, as will be seen in Part III of this treatise, I prefer another classification for clinical purposes.

In stage I, the earliest signs are seen in the upper fornix, the upper tarsal conjunctiva and the cornea; they are often so fine that at first they can only be seen with the biomicroscope. Small bunches of dilated capillaries appear under the conjunctival epithelium, producing the appearance of bright red dots on the surface, and mingled with these are aggregations of lymphocytes in follicle formation, which are seen as yellowish spots. At the same time, the cornea in the upper limbal region shows epithelial oedema, and grey spots of lymphocytic infiltration situated in (and often under) the epithelium; this is referred to as "epithelial keratitis". Some authorities (Kimura, Obayashi, Ikawa and Kitamura[8]) are of the opinion that trachoma in its earliest stages may be present without these corneal changes, but I have found them in every incipient case and I agree with Thygeson[9] that, in their absence, trachoma cannot be diagnosed clinically at this stage.

In stage II, the upper tarsal conjunctiva assumes a velvetty appearance, due to papillary hypertrophy. The hypertrophied papillae consist of conjunctival epithelium and subepithelial tissue infiltrated with lymphocytes and surrounding a central vascular core. Interspersed between the enlarged papillae are yellowish follicles, which by this time have increased considerably in size; in some cases the papillary hypertrophy is so marked that it obscures the follicles, but in the majority the latter are prominently seen. The appearance of the upper and lower fornices is similar, but the changes may be less marked in the lower palpebral conjunctiva. In addition, follicles may sometimes be seen in the bulbar conjunctiva, plica semilunaris and caruncle.

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As the condition progresses, greyish elevations, like sago grains, may form in the upper tarsal conjunctiva, due to cystic degeneration of subconjunctival and tarsal glands which have become strangulated by lymphocytic infiltration; these may rupture, liberating a gelatinous material. Sometimes the whole upper tarsal conjunctiva has a brawny, swollen appearance. The upper tarsal plate, at this stage, becomes thickened by lymphocytic infiltration, and may produce a form of ptosis, due to the resulting increase in weight and also, perhaps, to infiltration of Müller's muscle. In the cornea, further changes are seen; lymphocytic infiltration extends further into the cornea from the limbus, accompanied by extensions from the limbal capillary loops, the combination of infiltration and vascularization being known as "trachomatous pannus". In the active stages of the disease, the infiltration extends further into the cornea than the vascularization. Follicles, similar to those in the conjunctiva, may sometimes be seen at the limbus, and these may rupture and subsequently become filled in by clear epithelium, giving rise to clear, oval areas in the pannus, the so-called "Herbert's pits". The pannus tends to spread downwards towards the pupillary area, but the rate of progress varies considerably, and many cases of uncomplicated trachoma show very little corneal involvement, although slit-lamp examination will always show some evidence of this.

In stage III, the follicles in the conjunctiva become replaced by scar tissue. According to Duke-Elder[10], this is first seen as a white line, the cicatricial line of Arlt, running horizontally across the tarsus in the region where the ascending and descending conjunctival capillaries anastomose, but in my experience the first sign of scarring is often in the form of fine, stellate white lines situated in the upper third of the upper tarsal conjunctiva. In mild cases, particularly those which have been cured by early treatment, no further scarring occurs, and these

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cases, if not subsequently re-infected, may, when re-examined after one year, show little or no sign of previous trachomatous infection; this has been noted independently by Professor Ida Mann (personal communication) and myself. In more severe cases, however, the scarring increases, replacing the follicles and hypertrophied papillae, so that eventually the whole upper tarsal surface may become smooth and white; these cicatricial changes are always much less marked in the lower lid. In the cornea, the infiltration slowly recedes, and at this stage the limbal capillary loops appear to extend further into the cornea than the infiltration. Finally, a thin grey layer of scar tissue remains, in which can be seen attenuated or empty capillaries.

In stage lV, the trachomatous process is no longer active. Contraction of the scar tissue may, however, cause serious sequelae such as deformity of the upper tarsal plate, giving rise to entropion and trichiasis, which may in turn cause vascularization of the cornea and repeated corneal ulceration. The fornices tend to become obliterated, and symblepharon may form. Due to the involvement of the conjunctival glands and their ducts in the cicatrization, the conjunctiva and the cornea may become xerotic. The scarring process may extend into the lacrimal sac, causing a chronic dacryocystitis.

The duration of each stage of the disease, in the untreated case, varies enormously. Stage 1 may last from a few weeks to several months, while stage 11 may continue for 10 - 15 years. Stage 111 may then continue throughout life, although few patients over 60 show signs of activity unless they have suffered a fairly recent infection. In endemic areas, most patients become infected in early childhood, and adults in stage 1 and stage 11 are mainly recent arrivals in these areas.

Discussion as to the causative agent of trachoma has been prolific, and at times acrimonious, and the literature abounds

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with claims to have isolated the responsible organism. Practically every bacterium known to be found in the conjunctival sac has, at one time or another, been accused of being the specific pathogen, but no pure culture of any of these has ever produced the disease on experimental inoculation. Only two of these claims are of interest; Koch[11] isolated, from trachoma cases in Egypt, a bacillus which was later (Weeks[12]) proved to be the cause of Koch-Weeks conjunctivitis, and Noguchi[13] isolated B. granulosis (a variant of B. xerosis) from trachomatous North American Indians and with this produced a transient folliculosis in monkeys. Later attempts by other workers (Mayou[14]; Wilson[15]; Thygeson[16]) to produce trachoma by inoculating human volanteers with his material failed to confirm his findings.

Bacteria having proved unproductive, other micro-organisms were investigated, and in 1937 Cuénod and Nataf[17] advanced the theory that a Rickettsia was responsible, suggesting that lice acted as vectors. They claimed that, by anal inoculation of lice, they could produce rapid multiplication of the organism, but this was never confirmed.

The first presumptive evidence that a virus might be the cause of trachoma was produced by Halberstaedter and Prowazek[18], who discovered cytoplasmic inclusion bodies in the conjunctival epithelial cells of Javanese patients suffering from the disease. As these inclusions typically formed a cap or mantle over one pole of the nucleus of the cell, they named them "Chlamydozoa" and postulated that they were a type of virus and the responsible agent for trachoma. Numerous attempts were made to cultivate this virus during the following four decades, but, owing to lack of suitable media, these generally ended in failure. It is probable that the first successful cultivation, in the yolk sacs of embryonated hens' eggs, was performed by Macchiavello[19], who claimed to have produced the disease in a human volunteer inoculated with a filtrate of the emulsified yolk sacs, but in the stress of the Second World War his work was largely overlooked and could not be confirmed. The

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credit for the first production in quantity of the virus by this method must go to the Chinese workers T'ang, Chang, Huang and Wang[1], who discovered that the addition of streptomycin to trachomatous material, before inoculation of the yolk sacs, inhibited the growth of bacterial contaminants without affecting the virus, whereas various other antibiotics prevented its multiplication. Collier, Duke-Elder and Jones[2] repeated the Chinese experiments, and carried them a stage further by successfully inoculating a human volunteer. Since then, confirmation of these findings has come from various parts of the world, including Australia (Mann, Greer, Perret and McLean[4]), and it is now generally accepted that this virus, or Chlamydozoon, is the causative agent of trachoma. It may exist in several different strains; Collier[20] has reported that two of the virus strains which he has isolated differ from others in producing, in infected yolk sacs, compact collections of virus particles surrounding large, single, multilocular or multiple vacuoles, in addition to free elementary bodies, and he suggests that these may indicate atypical forms of the virus. The cultivation of the virus in all trachomatous areas may help to elucidate this problem. Snyder, Page, Murray, Daggy, Bell, Nichols, Haddad, Hanna and McComb[21] suggest that adenoviruses may play a part in producing the disease in some cases, but this has not yet been fully investigated.

At any stage of the disease, a secondary invasion of the conjunctivae by any of the common pathogenic bacteria may occur, and the combination of trachoma with repeated secondary conjunctivitis, if neglected or inadequately treated, greatly increases the severity of the disease. Indeed, it is now generally believed that the so-called "Egyptian" or "classical" trachoma, with its recurrent corneal ulceration, extensive pannus and marked scarring, which may result in virtual blindness, is due to this combination and not to infection with the trachoma virus alone (Ching[22]; Flynn[23]). This concept explains the great variation in the severity of trachoma

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which occurs in different parts of the world; in Egypt, for example, the dense fly population is constantly disseminating secondary infection, and the disease is seen in its most virulent and destructive form. Similarly, in the southern two-thirds of the Northern Territory of Australia, where the climate for nine months in the year is dry, hot and dusty, and where flies are numerous, trachoma is of the "classical" type, whereas in the northern one-third, which is less hot but more humid, and where flies are less of a problem, it is mostly of the uncomplicated variety, "trachome pur".

ENDEMIOLOGICAL FACTORS:

The various factors concerned in the endemiology of the condition may conveniently be discussed under the following headings:-

(a) geographical and racial;
(b) social;
(c) infective;
(d) associated diseases.

(a) Geographical and Racial.

There are few countries where trachoma is not endemic (Fig.1), but its incidence varies greatly from place to place. Egypt (its probably original habitat) and the adjoining countries show the highest overall incidence, but many other countries show an equally high incidence in certain regions, e.g. in parts of East, West, Central and South Africa, India, China, Russia and Japan. It is a common disease in Southern Italy, Yugoslavia, Czechoslavakia, Greece, Spain, Central and South America, less common in the U.S.A. and Canada, and rare in the United Kingdom, New Zealand and the Scandinavian countries. In Australia, it is commoner than is generally recognized. It tends to be more severe in hot, dry, dusty, tropical and semi-tropical climates, but in conditions of overcrowding and poor hygiene its

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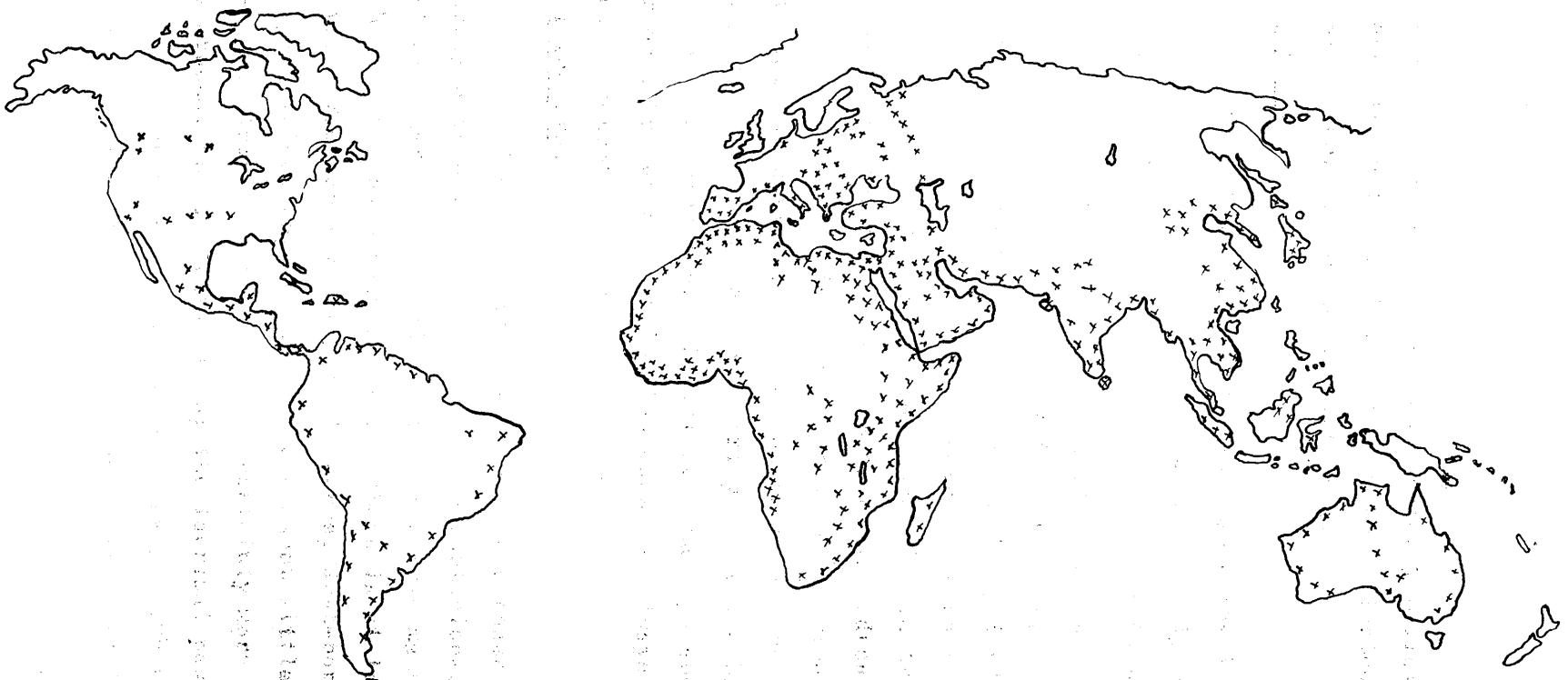

FIG. 1. MAP OF THE WORLD, SHOWING WIDESPREAD DISTRIBUTION OF TRACHOMA.

ravages may be seen in any area.

There is no evidence of any racial immunity to the disease. For many years it was generally believed that the Bantu and Negro inhabitants of Africa were not affected, but this has long since been proved to be fallacious.

(b) Social.

Age and sex do not influence the liability to infection. In areas of high endemicity the disease usually begins in early childhood, and is often due to contact with infected parents.

It is frequently stated that trachoma is predominantly a disease of poor people, living in crowded and insanitary conditions. This is true as regards "Classical" or "Egyptian" trachoma, which is a combination of trachoma and repeated secondary infection, but not with regard to "trachome pur" or uncomplicated trachoma. Experience gathered from examination of prosperous and educated Negroes in West Africa, and of the white population in the Northern Territory of Australia, has convinced me that an adequate income and comfortable living conditions are not necessarily effective barriers to the spread of the infection. Strict personal hygiene is an effective deterrent, but unfortunately this does not always coincide with improved economic status.

(c) Infective.

The infective nature of the disease has never been seriously doubted. It is known to be contagious, and contact with an infected person or fomites may be the sole means of spread, but this has by no means been proved. There is at least the possibility that the infection may also be fly-borne, dust-borne, or disseminated by droplet infection, and up to the present little has been done to investigate this. The disease is certainly more prevalent where flies abound, and in dusty areas; the lacrimal passages have been described as undergoing trachomatous changes (Charamis[24]), and it is possible that the virus may enter the nasal passages and be

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disseminated from there. Now that successful cultivation of the virus is possible, these problems should be elucidated.

The infectivity of trachoma appears to vary considerably. This may be due to some strains of the virus being more virulent than others, or it may be connected with the presence or absence of other conjunctival pathogens; cultivation and comparison of the characteristics of the virus from different regions should do much to solve this. My own investigations in the Northern Territory of Australia indicate that there is little difference in the incidence of the disease in the various areas there, but that the severity of the condition varies considerably due to the presence or absence of secondary infection.

An attack of trachoma does not render a patient immune to subsequent re-infection, and this causes one of the great difficulties in the control of the disease. This lack of immunity may be due to the fact that trachoma is a localised disease, confined mainly to the conjunctival sac and the cornea, so that antigen may not enter the systemic circulation in sufficient quantity to stimulate the production of antibodies, and the possibility remains that an immunizing vaccine may eventually be produced from cultivated virus.

(d) Associated Diseases.

From time to time, various systemic diseases, such as malaria or tuberculosis, have been noted in association with the onset of trachoma, but there is no evidence to show that this association is other than coincidental. Local eye conditions, however, and in particular acute conjunctivitis, undoubtedly influence the course of the disease. Trachoma diminishes the resistance of the conjunctiva to invasion by other organisms, and, should secondary bacterial or viral infection occur, the symptoms increase markedly in severity. An acute muco-purulent or purulent conjunctivitis developes, and corneal ulceration is a frequent complication; such

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an ulcer, if untreated, may perforate the cornea, leading to adherent leucoma, anterior staphyloma or phthisis bulbi. Pannus tends to extend further into the cornea during a superadded infection. Papillary hypertrophy increases to such an extent that it sometimes completely masks the follicles, and in such cases, if seen for the first time, the primary condition may be missed if the cornea is not examined.

I have frequently observed, in trachomatous native children in Africa and the Northern Territory of Australia, a profuse, muco-purulent rhinitis. Whether this is connected or not with the trachoma process I do not know, but it would be interesting to see if the virus could be cultivated from the secretion or from scrapings of the nasal mucosa.

SYMPTOMATOLOGY:

The symptoms of uncomplicated trachoma vary considerably, but in the majority of cases there is surprisingly little discomfort.

In stage 1, it is unusual for the patient to complain of any symptoms at all; the bulbar conjunctiva is rarely injected, and it is easy to overlook the disease unless the upper eyelids are everted and examined for follicles, and the corneae inspected carefully (with a slit lamp if necessary) for epithelial keratitis. These signs may be fairly obvious in one eye and almost non-existent in the other, but it is exceedingly doubtful if trachoma ever occurs uni-ocularly in the naturally-occurring form of the disease, although it can undoubtedly be produced experimentally. Enlargement of the pre-auricular lymph node is rarely found in the natural disease, but is common in the experimental form. Tsutsui[25] found this lymphadenopathy in cases having an acute onset with severe pain in the eyes, oedema of the eyelids, marked injection of the bulbar conjunctiva and profuse muco-purulent discharge. These cases are rare, and I have had no personal experience of them, but I have seen an identical picture in

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experimentally produced trachoma. The acute signs subside in two or three weeks, and further progress follows the pattern of those with an insidious onset.

The symptoms of stage 11 and stage 111 consist mainly of a gritty sensation in the eyes, with very slight mucoid discharge. There may be a slight injection of the bulbar conjunctiva, but this is never marked in uncomplicated cases. Indeed, it is remarkable how rarely, even in florid cases with marked papillary hypertrophy and numerous follicles, the patient complains of much discomfort. Rupture of limbal follicles may be followed by corneal ulceration, in which case the complaint is of severe pain, lacrimation and photophobia, and superficial circumcorneal injection is evident. Very occasionally, epithelial keratitis affects the central portion of the cornea, causing some diminution of vision.

In stage 1V, symptoms are due to the results of cicatrization, such as entropion, trichiasis, corneal opacities and xerophthalmia.

It cannot be emphasized too strongly that uncomplicated trachoma is not a severe disease leading inevitably to impaired vision or blindness. The danger lies in the trachomatous patient being exposed to repeated, uncontrolled attacks of secondary conjunctivitis; these produce the complications and sequelae which we are accustomed to describe as "classical" or "Egyptian" trachoma. It is important to remember this when considering the prognosis, as the probability is that, if such infection can be prevented or cured, the patient will retain good vision throughout life. This does not mean, however, that treatment should be directed solely to secondary infection when it occurs, and that the trachomatous process itself should be ignored. So long as trachoma is active, the liability to secondary infection remains great, and the only way to prevent this is to eradicate the primary condition.

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DIAGNOSIS:

The Expert Committee on Trachoma of the World Health Organization in its "Second Report"[26], recommended certain criteria of diagnosis, and these have been almost universally accepted. They are:-

1. follicles in the upper tarsal conjunctiva,
2. epithelial keratitis,
3. pannus,
4. scarring of the upper tarsal conjunctiva.

The presence of two or more of these signs is considered to be diagnostic of trachoma. In an established case the diagnosis is usually easy, and the main difficulty arises in mild or early cases. The presence of follicles in the upper tarsal conjunctiva should always arouse suspicion, and a thorough examination of the cornea for epithelial keratitis or pannus at the upper limbus should be carried out; if either of these is present, trachoma may be diagnosed with confidence.

The conditions most likely to be confused with trachoma are:-

(a) conjunctival folliculosis,
(b) inclusion conjunctivitis,
(c) pharyngoconjunctival fever,
(d) epidemic keratoconjunctivitis,
(e) molluscum contagiosum conjunctivitis,
(f) vernal conjunctivitis.

(a) Conjunctival Folliculosis

Conjunctival follicles, affecting mainly the lower fornix, are commonly found in children. The upper tarsal conjunctiva is unaffected, and there is never any corneal involvement. The condition gradually resolves, without scarring. According to Duke-Elder[27], it is merely a local expression of

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the adenoid activity so frequently found in youth."

In adults, folliculosis may occur due to the instillation of drugs, such as atropine or eserine. The lower fornix is mainly involved, the cornea remains clear, and there is often an associated moist eczema of the skin of the eyelids.

(b) Inclusion Conjunctivitis.

This disease is interesting in that it produces, in conjunctival epithelial cells, inclusion bodies which are morphologically similar to those of the trachoma virus, and the responsible organism has recently(Jones, Collier and Smith[28]) been cultivated by a similar method. The symptoms, which are acute, consist of irritation in the eyes, photophobia and mucopurulent discharge. The eyelids may be slightly swollen. A pre-auricular lymphadenopathy appears in two or three days, and about the seventh day follicles begin to become obvious. These are always more numerous in the fornices and the lower palpebral conjunctiva than in the upper tarsal region, and are never found in the bulbar conjunctiva. There are no corneal changes. The acute symptoms subside in about four weeks, and although the follicles may remain for many months they eventually resolve, leaving no scarring. The disease is most commonly found in new-born infants, who are infected at birth from the mother's genito-urinary tract (Lindner[29]), but may occur in older children and adults in epidemic form, often after swimming in communal baths.

The exact relationship of the virus of inclusion conjunctivitis to that of trachoma has not yet been decided. It seems probable, in view of the fact that the disease causes no corneal involvement or cicatrization, that the two viruses are distinct, although closely related.

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with claims to have isolated the responsible organism. Practically every bacterium known to be found in the conjunctival sac has, at one time or another, been accused of being the specific pathogen, but no pure culture of any of these has ever produced the disease on experimental inoculation. Only two of these claims are of interest; Koch[11] isolated, from trachoma cases in Egypt, a bacillus which was later (Weeks[12]) proved to be the cause of Koch-Weeks conjunctivitis, and Noguchi[13] isolated B. granulosis (a variant of B. xerosis) from trachomatous North American Indians and with this produced a transient folliculosis in monkeys. Later attempts by other workers (Mayou[14]; Wilson[15]; Thygeson[16]) to produce trachoma by inoculating human volanteers with his material failed to confirm his findings.

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eyelids they may give rise to a chronic follicular conjunctivitis. Usually the cornea remains clear, but in rare cases pannus, similar to that of trachoma, developes (Thygeson[32]). In these cases, however, the characteristic lesions on the lid margins clinch the diagnosis.

(f) Vernal Conjunctivitis.

This is a commom disease in tropical climates, and in the summer months in temperate zones. It is probably an allergic phenomenon, but its exact aetiology is unknown. Two forms occur, the palpebral and the limbal, and these may co-exist. In the palpebral form, the upper tarsal conjunctiva shows milky, flat-topped papillae which, while typical, may be mistaken by inexperienced observers for trachomatous follicles; similar, but less marked changes are found in the lower lid, but the fornices are never involved. In the limbal form, a gelatinous swelling is seen in the bulbar conjunctiva at the limbus, and this may completely surround the cornea. Very rarely a type of pannus, more gelatinous in appearance than that of trachoma, is found. It is not uncommon to find vernal conjunctivitis and trachoma co-existing, and in such cases it is usually the limbal form of the former which is present.

There are various laboratory aids to the diagnosis of trachoma, but some of these, involving complement fixation tests or the cultivation of the virus in the yolk sacs of embryonated hen eggs, are not suitable for areas where the facilities are limited. The examination of scrapings of the upper tarsal conjunctival epithelium for the presence of Halberstaedter-Prowazek inclusion bodies may, however, be readily undertaken. The material for this procedure is collected by everting the upper eyelid and rubbing the exposed conjunctival surface firmly with a platinum loop or metal spatula; I have found local anaesthesia

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unnecessary for this, even in very young children. Smears of this material are then made on clean microscope slides, allowed to dry in air for five minutes, and stained with Lugol's iodine or Giemsa's solution.

The Lugol's iodine method, as described by Gilkes, Smith and Sowa[33], stains deep orange-brown the carbohydrate matrix in which the inclusion bodies lie, and this shows in affected epithelial cells, when examined with the oil-immersion objective of the microscope, as dot-like particles in the cytoplasm. Unaffected cells stain golden-yellow. This method enables inclusion bodies to be identified rapidly, and for confirmation the slide may then be washed with xylol or toluol, decolorized and fixed with 95% methyl alcohol, and stained with Giemsa's solution.

The method of staining with Giemsa's solution, which I prefer, is the slow one described by Mackie and McCartney[34]. With this, the inclusion bodies show typically as purplish-red dots arranged in a crescentic fashion around one pole of the cell nucleus (Fig.2); the purplish-red colour is due to the presence in the inclusions of both initial bodies, which stain dark blue, and elementary bodies, which stain pink. The initial bodies may vary in size from 0.5 micron to 1.5 microns, and are usually round in shape, while the elementary bodies are about 0.25 micron and may be round or oval. The inclusions may vary considerably in appearance, in some instances consisting of a few dots at one end of any epithelial cell, and in others completely filling the cytoplasm (Fig.3); if composed entirely of elementary bodies they appear red in colour. They must be distinguished from extrusions from the cell nucleus, which have a much more solid appearance, and from pigment granules, which are generally irregular in shape and stain black.

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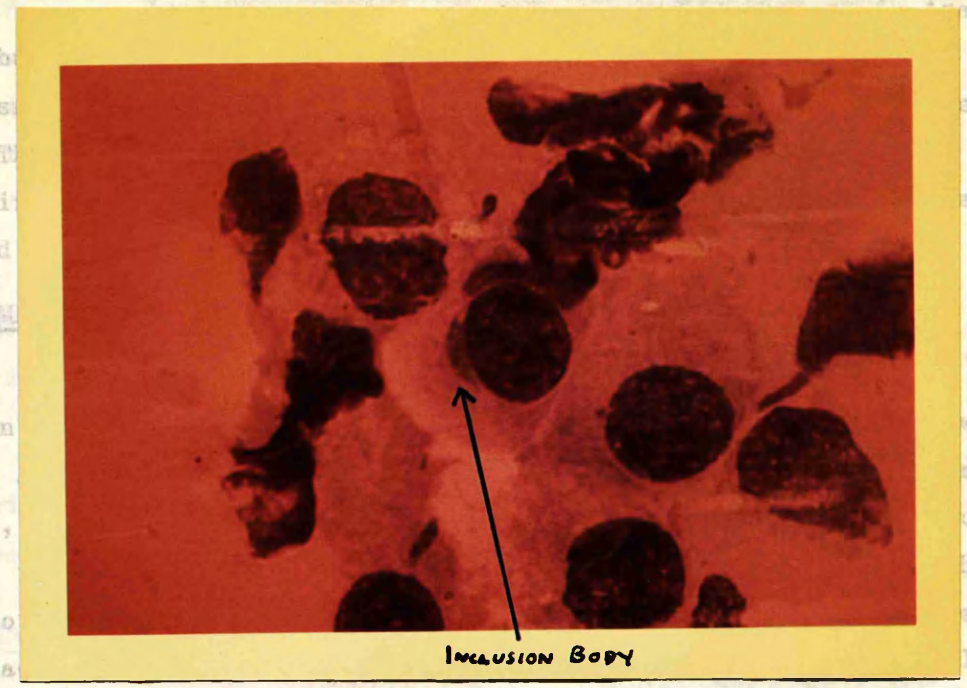

Fig. 2. Conjunctival scraping. Epithelial cell in centre of field shows crescentic Halberstaedter-Prowazek inclusion body forming cap on nucleus. Stained Giemsa. x 1000.

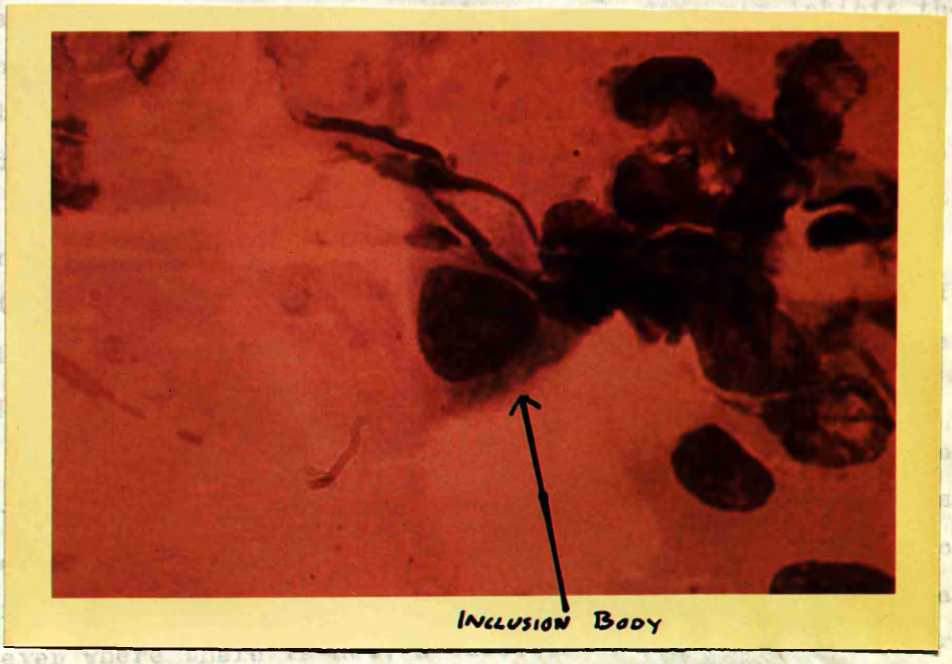

Fig. 3. Conjunctival scraping. Halberstaedter-Prowazek inclusion body fills one end of cell in centre of field. Stained Giemsa. x 1000.

Inclusion bodies are not invariably present in trachoma, but I have found them, often after prolonged examination of the smear, in about 30% of untreated cases with active follicles. The only other condition in which similar inclusions occur is inclusion conjunctivitis, but the absence of corneal changes differentiates this from trachoma.

TREATMENT:

The sulphonamides and the antibiotics are now the most commonly used drugs in the treatment of trachoma. They are known to exert a specific action on viruses of the psittacosis-lymphogranuloma group, to which the trachoma virus belongs; this action is thought to be viristatic rather than viricidal, which may explain why they are not always completely effective. The sulphonamides work best when administered orally, while the antibiotics are usually applied topically in the form of drops, ointments or oily suspensions. Not all of the antibiotics, however, are effective. Streptomycin, as was shown by T'ang and his colleagues[1], does not inhibit the growth of the virus, and although penicillin, used either locally (Bietti[35]) or parenterally (Gilkes, Smith and Sowa[36]; Smith[37]), has its advocates, I have not been impressed by its usefulness; cases which I have treated with local applications have remained virtually unchanged, while those receiving intramuscular injections have shown some temporary improvement but have invariably relapsed. Collier, Duke-Elder and Jones[38] had a similar experience when treating a case of experimentally-produced trachoma.

Combined treatment with oral sulphonamides and topical antibiotics is often used, the former being given for two weeks and the latter instilled for eight. If, however, there is a previous history of sensitivity to sulphonamides, these are contraindicated, and, even where there is not, a close watch must be kept for drug reactions. While many cases are undoubtedly healed after a single course, resistant cases occur, and in these treatment must be prolonged; there is a possibility, which requires to be investigated,

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that some strains of the virus are more resistant than others. If prolonged treatment is required, I prefer to continue this with local antibiotics, as the danger of systemic disturbances from these is negligible.

Corneal ulceration is a frequent complication in cases which have become secondarily infected; it is not caused by the trachoma virus itself. If present, atropine instillations should be added to the other treatment until the cornea has healed.

The sequelae of the disease, such as entropion and trichiasis, are treated surgically, usually by a wedge resection of the tarsus.

CRITERIA OF CURE:

Trachoma may be considered cured when all follicles have disappeared, the conjunctiva is smooth, and the pannus vessels have become empty and attenuated. In most cases some conjunctival scarring will remain, and this may be considerable in extent, but some early cases may resolve completely under treatment, the conjunctivae and corneae later presenting an entirely normal appearance. In general, if treatment is commenced before scar tissue has begun to form, the final result will be a network of fine, stellate scars in the upper tarsal conjunctiva and a thin, crescentic grey opacity, containing empty blood vessels when viewed with the slit lamp, in the cornea at the upper limbus. The cornea near the upper limbus may show Herbert's pits, but these are not diagnostic of healed trachoma since they may be found in cases showing active follicles and pannus. Cases which show some scarring before treatment usually show more marked scarring when healed.

The absence of Halberstaedter-Prowazek inclusion bodies from conjunctival scrapings cannot be regarded as one of the criteria of cure, since they are not always found in active cases, and when

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present they tend to disappear within a week of commencement of treatment. The finding of these, however, in apparently healed cases, is of significance, as this indicates either that the condition is merely dormant or that re-infection has occurred. In the latter connection, it must be remembered that trachoma produces little or no natural immunity, and that in endemic areas re-infection is a constant threat.

The topical application of cortisone has been advocated by Nataf, Maurin and Dupland[39] as a test of cure. They found that some cases of apparently healed trachoma showed signs of fresh activity after several instillations of the corticoteroid, and they concluded that in these cases the condition had merely become dormant. I have had similar experiences, and believe this to be a valuable test.

PROPHYLAXIS:

Strict personal hygiene is probably the best prophylactic againts trachoma. The hands should be washed immediately after contact with a known or suspected case, and the communal use of towels should be prohibited. In areas where flies are prevalent, steps should be taken to eradicate them. Cases of acute conjunctivitis should receive prompt and adequate treatment. These points should be emphasized in lectures to the public in regions where the disease is rife.

The cultivation of the virus has stimulated research into the possibility of producing a vaccine which could be used prophylactically and therapeutically(Grayston, Wang, Woolridge, Yang and Johnston[40]), and if this can be achieved a great advance will have been made in the control of the disease.

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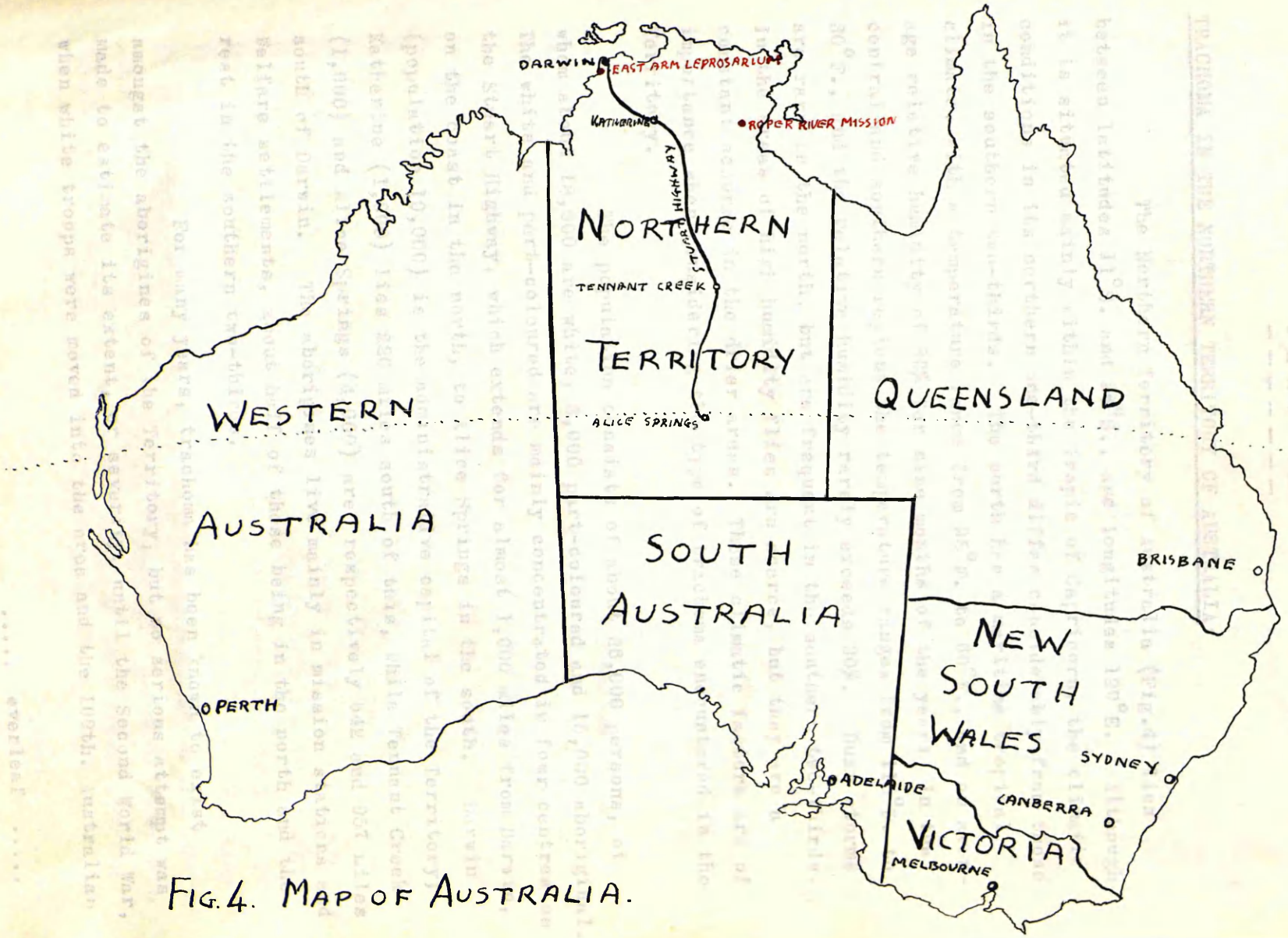

FIG. 4. MAP OF AUSTRALIA.

PART III

TRACHOMA IN THE NORTHERN TERRITORY OF AUSTRALIA:

The Northern Territory of Australia (Fig.4) lies between latitudes 11°S. and 26°S., and longitudes 129°E. Although it is situated mainly within the Tropic of Capricorn, the climatic conditions in its northern one-third differ considerably from those in the southern two-thirds. The north has a maritime tropical climate, with a temperature range from 95°F. to 60°F., and an average relative humidity of 80% for nine months of the year; in the central and southern regions the temperature ranges from 115°F. to 30°F., and the relative humidity rarely exceeds 30%. Dust storms are rare in the north, but are frequent in the southern two-thirds. In the areas of high humidity flies are scarce, but they are a constant scourge in the drier areas. These climatic factors are of importance when considering the type of trachoma encountered in the Territory.

The population consists of about 36,000 persons, of whom about 18,000 are white, 3,000 part-coloured and 15,000 aboriginal. The white and part-coloured are mainly concentrated in four centres on the Stuart Highway, which extends for almost 1,000 miles from Darwin, on the coast in the north, to Alice Springs in the south. Darwin (population 10,000) is the administrative capital of the Territory; Katherine (1,000) lies 220 miles south of this, while Tennant Creek (1,000) and Alice Springs (4,000) are respectively 642 and 957 miles south of Darwin. The aborigines live mainly in mission stations and Welfare settlements, about half of these being in the north and the rest in the southern two-thirds.

For many years, trachoma has been known to exist amongst the aborigines of the Territory, but no serious attempt was made to estimate its extent, or severity, until the Second World War, when white troops were moved into the area and the 109th. Australian

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General Hospital was established at Alice Springs. When aborigines from the surrounding area began, in 1942, to attend this hospital for treatment, it was found that the incidence of eye disease amongst them was high, and that practically all of them exhibited the signs and symptoms of "classical" trachoma - in passing it may be mentioned that most Australian ophthalmologists were at that time, and still are, unaware that the disease can exist in an uncomplicated form - and that this might constitute a threat to the health of the troops in the area. As a result, surveys of the native population were undertaken, at first by the Australia Military Forces and later by the Commonwealth Department of Health. The results of these have been well summarized by the Rev. Frank Flynn[23], a Roman Catholic priest who is also a trained ophthalmologist, who carried out many of these surveys. Schneider[41], to a lesser and more limited extent, contributed corroborative evidence. These surveys showed that trachoma was present in the aborigines throughout the Territory, and that, in most instances, over 50% of the native population were affected, There was a marked difference, however, in the severity of the disease in the northern region when compared with the centre and south. In the north it was mainly mild and uncomplicated, while in the other two areas the "classical" variety was common.

During this time, little attention was paid to the possibility of the disease existing in the white population of the Territory. It had been known to exist in "classical" form, throughout Australia (particularly in Queensland and the northern part of South Australia) at the end of the last and the beginning of this century, but as, with the passing of the years, less and less cases of this type were seen, it came to be assumed that it was no longer present in those of European descent. An interesting article, published in the Medical Journal of Australia by Rodger and Priestley[42] in 1915, gives an excellent description of uncomplicated trachoma in school children in western Queensland, but this seems to have been ignored by the Australian ophthalmologists of that time. By the

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beginning of the Second World War, it was generally accepted that white Australians did not suffer from trachoma, and all cases of entropion and trichiasis were ascribed to other causes. Nevertheless, many in the rural areas continued to suffer from "granular conjunctivitis", and often received copper sulphate treatment from their local general practitioners.

In 1954, Mann, while investigating eye disease in the Kimberley region for the Western Australian Government, discovered that not only aborigines but white school children were affected (Mann[43]), and in subsequent surveys (Mann[44,45]) she showed that similar conditions existed in other regions of that State. Meanwhile medical officers of the Northern Territory Medical Service were beginning to report cases in the white population of the Territory, and this, combined with the fact that large numbers of the aborigines there were now known to be infected, resulted in the decision of the Commonwealth Department of Health to appoint an ophthalmologist to investigate and treat the eye disease in this region. In July, 1959, I became the first to hold this appointment.

The Northern Territory is a vast area of over 500,000 square miles, and as the sole practicing ophthalmologist I found it impossible, in the two years which I spent there, either to cover the whole region fully or to confine my activities solely to the investigation of trachoma. Nevertheless, from my base in Darwin I was able to visit all the larger centres and many of the mission stations and Welfare settlements, and to examine a large cross-section of the total population. From this, I was able to estimate that 50% had trachoma; 85% of this occurred in the aborigines and part-coloured, and 15% in the whites. There was no difference in the incidence of the disease in the various areas, but I confirmed Flynn's[23] findings that in the north it was mainly "trachome pur", whereas in the centre and south secondary bacterial conjunctivitis was a common complication. Bacteriological investigations showed that, in the complicated cases, the commonest secondary invaders were the staphylococcus aureus and

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and the bacillus of Koch-Weeks, while occasionally Morax-Axenfeld bacillus was involved. Complicated trachoma was rarely found in the white population in any of the areas.

CLINICAL CLASSIFICATION OF TRACHOMA:

The MacCallan classification possesses the disadvantage that it is a pathological one, not always easily applicable to the clinical appearance of the disease. In an attempt to overcome this, Mann[44] introduced her clinical classification, in which the following stages were described:-

Stage A, active and infectious trachoma;
stage B, healed trachoma with good vision;
stage C, healed trachoma with impaired vision;
stage D, healed trachoma with loss of all useful vision.

Later, she modified this to include stage A-B, a transition stage in which the disease is still active but there is also evidence of healing.

In my investigations of trachoma in the Northern Territory I found that the Mann classification was useful as a basis, but did not adequately cover the progress of the active stage of the disease. Accordingly, I modified stage A, dividing it into four sub-divisions:-

A.1, active trachoma with no scarring (Fig.5),
A.2, active trachoma with minimal scarring (Fig.6)
A.3, active trachoma with marked scarring (Fig.7);
A.4, active trachoma with marked scarring plus defective vision due to corneal complications.

Stage A-B was discarded, and stages B(Fig.8), C and D were retained as in the original classification. In this form, the Mann classification is now used throughout the Northern Territory.

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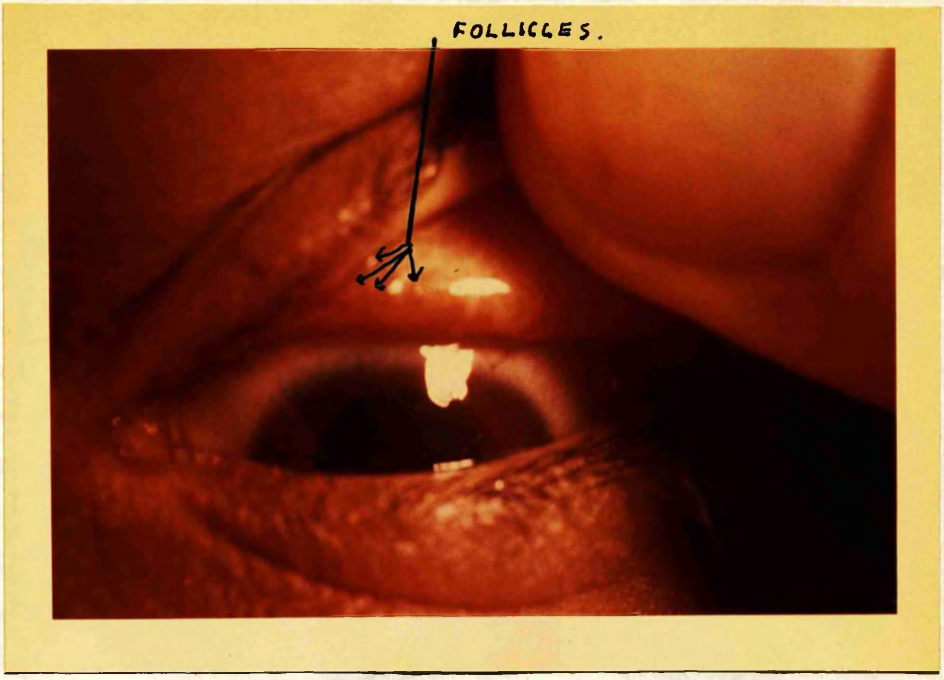

Fig. 5. Trachoma, stage A.1. Follicles in upper tarsal conjunctiva. Pannus at upper limbus.

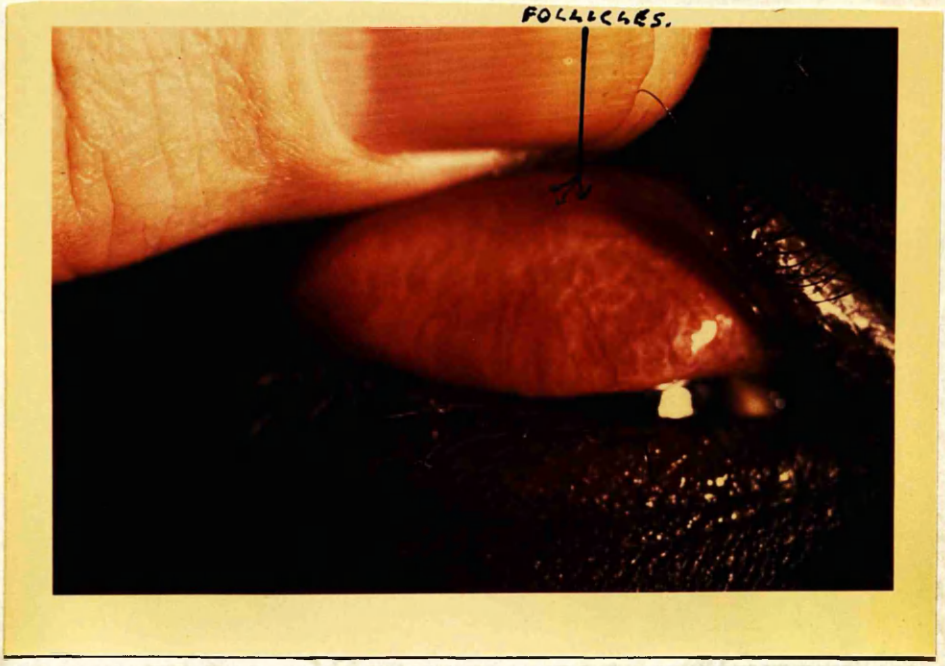

Fig. 6. Trachoma, stage A.2. Follicles in subtarsal sulcus. Slight scarring of upper tarsal conjunctiva.

Fig. 7. Trachoma, stage A.3. Marked scarring and active follicles upper tarsal conjunctiva.

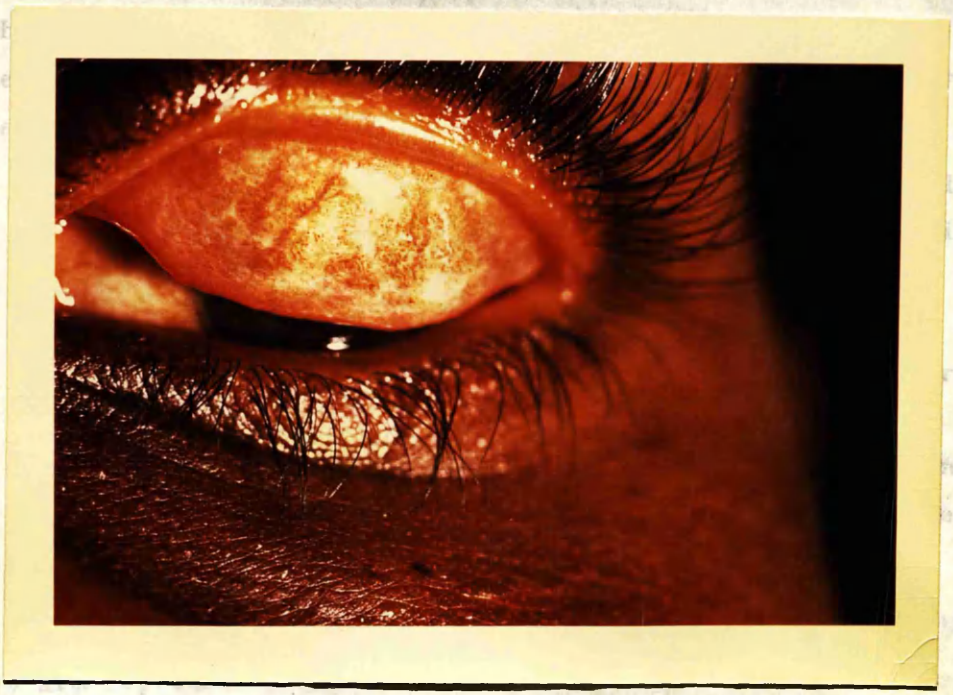

Fig. 8. Trachoma, stage B. Marked scarring of upper tarsal conjunctiva. No follicles.

TREATMENT OF TRACHOMA IN THE NORTHERN TERRITORY:

A routine course of treatment, based on the recommendations of the Expert Committee on Trachoma of the World Health Organization[26], was already in operation in some parts of the Territory on my arrival. This consisted of two weeks of sulphadiazine orally three times daily, combined with the topical application of chlortetracycline ointment twice daily for eight weeks. I found that, when patients conscientiously carried out this treatment, the results were good, 75% being cured after a single course; however, many patients forgot or neglected to take the sulphonamide regularly, while others were unable to continue the chlortetracycline instillations for more than one or two weeks because of irritation of the eyes. The latter difficulty was overcome by substituting chloramphenicol ointment, which proved to be well tolerated, for chlortetracycline, but the problem of adequate sulphonamide administration remained. About this time, two new products, a long-acting sulphonamide, sulphamethoxypyridazine, and an antibiotic, tetracycline in sesame oil, were made available to us for clinical trial, and experiments were planned to attempt to ascertain:-

(a) how the results of treatment with sulphamethoxypyridazine compared with those obtained with tetracycline in oil;
(b) how small a dosage of sulphamethoxypyridazine would be effective;
(c) whether twice weekly treatment with sulphamethoxypyridazine would be sufficient;
(d) whether treatment with either of these products alone was as effective as combined treatment with sulphonamides and antibiotics.

The areas chosen for these experiments were the Roper River Mission, East Arm Leprosarium and Darwin.

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Roper River Mission.

This mission station is situated in the northern region of the Northern Territory 300 miles south-east of Darwin and about 50 miles west of the Gulf of Carpentaria, its geographical position being 14.5°S. and 134.5°E. It is administered and staffed by the Church Missionary Society, and caters for a population of about 250 aborigines. The community is an isolated one, and as a result there is less fluctuation of population than in other aboriginal settlements; for this reason, and also because it was suspected that trachoma in this area, although of high incidence, was mainly of the uncomplicated variety, it was considered suitable for treatment studies.

As a preliminary, shortly before the supplies of sulphamethoxypyridazine and tetracycline arrived, the entire population of the mission was examined for evidence of trachoma. At the time of the examination 243 persons were in residence, and of these 220 (90.5%) were found to be affected. Table 1 shows the incidence of the disease according to the modified Mann classification.

TABLE 1.

INCIDENCE OF TRACHOMA AT ROPER RIVER MISSION.

A.1	A.2	A.3	A.4	B.	C.	D.
106	41	58	2	11	2	0

From this, it will be seen that, of the 220 persons affected, 207 (94%) had active trachoma, and only 13 (6%) could be considered inactive. However, there were none who could be classified as blind from the disease, and only 4 (1.9%) had defective vision.

The distribution of the various categories according to age groups is given in Table 2, and this shows, as one would expect, that the majority of the active cases was in the younger age groups.

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TABLE 2.

DISTRIBUTION OF TRACHOMA, IN AGE GROUPS.

	A.1	A.2	A.3	A.4	B.	C.	D.	Totals.
0-5 years	50	3	1	0	0	0	0	54
6-10	34	16	2	0	0	0	0	52
11-15	8	6	1	0	0	0	0	15
16-20	10	5	8	0	0	0	0	23
21-30	4	9	31	0	4	1	0	49
31-40	0	2	7	1	4	0	0	14
41-50	0	0	1	0	0	0	0	1
Over 50	0	0	7	1	3	1	0	12
TOTALS	106	41	58	2	11	2	0	220

Cultures from conjunctival swabs, taken at random from the population, were either negative or yielded growth only of coagulase-negative staphylococcus albus, indicating that secondary conjunctivitis was not a problem in the area, and that the disease as seen there could be regarded as "trachome pur". The clinical pattern of the disease tended to confirm this, as corneal ulceration was noted in only two cases (classified as A.4), and pannus rarely extended more than 3 mm. from the limbus. The two healed cases (stage C) with defective vision gave histories of previous trauma, which may have accounted for their corneal opacities. The eleven cases which were healed with good vision (stage B) showed fairly extensive scarring of the upper tarsal conjunctivae, but minimal cicatrization of the corneae at the upper limbus, little or no entropion and no symblepharon.

When treatment was commenced, 168 of the active cases were available. These were divided into four groups of 42, and

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TABLE 3.

DOSAGE SCALE OF SULPHAMETHOXYPYRIDAZINE IN TETRACYCLINE IN OIL

AGE	GROUP 1. SULPHAMETHOXYPYRIDAZINE DAILY FOR 15 DAYS	GROUP 11. SULPHAMETHOXYPYRIDAZINE DAILY FOR 8 DAYS	GROUP 111. SULPHAMETHOXYPYRIDAZINE TWICE WEEKLY FOR 4½ WKS.	GROUP 1V. 1% TETRACYCLINE IN SESAME OIL
Over 14 yrs.	2 tablets on first day, then 1 tablet daily for 14 days. (TOTAL 8 Gm.)	2 tablets on first day, then 1 tablet daily for 7 days. (TOTAL 4.5 Gm.)	2 tablets on first day, then 1 tablet twice weekly for 4 weeks. (TOTAL 5 Gm.)	Two drops in each eye, twice daily for 8 weeks.
8 - 14	1½ tablets on first day then ¾ tablet daily for 14 days (TOTAL 6 Gm.)	1½ tablets on first day then ¾ tablet daily for 7 days. (TOTAL 3.375 Gm.)	1½ tablets on first day then ¾ tablet twice weekly for 4 weeks. (TOTAL 3.75 Gm.)	
4- 8 yrs.	1 tablet on first day, then ½ tablet daily for 14 days. (TOTAL 4 Gm.)	1 tablet on first day, then ½ tablet daily for 7 days. (TOTAL 2.25 Gm.)	1 tablet on first day, then ½ tablet twice weekly for 4 weeks. (TOTAL 2.5 Gm.)	
1 - 4 yrs.	½ tablet on first day, then ¼ tablet daily for 14 days. (TOTAL 2 Gm.)	½ tablet on first day, then ¼ tablet daily for 7 days. (TOTAL 1.125 Gm.)	½ tablet on first day, then ¼ tablet twice weekly for 4 weeks. (TOTAL 1.25 Gm.)	

were treated as follows:-

group 1, sulphamethoxypyridazine tablets orally once daily for 15 days;

group 11, sulphamethoxypyridazine tablets orally once daily for 8 days;

group 111, sulphamethoxypyridazine tablets orally twice weekly for 4½ weeks;

group 1V, 1% tetracycline in oil drops twice daily in each eye for 8 weeks.

The dosage scale used in this experiment is illustrated in Table 3.

Of the 42 patients in each group, 37 attended regularly for treatment in group 1, 35 in group 11, 36 in group 111 and 34 in group 1V, so that in all 142 completed the prescribed course. When examined two months after the conclusion of treatment, 82(58%) were found to be cured according to the criteria described in Part 11. No further treatment was instituted at this time, but the patients were re-examined four months later, in order to conform with the World Health Organization recommendation that six months should elapse before final assessment. At this examination the situation remained unchanged, the 82 cured patients appearing completely healed, while the remaining 60 still showed evidence of activity; this supports the view which I hold, that two months is a sufficient time in which to assess the effects of treatment.

The results of treatment of the various groups are shown in Table 4.

TABLE 4.

RESULTS OF TREATMENT IN EACH GROUP

	Group 1. (37 Pats.)	Group 11. (35 Pats.)	Group 111. (36 Pats.)	Group 1V. (34 Pats.)	Total
CURED	20 (54%)	18 (51%)	22 (61%)	22 (64%)	82
NOT CURED	17 (46%)	17 (49%)	14 (39%)	12 (36%)	60

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Table 5 shows the effectiveness of treatment of the various categories in each group.

TABLE 5.

EFFECTIVENESS OF TREATMENT OF VARIOUS CATEGORIES.

CATEGORY		GROUP 1.	GROUP 11.	GROUP 111.	GROUP 1V.
A.1.	CURED	8 (47%)	8 (36%)	11 (61%)	13 (62%)
	NOT CURED	9 (53%)	14(64%)	7 (39%)	8 (38%)
A.2.	CURED	5 (38%)	4 (67%)	6 (54.5%)	4 (57%)
	NOT CURED	8 (62%)	2 (33%)	5 (45.5%)	3 (43%)
A.3.	CURED	7 (100%)	4 (80%)	5 (71%)	5 (83%)
	NOT CURED	0	1 (20%)	2 (29%)	1 (17%)
A.4.	CURED	0	2 (100%)	0	0
	NOT CURED	0	0	0	0

The results were subjected to statistical analysis using the X^2 test for independence, to ascertain if there was a significant difference between the various forms of sulphamethoxypyridazine treatment, or between the sulphamethoxypyridazine and the tetracycline treatment. Tables 6 and 7 illustrate this.

TABLE 6.

TEST OF SIGNIFICANCE OF DIFFERENCE OF VARIOUS FORMS OF SULPHAMETHOXYPYRIDAZINE TREATMENT.

	GROUP 1.	GROUP 11.	GROUP 111.	TOTAL
CURED	20 (20.5)*	18 (19.4)*	22 (20)*	60
NOT CURED	17 (16.5)*	17 (15.6)*	14 (16)*	48
	37	35	36	108

*Figures in parentheses indicate expected numbers.

$X^2 = 0.69$. For two degrees of freedom, this is not significant.

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TABLE 7.

TEST OF SIGNIFICANCE OF DIFFERENCE
OF SULPHAMETHOXYPYRIDAZINE AND TETRACYCLINE TREATMENTS.

	SULPHAMETHOXYPYRIDAZINE	TETRACYCLINE	TOTAL
CURED	60 (62.4)	22 (19.6)	82
NOT CURED	48 (45.6)	12 (14.4)	60
	108	34	142

$X^2 = 0.90$. For one degree of freedom, this is not significant.

The effectiveness of treatment of the various categories (excluding category A.4, in which the numbers involved were too small) was similarly analyzed, with the result shown in Table 8.

TABLE 8.

TEST OF SIGNIFICANCE OF EFFECTIVENESS OF TREATMENT
OF VARIOUS CATEGORIES.

	A.1.	A.2.	A.3.	TOTAL
CURED	40 (44.6)	19 (21.1)	21 (14.3)	80
NOT CURED	38 (33.4)	18 (15.9)	4 (10.7)	60
	78	37	25	140

$X^2 = 8.92$. For two degrees of freedom, this is definitely significant.

As Table 9 shows, there is no significant difference in the results of treatment of categories A.1. and A.2.:-

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TABLE 9.

TEST OF SIGNIFICANCE OF DIFFERENCE OF EFFECTIVENESS OF TREATMENT OF CATEGORIES A.1. AND A.2.

	A.1.	A.2.	TOTAL
CURED	40 (40)	19 (19)	59
NOT CURED	38 (38)	18 (18)	56
	78	37	115

$X^2 = 0$, i.e. there is no significant difference. A.1 and A.2 may therefore be considered as one category, and if this category is compared with A.3, a significant difference is found, as shown in Table 10:-

TABLE 10.

TEST OF SIGNIFICANCE OF DIFFERENCE OF EFFECTIVENESS OF TREATMENT OF CATEGORIES A.1 + A.2 and A.3.

	A.1 + A.2	A.3	TOTAL
CURED	59 (65.7)	21 (14.3)	80
NOT CURED	56 (49.3)	4 (10.7)	60
	115	25	140

$X^2 = 8.92$. For one degree of freedom, this is significant.

No toxic reactions were observed in any of the patients treated with the sulphonamide. Several of those who received tetracycline drops complained of intense smarting of the eyes after each instillation, but this did not prevent them from continuing treatment. Aborigines appear to have a greater tolerance to pain than Europeans and this probably accounts for their ability to continue the tetracycline treatment.

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The conclusions drawn from this experiment were:-

1. There was no significant difference between the results of treatment with oral sulphamethoxypyridazine and with topical tetracycline. Approximately 60% of cases of uncomplicated trachoma may be expected to be cured after a limited course of treatment with either of these drugs;
2. within the dosage range used, the smaller doses of sulphmethoxypyridazine were as effective as the larger ones;
3. twice weekly treatment with sulphamethoxypyridazine for 4½ weeks was as effective as daily treatment for 15 or 8 days;
4. treatment was more effective in the later stages of the disease.

East Arm Leprosarium.

In a previously published paper (McLean[3]) I described the incidence of trachoma in this closed community, which is situated 12 miles south-west of Darwin, and pointed out that the sulphones, although chemically similar to the sulphonamides, had no effect on its prevention, but the treatment of the affected patients was not discussed.

Of the 172 patients residing in the Leprosarium, 152 (88.4%) showed signs of active or healed trachoma; of these 109 (71.7%) were active, and 43 (28.3%) healed. The numbers in the various categories are shown in Table 11.

TABLE 11.

CATEGORIES OF TRACHOMATOUS PATIENTS AT EAST ARM LEPROSARIUM.

A.1	A.2	A.3	A.4	B.	C.	D.
30	35	38	6	34	8	1

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As would be expected in a medical institution, the incidence of secondary conjunctivitis was negligible, and the active disease existed in the uncomplicated form.

The 109 active patients were treated with oral sulphadiazine and topical chlortetracycline. The dosage of the sulphonamide was adjusted to the age of the patient, and was given three times daily for two weeks; chlortetracycline was instilled twice daily in each eye from the commencement of sulphadiazine therapy, and was continued for eight weeks. No toxic reactions to the sulphonamide were observed, and all patients completed the chlortetracycline treatment although a few complained of conjunctival irritation. After two months, the effects of treatment were assessed, and 84 (77%) were found to be cured, while 25 (23%) required further treatment. The results in the various categories are shown in Table 12:-

TABLE 12.

RESULTS OF COMBINED SULPHADIAZINE AND CHLORTETRACYCLINE THERAPY

	A.1.	A.2	A.3	A.4	TOTAL
CURED	21 (70%)	23 (65.7%)	35 (92.1%)	5 (83.3%)	84
NOT CURED	9 (30%)	12 (34.3%)	3 (7.9%)	1 (16.7%)	25

No significant difference in the results of treatment was found between categories A.1 and A.2, or between categories A.3 and A.4, but, as shown in Table 13, there was a significant difference between A.1 + A.2 and A.3 + A.4.

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TABLE 13.

TEST OF SIGNIFICANCE OF DIFFERENCE OF EFFECTIVENESS OF TREATMENT IN CATEGORIES A.1 + A.2 AND A.3 + A.4.

	A.1 + A.2	A.3 + A.4	TOTAL
CURED	44 (50.1)	40 (33.9)	84
NOT CURED	21 (14.9)	4 (10.1)	25
	65	44	109

$X^2 = 8.00$. For one degree of freedom, this is significant.

When the results were compared with those obtained at Roper River Mission, a significant difference, in favour of the combined treatment, was found. This is shown in Table 14:-

TABLE 14.

TEST OF SIGNIFICANCE OF DIFFERENCE OF EFFECTIVENESS OF TREATMENT AT ROPER RIVER MISSION AND EAST ARM LEPROSARIUM.

	ROPER RIVER	EAST ARM	TOTAL
CURED	82 (93.9)	84 (72.1)	166
NOT CURED	60 (48.1)	25 (36.9)	85
	142	109	251

$X^2 = 10.25$. For one degree of freedom, this is highly significant.

It was therefore concluded that combined therapy with sulphonamides and antibiotics was more effective than treatment with either of these groups of drugs alone. Once again it was noted that the later stages of the disease responded better to

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treatment than the earlier stages.

DARWIN:

Having arrived at the conclusion that combined treatment was more effective, it remained to be determined whether there was a significant difference between combined treatment with sulphadiazine and chlortetracycline and combined treatment with sulphamethoxypyridazine and tetracycline.

100 white and part-coloured patients in Darwin were selected for this part of the study, 46 being in category A.1, 29 in category A.2 and 25 in category A.3. It may be noted here that the majority of the white residents in Darwin are civil servants or their families, who have resided there for only two or three years, and so would not be expected to show signs of the later stages of trachoma; all whites taking part in this experiment were in categories A.1 and A.2. The part-coloured patients were distributed through each category and constituted the whole of category A.3.

Sulphamethoxypyridazine, in a dosage adjusted to the age of the patient, was given once daily for two weeks, and tetracycline in oil suspension was instilled twice daily in each eye. Unfortunately, after two or three days, all patients complained bitterly of intense conjunctival irritation due to the tetracycline suspension, and chloramphenicol ointment had to be substituted for this and continued for eight weeks. The results of this combined therapy are given in Table 15:-

TABLE 15.

RESULTS OF COMBINED SULPHAMETHOXYPYRIDAZINE AND CHLORAMPHENICOL THERAPY

	A.1.	A.2.	A.3.	TOTAL
CURED	36 (78.2%)	23 (79.3%)	23 (90.8%)	82
NOT CURED	10 (21.8%)	6 (20.7%)	2 (9.2%)	18

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When these are compared with the results obtained with combined sulphadiazine and chlortetracycline therapy at East Arm Leprosarium, no significant difference is found (Table 16).

TABLE 16.

TEST OF SIGNIFICANCE OF DIFFERENCE OF EFFECTIVENESS OF TREATMENT WITH SULPHADIAZINE + Chlortetracycline AND SULPHAMETHOXYPYRIDAZINE + Chloramphenicol.

	SULPHADIAZINE + CHLORTETRACYCLINE	SULPHAMETHOXYPYRIDAZINE + CHLORAMPHENICOL.	TOTAL
CURED	84 (86.6)	82 (79.4)	166
NOT CURED	25 (22.4)	18 (20.6)	43
	109	100	209

$X^2 = 0.80$. For one degree of freedom. this is not significant.

From these three experiments, it was concluded that:-

1. combined therapy with oral sulphonamides and topical antibiotics is more effective in trachoma than treatment with either of these alone; they appear to act synergistically when used together;
2. sulphamethoxypyridazine is as effective as sulphadiazine, and has the advantage that a smaller dosage is required;
3. the total dosage of sulphonamides commonly given in the treatment of trachoma is greater than is necessary;
4. of the three topical antibiotics used, chloramphenicol produced the least conjunctival irritation;
5. after a single course of oral sulphonamides + topical antibiotics, approximately 25% of patients will require further treatment;

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6. the response to treatment is greater in the later than than in the earlier stages of the disease;

7. if signs of activity are still present two months after the cessation of treatment, further treatment will be required.

ADDITIONAL OBSERVATIONS:

The patients who were not cured by these courses of treatment received further therapy. In order to avoid the risks of skin and systemic reactions or blood dyscrasias due to sulphonamides, topical antibiotics alone were used for these, and were continued until all signs of activity had disappeared. In most cases an additional two to three months of this treatment was sufficient, but in a few it had to be prolonged for about one year. Chloramphenicol was the most commonly used antibiotic, but in the most resistant cases chlortetracycline and oxytetracycline were also used. Occasionally, when treatment was switched from one antibiotic to another, rapid healing occurred, but no one antibiotic was consistently more effective than the others.

In this series of experiments, none of the patients receiving sulphonamides gave a history of sensitivity to these drops, and no toxic reactions occurred. This, however, was unusual; in the Territory as a whole, 0.5% of trachomatous patients stated that they were sensitive to sulphonamides and were treated solely with antibiotics, while a further 1% had to stop sulphonamide treatment because of signs of toxicity. For the most part these were mild, consisting of transient skin rashes, headache or nausea, but one white child of 8 years of age developed erythema multiforme bullosum while taking sulphamethoxypyridazine. The specialist physician who attended to her was not convinced that the drug was responsible, but I think that it was the probable cause. Fortunately with antibiotic and corticosteroid therapy she recovered completely.

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In the central and southern regions of the Territory, trachoma was complicated by secondary infection in 95% of the aboriginal cases, 50% of the part-coloured, and less that 2% of the white. Corneal opacities, due to extensive pannus or resulting from corneal ulceration or trichiasis, caused defective vision in 10% of the aboriginal patients and 3% of the part-coloureds, but the incidence of blindness was less than 1%. The living conditions of the aborigines are similar throughout the Territory and climatic factors appear to be responsible for the prevalence of the complicated form in the centre and south. In the north, the high humidity restricts fly-breeding and the dissemination of infection by dust, while exactly the opposite is found in the other two regions.

Combined therapy was used routinely, except when sulphonamides were contraindicated, in the central and southern regions. When secondary infection was present, the antibiotic was instilled four-hourly until this had resolved, and atropine was used where there was any corneal ulceration. Where treatment could be closely supervised the results after a single course were comparable to those obtained in the north, but in many of the Welfare settlements, due to a shortage of nursing staff, this could not be achieved, and in these areas we were fortunate if a 60% cure rate resulted. On the average, about 50% were cured.

In the northern region, following Smith's[37] report of an apparent cure of trachoma with intramuscular penicillin, it was decided to assess this form of treatment on a small number of patients. 1,000,000 units of penicillin G were given intramuscularly to ten patients daily for five days; one week later, there was some apparent improvement in that the papillary hypertrophy was less, but within a month all had reverted to their condition previous to treatment. As I had previously, in West Africa, treated trachomatous patients with topical penicillin, with complete lack of success, it was concluded that it would be of little value to continue treatment with this antibiotic.

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P A R T IV.

DISCUSSION AND CONCLUSIONS

IMPORTANCE OF TRACHOMA:

It is undoubtedly true that trachoma is the most prevalent eye disease in the world. Its severity, however, varies considerably, and evidence is accumulating that this is due to the presence or absence of secondary infection. Where the latter is negligible, or can be rapidly and effectively controlled, the primary condition is relatively innocuous and the danger of its producing blindness or even defective vision is slight, but there are large areas where, owing to lack of medical facilities, low standards of personal hygiene and inadequate sanitary control, the problem of "classical" trachoma remains.

The disease is present throughout the Northern Territory of Australia and its incidence is high. That it is mainly of the uncomplicated variety in the northern region, while in the centre and south secondary infection is common, appears to be due to climatic factors, especially the degree of humidity. There is, however, no difference in the incidence of the primary disease in the various areas. Defective vision resulting from the condition is negligible in the northern region, and is likely to decrease in incidence in the other regions, due to active treatment campaigns. If these are continued, the disease should, within a few years, cease to be a problem of significance in the Territory.

DIAGNOSIS:

Follicles in the upper tarsal conjunctiva, epithelial keratitis, pannus and scarring of the upper tarsal conjunctiva are the major signs of trachoma, and the presence of two or more of

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these is diagnostic of the disease. Difficulty in diagnosis is most likely to arise in mild or early cases, which must be differentiated from such conditions as conjunctival folliculosis, inclusion conjunctivitis, pharyngoconjunctival fever, epidemic keratoconjunctivitis, molluscum contagiosum conjunctivitis and vernal conjunctivitis; the points of difference of these from trachoma have already been discussed. In areas of high endemicity, it is advisable to treat all doubtful cases as trachomatous.

CLINICAL EFFECTS:

In the majority of cases, the clinical effects of uncomplicated trachoma are slight. During the active stages, the patient usually complains of some discomfort, mainly in the form of a gritty sensation in the eyes, and there may be a slight mucoid or watery discharge from the conjunctival sac, but the condition may be practically symptomless. It is rare for epithelial keratitis or pannus to extend so far into the cornea as to cause diminution of vision. In the healed stage, if scarring, is extensive, some degree of entropion will be present, and this may be severe enough to cause trichiasis and resultant corneal ulceration and opacification, but it is rare to find this in cases which have not been secondarily infected.

In complicated cases, one or more attacks of acute conjunctivitis, of bacterial origin, occur. This may cause the patient to seek medical attention for the first time, and in such cases papillary hypertrophy due to the secondary infection may obscure the follicles in the upper tarsal conjunctiva, with the result that the primary condition may be overlooked if the cornea is not examined for epithelial keratitis or pannus. Corneal ulceration is a common complication of these attacks, and pannus increases considerably; from these, severe and permanent visual impairment may result. Repeated attacks of conjunctivitis increase the

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liability to extensive conjunctival scarring, entropion, symblepharon and xerophthalmia.

TREATMENT:

Oral sulphonamides and topical antibiotics have superceded other forms of therapy for trachoma. The experiments described in Part III indicate that combined treatment with these is more effective than treatment with either of these groups of drugs alone, and that with such treatment about 75% of cases may be cured after a single course. The remainder will require more prolonged treatment, and for this, in order to avoid the risk of sulphonamide reactions or blood dyscrasias, antibiotics in topical form should be used.

Sulphadiazine appears to be as effective as sulphamethoxypyridazine, but the latter has the distinct advantage that a smaller dosage is required, and for this reason should be the sulphonamide of choice. As regards the antibiotics, it has been my experience in the Northern Territory that chloramphenicol is best tolerated by the patients, particularly when treatment has to be prolonged. I have not found penicillin to be of any value in treatment.

As a routine form of treatment I would suggest the oral administration of sulphamethoxypyridazine twice weekly for four weeks, combined with the twice daily instillation of oculentum chloramphenicol for eight weeks, provided that there is no history of sulphonamide sensitivity and that the patient can be observed frequently for signs of drug reaction. If, two months later, the condition is still active, chloramphenicol should be continued for a further eight weeks, after which, if still not healed, chlortetracycline or oxytetracycline should be tried. My impression is

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that these resistant cases are caused by a different strain of the virus, but I have no proof of this. In any case, some of them require treatment for about one year before they are cured.

When secondary infection is present, the antibiotic should be instilled four hourly until this has subsided, and then continued twice daily for the remainder of the eight week period; if there is any corneal ulceration, gtt. atropine 1% should be instilled three times daily until this has healed.

Where there is a history of sensitivity to sulphonamides, sulphamethoxypyridazine must never be used. These cases should be treated solely with local antibiotics.

CONTROL:

Ideally, in order to eradicate the infection in areas where it is known to exist, everyone should be examined for trachoma, but this is rarely a practical possibility. However, as the disease is most active in the early years of life, every effort should be made to examine all pre-school and school children at least once every six months, and all cases should be treated immediately. The parents of affected children should also be examined and treated if necessary. In this way, the incidence of the disease can be greatly reduced. I also consider it advisable that all treated cases should be examined once a year for evidence of re-infection.

Health authorities should initiate campaigns against flies where these are prevalent. In addition, by means of lectures, they should instruct the public in personal hygiene and should stress the value of immediate treatment of all eye infections.

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CONCLUSIONS:

1. Uncomplicated trachoma is not a severe disease, and, if properly treated, should not result in visual impairment.

2. The combination of oral sulphonamides and topical antibiotics is the most effective method of treatment.

3. Sulphamethoxypyridazine, because of the lower dosage required, is the sulphonamide of choice.

4. Chloramphenicol, when applied topically, has the advantage over other antibiotics that it produces less local reaction.

I am indebted to the Director-General, Commonwealth Department of Health, Australia, for permission to publish the results of the experiments which I conducted in the Northern Territory, and to the medical officers and nursing staff of the Northern Territory Medical Services for their co-operation. I am also grateful to Mr. Town Hopkins, of Lederle Division, Cyanamid Co. of Australia, for the generous supply of sulphamethoxypyridazine and tetracycline in oil used in these experiments.

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