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## Etiology and treatment of trachoma

Charles Gass

*University of Nebraska Medical Center*

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THE ETIOLOGY AND TREATMENT OF TRACHOMA

BY

CHARLES GASS

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SENIOR THESIS

PRESENTED TO

THE COLLEGE OF MEDICINE

UNIVERSITY OF NEBRASKA

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OMAHA 1939

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## CLINICAL MANIFESTATIONS

"The clinical picture of trachoma offers numerous variations and differences in individual instances, it nevertheless follows a more or less general pattern, recognizable and therefore diagnosable by the experienced observer. The disease is essentially a chronic infection of the human conjunctiva and cornea, sometimes involving the adnexa of the eye. Occasionally beginning with acute onset, it most frequently appears with slowly developing, insidious, almost negligible symptoms. The common observation is the involvement of both eyes, but from time to time undoubted examples of monocular disease are seen, ranging in incidence from one per cent, according to Meyerhoff, 1.39 per cent by Puscariu, and Cattaneo, 3.95 per cent by Blatt, 4 per cent by v. Rotth, to 6 per cent by Nagel and Augstein. It is characterized by hypertrophy of lymph tissue, thus causing the formation of follicles, and accompanied by a break in the continuity of the blood vessels going to the limbus, trachoma eventually invades the cornea in the form of cloudy infiltration and vascularization, technically designated as pannus, with resultant partial or complete impairment of visual acuity. Ultimately cicatrization of the conjunctiva occurs, and this feature with corneal involvement comprises the important factor both in differential diagnosis and in permanent injury. The discomforts resulting from trachoma may include increased lachrymation, the sensation of extraneous material under the lids, discharge, pain and extreme photophobia, while the disabilities may embody impaired vision or blindness,

opacity, ulceration and scarring of the cornea, entropion and trichiasis, ptosis of the lids, secondary involvement of the iris, and so forth." (J, 8)

#### STAGES OF TRACHOMA

The one clinical classification that has been most universally adapted is that of MacCallan, which divides the disease into four stages. "Stage I, or Trachoma I, is characterized by the presence of diminutive follicles alone, which are semi-transparent and to the unaided eye avascular, or present with a generalized subepithelial infiltration which gives the conjunctiva a red velvety appearance. In either case, there is little, if any, exudate. This phase progresses into Stage IIa or Stage III. In Stage II, or Trachoma II, there is generalized roughening of the conjunctiva with numerous follicles on both tarsal and retrotarsal tissues. The follicles appear to be fragile and rupture readily with the usual manipulation of examination and treatment. This appearance (IIa) differs from another manifestation of the same stage (IIb) where the conjunctival response consists not of a follicular but of a papillary hypertrophy. In Stage II, secondary bacterial infection becomes more frequent and conjunctival discharge the general rule. Other forms of Stage II indicate superimposed conditions, as vernal catarrh in IIb", and gonococcal infection in IIc. In Stage III, or Trachoma III, there is a beginning absorption of follicles with a simultaneous replacement by cicatricial tissue. Milk-white plaques are frequently observed on both conjunctiva and cornea. Discharge when present is for the most part increased lachrymation with relatively few cells. Cicatrization may continue to completion and recovery.

In general, however, cicatrization remains incomplete, thus making it possible for the disease to revert to Stage II by recrudescence or reinfection. In Stage IV, or Trachoma IV? scar tissue superseces the normal epithelium, and in fact cicatrization reaches into the deeper tissues beyond the conjunctiva. Since Stage IV is the arrested phase of trachoma, different degrees of healing are abserved, varying from the slight alterations following mild infections to the grossly thickened and deformed lids resulting from severe and prolonged disease.

Vascularization of the cornea, or pannus, may appear in all stages of the disease and is generally accompanied by corneal opacity. Sometimes made out with difficulty, if at all. in Stage I, it is usually apparent to the naked eye in Stage II. In Stage III, the vessels become more marged even though the conjunctiva may be undergoing resolution, and in the final stage, the capillaries usually disappear, disintegration of the finer capillaries begins, and the larger vessels remain as hollow tubes, often discernible with difficulty. Vascularization of the cornea may begin weeks or months or longer following onset, but in any case the vessels originate as capillary offshoots of the vessels in the bulbar conjunctiva. Making their first appearance at the superior limbus, they appear superficially as tiny loops which may anastomose with each other, or as sprigs apparently ending blind in the corneal tissue. In time, vessels may appear in the cornea centripetally from the entire circumference of the cornea. The capillaries extend from the lumbus by growth toward the center giving rise

to vessels which may penetrate into the deeper lamellae of the cornea. Pannus does not necessarily develop pari passu with the conjunctival lesions, so that severity of one does not imply severity of the other. This is particularly observed in exacerbative attacks where the retrogressed pannus may return with a rapidity and severity completely out of proportion with the follicular or papillary involvement of the conjunctiva.

During the development of pannus, cellular changes may also occur at the limbus giving rise to grossly visible follicles. Attention was first called to this phenomenon by Herbert who, tracing the progress of the corneal follicle, described it as later rupturing and cicatrizing, creating formations now generally designated as Herbert's pits, or ocellles, and regarded as pathognomonic of trachoma. Meyerhoff found marginal pits in about half the patients with pannus, thus indicating the manifestation to be fairly common occurrence.

(A, 1, 2, 3)

## PART I

## ETIOLOGY

## HISTORICAL BACKGROUND

Trachoma may have been recognized in antiquity, as indicated by an ancient Egyptian manuscript, the Papyrus Ebers, which dates back to a period of time estimated to be between 1553-1500 B. C. In this manuscript the expression "hetae m mrt" occurs, which has been accepted as a reference to trachoma. The disease must not have been very prevalent, for it was not referred to until 1481. The first reference was made by Rabbi Meshoolam Ibn Menahem. In another century reference was made to trachoma by the Venetian physician, Prosper Alpinus, who practiced medicine in Cairo from 1580 to 1582. From that time onward trachoma became permanently and commonly implanted in Egypt. (B, 1)

Trachoma may have been present in the ancient Orient, but definite proof is lacking. Mijaschita states that trachoma existed in Japan as far back as 1200 years ago. (B, 6)

Herodotus (482-424 B.C.) is thought to have been the first of the Greeks to refer to trachoma, the evidence consisting of his comment concerning the discharge of two of thirty-two soldiers at Thermopylae because of ophthalmia. Hippocrates (460-377 B.C.) wrote a description of ophthalmia and trichiases, and for treatment recommended applications of copper acetate and fresh grape-juice. So, also, Plato (427-348 B.C.), Aristotle (384-322 B.C.), and Plutarch (50-120 A.D.) were aware of trachoma. (B, 6)



The Romans introduced such descriptive terms as as-  
pritudo and lipitudo, the former meaning roughness and the  
latter blar-eyed. The expressions are first encountered in  
De Medicina (VI, 6, 27) by Celsus (25 B.C.-50 A.D.). The  
word trachoma was coined by Dioscorides about 60 A.D. Some  
terminology was added by Galen, Cassius Felix, and Paulus of  
Aegina, and Paulus also introduced scraping of the lids as  
well as an operating procedure for trichiasis.

However, even though trachoma was a well established  
entity, Europe did not become acutely aware of the disease  
until the nineteenth century, when it began to spread at an  
alarming rate of speed. The Napoleonic expedition into Egypt  
in 1798 is held responsible for the spread of trachoma through-  
out Europe. (B, 4,5)

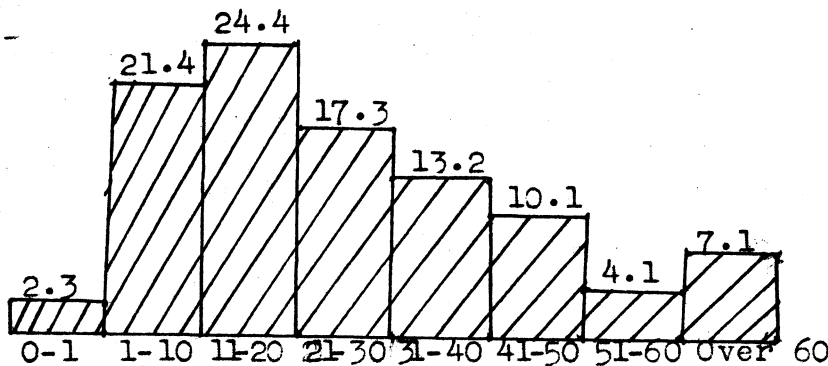
The history of trachoma among the native inhabitants of  
the New World is vague and indefinite. However it seems that  
trachoma is of fairly recent origin among the Indians and  
probably was disseminated among them by the white settlers.

Among the whites of this country trachoma increased rap-  
idly from 1850 onward as immigration changed from predominantly  
British, Irish, German, and Scandinavian to predominantly  
Italian, Austrian, Slavic, Russian, and Turkish. In 1897 the  
Treasury Department, then in charge of immigration, classified  
trachoma as "dangerous contagious" and thereby excluded from  
entry, trachomatous individuals. With the enforcement of this  
regulation and effective measures of eradication, the disease  
has been to a great extent eliminated, so at the present time  
trachoma occurs as a rural endemic disease having a peculiar  
belt of incidence running through West Virginia, Kentucky,  
Tennessee, southern Illinois, Missouri, and Arkansas. (B, 3,7)

## PREDISPOSING FACTORS IN THE PATHOGENY OF TRACHOMA

### AGE

Trachoma may occur at any age, but approximately half the patients fall within the first two decades of life. If trachoma occurs in a child under one year of age, the highest incident will be from the ninth to the twelfth month. (C, 5,7)



Percentage Distribution Of Trachoma by Age Decades

### RACIAL SUSCEPTIBILITY

A racial resistance to trachoma has been considered in order to explain the apparent low incidence of trachoma among certain racial groups. Burnet first introduced the concept that Negroes are resistant to trachoma. This has been both denied and confirmed repeatedly. Howard believes susceptibility to trachoma is in inverse ratio to the pigmentation of the skin and suggests a classification as the following in the order of their severity: American Whites; peoples of Southeast Europe; Japanese, Egyptians, natives of India, Chinese, the American Indian, mixed-blooded Negroes, and the full-blooded Negro. Trachoma is exceedingly rare among the full-blooded Negroes of the United States, but it has occurred with sufficient frequency among the Negroes of the West Indies,

Brazil, and Africa to admit that the Negroes are not naturally resistant to the disease. Gifford suggests that the discrepancy observed in the Negroes of the United States may be due to lack of sufficient contact between the whites and blacks.

The statement has been made several times that the Jews are more susceptible to trachoma than any other race. However in actuality the disease is no more common among Jews than among other peoples.

Axenfeld states that there is no racial resistance to trachoma, although he believes that the Negroes have greater tolerance for the disease than white people. This is in agreement with the observations of Meyerhoff and Tscirkowsky who also deny that acquired immunity has any relation to race.

#### SEX

Sex seems to play a very small part in the incidence of trachoma. Statistics from different areas differ in favoring one sex over the other. When all the statistics are placed together it becomes apparent that there is no predominance of one sex. Before closing this part of the subject, it must be brought out that the female sex is more responsible than the male in the propagation of the disease, since their intimate contact as mothers and nurses affords increased opportunities for dissemination. (C, 1,8)

#### HYGIENIC CONDITIONS

Most authorities agree that the incidence of trachoma closely corresponds to the hygienic conditions of the area where it is prevalent. It has been observed that among people who are not careful about their personal hygiene that there is a tendency for trachoma, once started, to spread to others in their surroundings. (C, 4)

## ETIOLOGY, GENERAL CONSIDERATIONS

Because there is no definite proof as to the cause of trachoma, and due to the fact that the transmissibility of trachoma to animals and man has been difficult to demonstrate with complete regularity, we will have to include in this discussion many alternative explanations. Many ophthalmologists have attempted to prove that trachoma is not a specific infectious disease and have substituted many explanations. Later in this discussion it will be shown that the accumulative evidence would indicate that trachoma is a specific infectious disease.

### NUTRITIONAL DEFICIENCY

The high incidence of trachoma among the poverty-stricken and the undernourished has been responsible for the belief that trachoma is directly related to a faulty nutrition. One of the largest arguments in favor of this belief is that trachoma often increases in incidence in the time of famine. Some authors state that trachoma is a direct result of a vitamin A deficiency. This contention has some degree of plausibility because vitamin A seems to maintain the natural resistance of the mucous membranes to its invasion by bacteria.

Hetler and James in a series of well-controlled experiments, set out to determine the effect of faulty and deficient diets on monkeys, rats, rabbits, and guinea pigs. Their experiments would tend to prove that the diet played no part in the susceptibility of the animal to trachoma.

Experiments conducted at the United States Trachoma Hospitals at Rolla, Missouri, and Richmond, Kentucky, furnishes

more proof that the diet plays no part in trachoma. They discovered that patients established on a well-balanced diet, reinforced with vitamins A,B,D, and G, showed no greater clinical improvement ophthalmologically than those maintained on the usual hospital diet. (C, 1,2,3,5,6)

#### TUBERCULOSIS

Even the earlier scholars of the disease believed that trachoma was associated with tuberculosis, and the present day literature supplies some articles in favor of this view-point. Pascheff, today, believes that tuberculosis is the underlying and responsible factor in trachoma. The fact that epithelioid cells occur in both conditions has been unnecessarily emphasized, since this coincidence proves little if anything. Except for differential leucocyte estimations and tuberculin skin tests, which may or may not be of significance, little is advanced to support the interrelationship. Experimental evidence gives conclusive proof of a complete independence of the two diseases. Tuberculin skin tests made by Drs. D.E. Rice, and J.E. Smith at Rolla, Missouri, indicate that the frequency of reactions among trachomatous patients is no greater than is to be anticipated among normal human beings of a similar age group. (D, 4)

#### SYPHILIS

A number of observers contend that a luetic infection furnishes a terrain perfectly suitable for the initiation and development of trachoma. Some authors state that the symptoms of trachoma are dissipated by antiluetic treatment. Others have pointed out the apparent similarities in the histological response of the two diseases. In the experience of the Trachoma Hospital of Missouri, it has been found that patients with

trachoma are rarely syphilitic as determined clinically and by the Wassermann test. (D, 3,2,1,5,6)

#### PROTOZOA

Burchardt in 1897 was the first to associate a protozoon with trachoma. He reported finding numbers of sharply defined, non-nucleated, oval, solid bodies occurring in the conjunctival epithelium of patients with trachoma.

Kastalsky in 1898 reported finding, in forty cases of trachoma, some homogeneous, hyalin, circular bodies measuring from 10 to 15 in diameter in the subepithelial layers of the conjunctiva.

In 1908, Rahlmann described protozoan forms occurring in trachomatous tissues.

Czaplewski, in 1913, reported finding in follicular contents large cellular bodies of varying shape and size. He considered these bodies as organisms and classified them as amoebae.

In all of these instances the belief and proof of a protozoan cause of trachoma rests only on microscopic examination. At the present time, these observations are discounted as artefacts, tissue cell structures, and even possible misinterpretations of cell changes associated with injury and necrosis. (J, 8)

#### FUNGI

The Italian school has been the great contenders of the theory that the Blastomyces is the cause of trachoma. In 1896, both Gonella and Guarnieri published independently the first observations on the presence of Blastomyces in trachoma.

Their attempts to cultivate the organism were negative. In 1908, Lodato also reported finding Blastomyces in sections of trachomatous conjunctiva and in the follicles. Addaria in 1909 reported finding the organism in sections, but was unable to cultivate it.

Stiel, in 1913, stated that he found the organisms in tissue sections and that he cultivated it on Drigalski's agar, and that he transmitted the disease with the culture in two separate cases.

In 1931, Ochi described a large oval organism, Cryptococcus, which he found in tissue sections and was able to cultivate it. Later workers denied the importance of this organism, considering it instead as a mast cell and its granules.

In 1890, Noiszewski, associated the streptothrix with trachoma. He obtained cultures of the organism, which he inoculated into rabbits. He felt that in this way trachoma had been transmitted, and therefore regarded this organism as the causative agent. Since trachoma is not transmissible to rabbits, it necessarily follows that the organism is unimportant etiologically.

The literature on fungi associated with trachoma, for only once was the blastomyces cultured, nor is there any proof that any of the other fungi cause trachoma. (J, 8)

## BACTERIA

### Cocci

Different cocci have been isolated repeatedly as the causative agent of trachoma. The descriptions given the various cocci has been incomplete, and it is difficult to say whether they are the same or really different from each other. To the trained bacteriologist the cocci described must be identi-

fied as staphylococci and pneumococci. The evidence, however, is more conclusive than in the case of the protozoa and fungi theory for, the evidence in support of the cocci included inoculations of animals and man. The reports of the transmissions of trachoma to animal in this case may be disregarded for trachoma can not be transmitted to the animals used in the experiment. The reports of the transmission to man can not be regarded so lightly, but they also may be disregarded for the descriptions of the reactions of the conjunctiva indicates that it was mild, the corneal involvement was lacking, and the condition disappeared spontaneously within relatively short intervals. (E, 9)

The following are some of the rod-shaped organisms which have been advocated as the causitive agent for trachoma: the Koch-Weeks bacillus; the diphtheroid organism; the bacillus trachus; the bacterium granulosis; the *Corynebacterium ramificans*. These organisms have not stood the test of time, which, more than any other factor, constitutes the most conclusive argument for the acceptability of a causative agent. Many of these theories are based only on microscopic evidence of their experimental proof has rested in the transmission of the disease to an animal that has been proven to be immune to trachoma. (E, 5,8,7,3,4,11,10)



## ORGANISMS REPORTED ASSOCIATED WITH TRACHOMA

ORGANISM	OBSERVER	DATE	EVIDENCE
MICROSPORON TRACHOMATOSUM	Noieszewski	1890	Inoculation in rabbits reported Pos.
Three Varieties	Santucci	1907	Microscopic
BLASTOMYCES	Gonella	1896	Microscopic
	Guarnieri	1896	Microscopic
	Lodato	1908	Microscopic
	Addario	1909	Microscopic
	Spoto	1910	Microscopic
	Stiel	1913	Microscopic, and cultural; inoculation in man reported Pos.
PROTOZOON			
Coccidia	Burchardt	1897	Inoculation in man was Neg.
Hyaline bodies	Kastalsky	1898	Microscopic
Plasmodia	Elze	1905	Microscopic
	Rahlmann	1908	"
	Von Krudener	1909	"
	Junius	1910	"
	Sakaguchi	1912	"
	Amoeba	Czaplewski	1913
CRYPTOCOCCUS	Ochi	1931	Microscopic & Cult.
		1935	Inoculation in man reported Pos.
BACTERIA			
Cocci	Sattler	1881-2	Inoculation in man reported Pos.

ORGANISM	OBSERVER	DATE	EVIDENCE
	Michel	1886	Inoculation in man reported Pos.
	Poncet	1886	Microscopic
	Kucharsky	1887	Inoculation in man Neg. Pos. in cat. ,
	Oteubra, Socor, & Neyel	1887	Inoculation in rabbits reported Pos.
	Schmidt	1887	Inoculation in birds reported Pos.
	Staderini	1887	Inoculation in rabbits reported Pos.
	Petresco	1888	Inoculation in dogs and cats reported Pos.
	Basevi	1899	Inoculation in man reported Pos.
	Snyder	1899	Inoculation in 4 species of animals reported Pos.
	Motegi	1933	Inoculation in man reported Pos.
Rod-shaped	Hirschberg and Krause	1881	Microscopic
	Koch	1883	Microscopic
	Kartulis	1887	Inoculation in man. 1 Pos. report
	Shongolowicz	1890	Inoculation in animals reported Pos.
	Muller	1897	Inoculation in rabbits reported Neg.

ORGANISM	OBSERVER	DATE	EVIDENCE
	Edwards	1910	Inoculation in monkeys - Neg.
	Williams	1913	Microscopic and Cult.
	Noguchi	1928	Inoculation in apes and monkeys reported Pos.
	Orlov	1929	Inoculation in rabbitiritis and ulceration.
	Lumbroso and Van Sant	1931	Inoculation in man and monkeys reported Pos.
	Socias	1936	Microscopic
RICKETTSIA	Busacca	1934-7	Microscopic, observed in man
	Cuenod	1935-7	in animals inoculated untreated human tissues.
	Poleff	1936	
VIRUS	Bertarelli and Cecchetto	1908	Evidence presented in the chapter on the virus.
	Marongiu	1908	
	Nicolle, Cuenod, and Blaizot	1912	
	Thygeson et al.	1935	
	Julianelle et al.		
INCLUSION BODY	Halberstadter and v. Prowazek	1907	Presence in man and apes and monkeys inoculated with trachomatous tissues.

## BICKETTSIAE

Because there has been such inconclusive and contradictory evidence in support of the different bacteria casually concerned in trachoma, there has been many investigations for some other variety of infectious agent. Many of these investigators, in recent years, have been diverted toward the rickettsial organisms.

The first published account on a rickettsial etiology of trachoma was in 1933, by Busacca. Since that time several articles have been published stating that the corneal scrapings during trachoma stained with Giemsa, contained small red-staining bodies ( $0.5\mu$  to  $0.8\mu$  by  $0.2\mu$ ). These bodies were observed in masses and isolated pairs, while other nondescript granules appeared blue. Busacca considered them rickettsiae; and because they were not observed in preparations from normal individuals or patients with folliculosis, chronic catarrhal conjunctivitis, lymphatic keratoconjunctivitis, and several other non-ocular conditions, he felt they were specific for trachoma. Guinea pigs and dogs were injected intraocularly with scraped trachomatous tissues and suffered a transient slight pannus. Intratesticular inoculation of dogs yielded no information, while similar injections in guinea pigs, carried out for seven serial passages, induced interstitial infiltration, usually perivascularly, with accompanying obliteration of germinal epithelium and the appearance of rickettsia-like structures in the mesothelial cells.

In 1935, Cuenod observed in Giemsa-stained preparations of follicular contents small particles stained pale blue or violet, aggregated in irregular masses between the epithelioid and mononuclear cells. Usually oval, sometime circular, but rarely rod-shaped, the bodies were also found in epithelioid, mononuclear, and Leber cells. He called them "Plastilles" and did not classify them. Finally Cuenod and Nataf reported that the "plastilles" were actually rickettsiae. Furthermore, he described several experiments designed to show that the rickettsial structures cause trachoma and multiply in the human louse.

More recently Poleff induced folliculosis in hens and guinea pigs by intraocular injections of trachomatous material. Examining scrape smears of the follicles which developed on the lids, he found rickettsia-like bodies, which he identified as those reported previously by Busacca and Cuenod. Poleff considers, on hypothetical grounds, the possibility that the rickettsial bodies enter into the structure of the epithelial cell inclusion, but wisely reserves his opinion. In a later paper he describes the technique used in cultivation and considers the rickettsial forms as a phase of the inclusion bodies.

Foley and Parrot have recently added their support to the rickettsial concept. Their evidence, however, is not striking, since it consists purely of a study of inclusion bodies in spontaneous trachoma.

Upon consideration and reflection, it seems inevitable that Rickettsia be brought forward as a candidate among the

the many suggested agents of trachoma. With the generalized vagueness and doubt of the various organisms advanced, it was to be expected that an entirely new variety would be offered sooner or later. So, indeed, three different groups of workers, stimulated by Busacca, have now filled the remaining possibility of known microorganisms capable of transmitting infections. While it is admitted that our knowledge of rickettsial diseases is far from complete at the present time, nevertheless, if the information available with regard to the diseases known is correct, such infections are characterized by at least three predominant factors. First, rickettsial diseases are transmitted by some variety of Arthropod vector; second, they have a sudden onset and run an acute course; and third, they are always followed by a definite and permanent immunity. Because of these features of rickettsial diseases, it would seem that it cannot be considered the cause of trachoma, for none of these are compatible with trachoma. If, however, the "Rickettsia" of trachoma comprise a new variety differing from those already established, and a broader definition of the term is desirable, the proponents of this exposition must bring forward the necessary evidence. (E, 1,2,4,9)

## THE INCLUSION BODY OF TRACHOMA

While on an expedition to Java with the avowed intention of studying syphilis, Halberstaedter and v. Prowazek took the occasion to investigate trachoma as well. After inoculating baboons with secretions from trachomatous patients, they examined Giemsa-stained preparations of scrapings from the conjunctiva of the animals and discovered within the epithelial cells collections of granules that have since been known indiscriminately as inclusion bodies, epithelial cell inclusions, trachoma bodies, Halberstaedter-Prowazek bodies, and, because v. Prowazek first made the observation, Prowazek bodies. Since similar structures were also found in preparations made with material taken from patients suffering from trachoma, Halberstaedter and v. Prowazek attached considerable significance to their discovery, concluding that the inclusion body is the infectious agent of trachoma. A free translation of their original communication describes the inclusion body as "dark-blue-staining heterogeneous in the light-blue-staining protoplasm, adjacent to the nucleus of the epithelial cell. The inclusions, which at first are small and round or oval, become gradually larger, assuming a mulberry-like shape, and undergo an increasing dissolution with progressive multiplication, which begins in the center. Eventually, most of the bodies fit hood-shaped on the nucleus. Then, inside the inclusion, red-staining, distinct, delicate particles appear and they progress with such rapidity that

they cause a gradual disappearance of the blue-stained masses. Finally, they occupy the greater portion of the protoplasm, with the blue-stained structures visible as small islands in their midst."

"The amorphous blue masses of the inclusion possess a great acidity for the blue constituent of giemsa stain, as do the nucleoli, and they are probably identical with plastin. On the other hand, the sharply outlined, distinct, red-staining granules, which measure about 0.25 $\mu$  in size, are the carriers of the virus itself. They multiply rapidly and as they become larger they divide into two bodies, having the appearance of a colon."

Halberstaedter and v. Prowazek considered that the red-staining granules were the primary forms of the incitant of trachoma, and that upon invading the epithelial cell they stimulated a counter-reaction in the cell which resulted in a mantle or envelope (plastin) covering the granules. Because of the mantle, they classified the parasite as a Chlamydozoon and regarded it as belonging to a group of diseases including smallpox, rabies, scarlet fever, fowl cholera, molluscum contagiosum and jaundice of Bombyx mori-- in other words, what are accepted at the present time as virus diseases. They furthermore expressed the opinion that the conjunctival epithelium is the portal of entry in trachoma and the chief source of dissemination of the incitant.

Halberstaedter and v. Prowazek performed their task in a short paper or two, and little has been added to their observations, in spite of the reams of paper consumed by the workers who followed them.



Immediately after this discovery of the inclusion body, investigators in great numbers throughout the world were stampeded into a frenzy by the questions obviously raised.

Almost simultaneously with the publication of Halberstaedter and v. Prowazek, Greeff, during a study of trachoma in East Prussia, discovered small granules arranged in pairs, both contained in the epithelial cells of the conjunctiva and free in the secretion. Similar bodies were observed in a volunteer specifically inoculated with material containing these structures. Later Greeff stated that he believed the bodies played no part in the causation of trachoma.

Later Stargardt, Schmeichler, and Heymann published their report on the inclusion body being the cause of trachoma. However, they offered little proof to substantiate their claim.

The Incidence of inclusion bodies in trachoma has repeatedly occupied the attention of investigators. Numerous statistical studies have been made wherever trachoma is found, and the accumulated data shows a great individual variation. The variations range from 0 to 100%. The following table is the total result of cases reported by 61 investigators.

EARLY PHASE			LATE PHASE			TOTAL		
With Inclusions			With Inclusions			With Inclusions		
Studied-Number-	%		Studied-Number-	%		Studied-Number-	%	
2209	880	40	2088	360	17	5777	1784	31

The combined evidence would indicate that in the epithelial cell during trachoma there occurs a formation designated as the inclusion body which certain authors regard as the infectious agent. Similar inclusion bodies may be

found in other follicular diseases, as inclusion blennorrhoea and swimming-bath conjunctivitis, in the genital tract, and, according to a few observers, in veterinary conditions such as hog cholera and catarrhal vaginitis of cows. In spite of numerous attempts, it has not been possible to demonstrate its living nature by means of propagation. Its occasional occurrence in trachomatous animals and its more frequent occurrence in experimentally infected human beings have been accepted by certain workers as proof of its viability. Other investigators, however, believe it represents a product of disturbed cellular metabolism, a manifestation of cellular reaction, ingested foreign material such as cells and bacteria, and even a harmless parasite synchronously present but not unrelated to trachoma. The living and specific nature of the inclusion body is unproved, neither has it been possible to demonstrate its inanimate or non-specific nature.

(F, 1 - 11)

## THE RELATION OF VIRUSES TO TRACHOMA

The survey of the literature on the organisms cultivable in trachoma revealed that a number of suspected agents have not withstood the test of time. It showed, moreover, that very early during the bacteriological studies numerous investigators pointed out the non-specificity of the bacterial flora in trachoma. Later work demonstrated that the bacteria encountered in this disease are the same as those cultivated from other ocular conditions and even from the normal conjunctiva. The possibility that the infectious agent of trachoma, therefore, might be not a cultivable organism but a virus occurred to a number of workers as far back as 1905, at a time when bacteriologists were becoming increasingly conscious of this group of agents. The concept of the viral origin of trachoma thus antedates the discovery of the inclusion body which certain workers today point to in support of the virus theory.

Filtration was first attempted in 1905 by Pfeiffer and Kuhnt. They reported on the infectivity of filtrates of human trachomatous material obtained by filtration through Berkefeld candles, the size of which they neglected to state. The unfiltered material was not tested, and, while human volunteers were inoculated with the filtrate, the number of volunteers is not given. In any event, they found that the filtrates studied were not infectious and concluded that the infectious agent of trachoma is not filterable.

Baiardi, Hess and Romer reported studies on the filtrates of trachomatous material. All stated that the filtrate did not cause trachoma.

In 1908, Bertarelli and Cecchetto in Italy, using trachomatous tissues from a monkey infected directly from a patient were passed through a Berkefeld filter impervious to *Bact. prodigiosus*, and the resultant filtrate was inoculated into a single monkey of the same species. These two investigators stated that the resultant reaction was typical of trachoma.

Nicolle, Cuenod, and Blaizot reported that the trachomatous agent is a filterable virus. They reported two cases in which a filtrate of trachomatous tissue caused trachoma in the volunteer. They used a modified Berkefeld V filter, which was improvised by cutting a disk out of the candle and sealing it in a glass tube, an apparatus impervious to cultures of *V. cholerae*.

In 1931, Olitsky, Knutti, and Tyler conducted six experiments, in which the original tissues derived from the patients caused typical experimental trachoma in six of twelve monkeys. Filtrates through Berkefeld V candles were found to be without effect in five experiments on thirteen monkeys. In a single experiment, however, in which three monkeys were inoculated with a filtrate capable of inducing specific infection, only one was actually infected. Two additional experiments performed with filtrates of tissues from infected monkeys were negative. Thus, for the first time, a sufficient number of experiments were performed to illustrate an important

fact, that the process of filtration itself may be irregular. Previous experiments demonstrating filterability had been based either on a single experiment with a single monkey, or on two experiments each with a single animal. Consequently, any irregularities in the process of filtration itself, unassociated with variations in infectivity or in individual susceptibility, might well escape observation. (G, 8)

Cattanea carried out four experiments on filtration, using for the purpose Berkefeld V. and W filters, and ultra-filter (Septina, small model), and collodion membranes of unstated size and porosity. A total of seventeen human beings were inoculated, seven with normal conjunctivae and ten with the conjunctivae of old, arrested trachoma cases; also two M. rhesus monkeys that had been inoculated previous to this study with Bact. granulosis. One individual inoculated with unfiltered material developed trachoma as a result; filtrates of one variety or another were administered to the other individuals without creating any significant disturbance. One of the monkeys received a combination of Bact. granulosis and filtrate, both animals, however, remained unaffected. In concluding, therefore, that transmission of trachoma with filtrates was negative, Cattaneo enjoins the reader to remember that lack of infectivity may have been referable to a loss of virulence during filtration rather than to an inability of the agent of permeate filters.

Thygeson and Proctor succeeded in transmitting trachoma to baboons by means of collodion-filtered material. In four experiments, conjunctival scrapings pooled from three to four patients were filtered through membranes of  $0.75_{\mu}$  a.p.d.

In this way, bacteriologically sterile filtrates were obtained and inoculated into five baboons. In each instance, experimental trachoma followed. Shortly after, the same authors with Richards published the results of an excellently controlled experiment on a volunteer. Material from ten Indian children with trachoma was passed through a membrane with 0.6 a.p.d., impervious to *Bact. granulosis* and *H. influenzae*. The filtrate, while bacteriologically sterile, contained demonstrable elementary bodies. Inoculation of the volunteer was followed by an incubation period of five days and then by an acute inflammation during which both inclusion bodies and free elementary forms were present in large numbers. A doubtful diagnosis of trachoma was no longer tenable when at six weeks the cornea exhibited the infiltration and vascularization characteristic of pannus.

In summary, out of fifty-nine experiments the infectious agent was present in the filtrate in fourteen cases, a frequency of about 23 percent. This makes no allowance, however, for the imposing number of experiments by ten groups of workers who failed to detect filterability. On the basis of this analysis, it is suggested, not that the infectious agent of trachoma is incapable of filtration, but rather that it is not readily filterable, regardless of the method of filtration employed.

In attempting to explain the apparent inconsistencies in the publications of different workers, it seems possible on reflection that successful filtration depends upon the

quantity of free or unattached virus, or if it be assumed the disease is an epitheliosis, upon the degree of epithelial cell degeneration. When cellular disintegration is slight, it is not unlikely that liberated virus is present in quantities insufficient for successful filtration.  
(G, 1,2,3,4,5,6,7,9,10,11)

#### PROPERTIES OF THE INFECTIOUS AGENT

##### Grinding \*

The work of Stewart, Thygeson, and Julianelle indicates that the infectious agent of trachoma survives grinding without difficulty.

##### Centrifugation \*

Julianelle, Stewart, and Thygeson found that prolonged centrifugation of trachomatous material carried most of the active virus to the sediment. Shorter periods and lower speeds, however, left sufficient quantities in the supernatant fluid to cause infection in animals.

##### Drying \*

Hess and Romer first reported that material dried and kept pulverized for four weeks was not infective. Later, Cuenod, Blaizot, and Nicolle reported that drying trachomatous tissues for thirty minutes at 32° C. caused complete inactivation.

##### Freezing and Thawing \*

According to Julianelle and his associates, the infectious tissues are inactivated by successive freezing (-10°C.) and thawing (+ 10° C.). These workers discovered that simple freezing has little effect, for the tissues still had the

power to infect animals after being maintained in a frozen condition as long as twenty-four hours.

#### Heat\*

The heat inactivation point has been determined by many authors, and their results vary considerably. Hess and Romer found the heat-inactivation point to be between 58° C. and 63° C. over a period of thirty minutes. Botteri found it to be three hours at 43° C., Cuenod, Nicolle, and Blaizot found it to be thirty minutes at 50° C.. Julianelle and his associates found the heat-inactivation point to be between 45° C. and 50° C. for fifteen minutes.

#### Behavior of The Virus Before Glycerine\*

A number of workers have studied the effect of glycerine on trachomatous tissue. These workers include; Cuenod, Nicolle, Blaizot, Baroni, Michail, Busacca, and Schering-Kahl-Baum. Their reports would indicate that the glycerine did not act as a preservative or as an inhibiting agent.

#### Behavior of The Virus Before Acid and Alkali\*

Stewart found that an acidity of pH 6.4 in saline or Tyrode's solution inactivated the infectious agent rather quickly. Alkali was found to also destroy the infectivity of the tissue, but the exact pH was not given.

#### Behavior of The Virus Before Bile\*

Julianelle found that the infectious agent was completely inactivated by incubation at 37° C. with ox bile, for fifteen minutes. (I, 1,2,3, J, 8)



In concluding this portion of this paper it must be concluded that the infectious agent of trachoma is characterized by low infectivity, occasional filterability, marked tissue specialization, ineffectual immunogenic properties, slight propagative capacity, and sensitivity to deleterious agents. The properties of the inclusion bodies may be used as an indication that the causative agent is a virus. In conclusion, the two concepts that the virus or the inclusion bodies may be the causative agent of trachoma are not so divergent as it may appear. (H, 1,2,3)

PART II  
TREATMENT OF TRACHOMA

The history of the treatment of trachoma dates as far back as the XVIII Dynasty in Egypt. Pots were found in the tombs of ancient Egypt that contained oxides of copper and zinc, sulphates of lead and antimony. The pigment which these pots contained was used for darkening the edges of the eyelids as well as for treating conjunctivitis; it has been in use since the earliest times; a wall sculpture at Beni Hassan, of about the nineteenth century B.C., shows thirty-seven Bedouin chiefs bringing some of it as a present to the prince of the nome. Under the name "kohl" it is in use at the present time. Before the old Empire, a green powder, native carbonate of copper, was used as an eye paint, but this practice seems to have become old-fashioned even when the Pyramids were being built. (B, 1,6)

To give a complete account of the present day treatment would involve several volumes of work. However, most authorities agree on the fundamentals, and vary only in their routine or in the strength of the drugs used.

Asking the one question, "What is your method of treatment for trachoma?", is like asking, "What is your treatment of pulmonary tuberculosis?". In considering the treatment of trachoma as many aspects of the disease have to be taken into account as have to be considered in the different varieties of pulmonary tuberculosis.

The following is the method of treatment in the separate stages of the disease. This is the method used by MacCallan, who is, at the present time, the president of the international organization against trachoma. This treatment is accepted by most ophthalmologists as fundamentally correct, their variations, as a rule, are in the strength of the drugs used or in the routine of administration.

#### GENERAL CONSIDERATIONS

No medical man, nurse or hospital attendant should engage in the treatment of trachoma without putting on protective goggles and indiarubber gloves. If, in spite of these precautions, a spirt of discharge enters the eye of one of them, the conjunctival sac must be washed out thoroughly with a stream of lotion; water will do, if nothing else is immediately available, poured on to the everted lids from a container. After this the lids should be thoroughly swabbed with silver nitrate solution 2 per cent. This should be repeated daily for not less than three days. (J, 6)

"The trachomatous eye should not be occluded. It is of great importance to remember that the eye of a trachomatous person should not be occluded with a pad or bandage, except for an hour or so after mechanical treatment to prevent hemorrhage."

#### Treatment of Stage I, Trachoma I

The manifestation of this stage is the subepithelial lymphocytic infiltration, which in many cases is concentrated into so-called follicles. This is the reaction to the trachoma virus, and may be defensive in character; therefore the individual destruction of follicles may be not only useless but harmful,

as well as being impossible.

When there is no complication by a superimposed bacterial conjunctivitis the exhibition of mild astringent drops is indicated, such as zinc sulphate solution of one quarter of one per cent. When there is a conjunctival discharge the whole conjunctiva should be swabbed daily with silver nitrate solution two per cent by the surgeon himself for several days or weeks, as may be found to be necessary. The drug is to be applied to the everted lids with a pledget of cotton-wool wound round the end of a sterilized glass rod: the cotton-wool must be of good quality or it will be impossible to make a neat brush. The action of the silver nitrate is to cause a coagulation of the albumin of the superficial epithelial layers of the conjunctiva, which become white. A transudation from the blood-vessels occurs under the coagulum, which is thrown off containing the superficial epithelial cells and conjunctival bacteria.

This action of silver nitrate is not imitated by any of the organic silver compounds, which should not be used.

The patient should use at home for bathing the eyes eusol solution, 1 to 10 strength, or perchloride of mercury solution, 1 to 5000. The eyelids should be anointed at night with any simple ointment to prevent the lids sticking together in the morning.

Treatment by means of subconjunctival injections is a reasonable and proper treatment if pursued carefully by the doctor himself. The injection should be above the cornea about 6 mm. behind the limbus into the subconjunctival tissue and directed towards the fornix, and should be 1.5 or 2 cc. of sterilized normal saline solution; after a few days, when this has been abs-

sorbed, another injection of 1.5 c.c. of a mixture of 1 per cent. cyanide of mercury and 1 per cent. novocain, to which has been added a few drops of adrenalin chloride solution 1 in 1000. This may be followed by a considerable amount of oedema and pain. If this is too severe to be borne, the subconjunctival injections of normal saline solution may be used again once or twice a week. Such treatment is in no way specific and should not be persisted with if not of apparent benefit.

There is a reason for supposing that subconjunctival injections may be of benefit in stage I. This is because there is a widespread subepithelial infiltration with lymphocytes, besides the trachoma follicles which may or may not be present, and the injection of normal saline solution may assist in their absorption. It is doubtful if the addition of cyanide of mercury, which is very painful, adds to the value of the fluid injection.

In a patient whose conjunctiva exhibits numerous follicles of Tr. I, careful treatment by a trachomatologist, and withdrawal from surroundings where there is liability to new infections, should lead to distinct improvement in about six months. It must not be forgotten that sometimes the tiny follicles of the stage I may disappear without the employment of any kind of treatment.

#### Treatment of Trachoma, Stage IIa

This stage is characterized by the bleb-like excrescences which rupture on pressure, exuding a gelatinous material.

The treatment consists in the rupture of the blebs by

mechanical means. If there is much discharge, indicative of a superimposed bacterial conjunctivitis, preliminary treatment by swabbing the everted lids with silver nitrate solution 2 percent should be carried out daily for several days.

Mechanical treatment is carried out under local anaesthesia for adults and under general anesthesia for children. Local anaesthesia is effected by the instillation of cocaine hydrochloride solution 4 per cent. into the conjunctival sacs three or four times, and the subcutaneous injection of novocain (or a substitute) solution 1 per cent. into both upper and lower lids.

Ten minutes should be allowed to elapse after making the injection to allow time for the anaesthetic to act. The conjunctiva should then be bleached with adrenalin chloride solution 1 to 1000.

A large number of different instruments have been invented for the convenience of the operator in breaking up the follicles, some of which are useful. MacCallan, his colleagues, and many other ophthalmologists use the Graddy forceps, a metal she-horn spatula and an ordinary surgical sharp spoon.

The upper lid is everted on a retractor and Graddy's forceps is applied to the conjunctiva; the blades should not be approximated with too much force, and are withdrawn carrying in their concavity the gelatinous contents of the blebs which have been ruptured by the passage of the instrument.

If blebs are present in the upper fornix the retrotarsal fold should be seized with a pair of toothed forceps and re-inverted to allow the conjunctiva to be scraped with the sharp spoon.

The lower lid should be scraped with the spoon, as unless the conjunctiva is loose, Graddy's forceps is not applicable.

It is desirable that this mechanical treatment should be carried out delicately, and it will probably be necessary to repeat it several or even many times. It need cause no great discomfort afterwards. The eyes may be tied up for an hour or so after the operation. If the operation is done with too much vigour there is a considerable amount of edema and pain.

If considered advisable the bleeding surface of the conjunctiva may be swabbed with a solution of cyanide of mercury or perchloride of mercury, 1 percent, but this adds to the subsequent distress, and it is only necessary in patients of the lower class who live in insanitary surroundings.

For patients suffering from trachoma in stage IIa with prominent gelatinous blebs there is no form of treatment, other than the mechanical expression of their contents, which can be recommended.

Cases in this stage are seen in which there are only a small number of moderate sized blebs visible, and it may be thought that this minor operation is unnecessary, and that sufficient effect can be obtained by the application of escharotic drugs to the conjunctiva. However, the process of cicatrization of the membrane is thereby retarded as compared with the effect of mechanical treatment.

The subsequent treatment must depend largely on the patient's condition. It is often only necessary to order the instillation of drops of a solution of zinc chloride or sulphate,

one quarter of one per cent. or one half of one per cent. twice a day. In other cases, such as those undergoing mass treatment in an out-patient clinic or dispensary it may be advisable to swab the conjunctiva daily with a solution of cyanide of mercury or perchloride of mercury 1 per cent.

Often the first mechanical treatment or operation does not always obliterate all the blebs; this is especially the case when great care is taken to avoid any unnecessary pain and edema of the conjunctiva and lids. The operation should then be repeated as often as is necessary.

When treated as actively as possible the stage IIa may be transformed into stage III in about fifteen days.

The operator need not be afraid of his operation resulting in such cicatrization of the conjunctiva as will lead to inversion of the lid margin or entropion, for this is the result of inflammatory infiltration of the tarsus, and its subsequent cicatrization. It is rarely that cicatricial changes in the conjunctiva alone lead to incurving of the eyelid. A proportion of all hospital patients who come to the hospital suffering from severe stage IIa or stage III develop entropion or trichiasis whether or not any mechanical treatment is carried out.

It is not uncommon for there to exist such a degree of blepharophimosis as to prevent the eversion of the lids for the purpose of treatment. In such cases it is necessary to perform a preliminary operation of canthoplasty.



In a few cases of stage IIa with a thickened upper tarsus and perhaps entropion, and in which there is no doubt that the conjunctiva of the upper fornix is cicatrized, a skilled operator may excise the tarsus and the conjunctiva which is adherent to it, thereby getting rid of the diseased conjunctiva, and the thickened, incurved tarsus, and curing the entropion. This operation is called combined excision tarsus and conjunctiva, Saunder's operation or Heisrath's operation.

#### Treatment of Stage IIb'

In this stage of active trachoma the subepithelial layer of the conjunctiva is heavily infiltrated with an inflammatory exudate, the surface is thrown into papillae, while follicles, if present, are fewer and concealed by the papillated conjunctiva.

In many cases it is advisable to commence treatment by curetting the palpebral conjunctiva under local anaesthesia, as described under stage IIa. After this a solution of cyanide of mercury or perchloride of mercury 1 percent may be swabbed on the bleeding conjunctiva; this treatment may be repeated daily until cicatrization begins to appear, the beginning of stage III.

In some cases curettage may not seem to be indicated; in such cases a daily swabbing with cyanide of mercury 1 percent, or a solution of copper sulphate 10 percent may be carried out until stage III is reached.

### Treatment of Stage IIb"

Most authorities agree that this is one of the hardest stages to treat. This stage does not respond very well to any known form of treatment, including sulphanilamide treatment, as will be discussed later in this paper. However, it is fortunate that this type of trachoma is not very common. The hard papules may be swabbed daily with silver nitrate solution, 2 percent, for a week or two. This often relieves the patient's subjective symptoms, though it has little influence on the pathological condition.

Some ophthalmologists believe that an operation is of benefit in this stage. The operation consists of a combined excision of the tarsus and overlying conjunctiva. However, recurrence of the papillary growths may take place following the operation.

### Treatment of Stage IIc

The conjunctiva should be swabbed daily with a solution of silver nitrate 2 percent, until there is little discharge. After this it is advisable to curette the conjunctiva. Following this a daily application of cyanide of mercury solution 1 percent should be applied. Later, a solution of copper sulphate, 10 percent, should be applied.

### Treatment of Stage III

Cicatrization has begun in this stage. Islands of inflamed conjunctiva or of trachomatous follicles are seen to be surrounded by a network of fine lines of connective tissue.

In this stage foci of post-trachomatous degeneration are frequently seen on the palpebral conjunctiva.

The usual treatment of this stage is with the use of copper sulphate. The solid copper sulphate stick was used more a few years ago than it is at the present time. However, it is still being used by many excellent ophthalmologists. The stick form causes great pain and may result in greater injury and resulting excessive cicatrization. The stick form is rubbed over the palpebral conjunctiva, with great care being taken not to touch the cornea, or allowing the treated area to touch the cornea for some time. At the present time a 10 percent solution of copper sulphate is swabbed on the infected area, being careful to mop up any excess. Copper should not be used if there is present any superficial punctate keratitis. This treatment is carried out for about two weeks, and then altered with perchloride of mercury, 1 percent.

The foci of post-trachomatous degeneration should be opened with a sharp scalpel, after the cornea and conjunctiva have been anaesthetized with cocaine hydrochloride 4 percent or pontocaine - one half of one percent.

In some cases a good adjuvant treatment for this stage is the subconjunctival injections of normal salt solution.

The combined excision of the tarsus and conjunctiva may be carried out if there are many islets of inflamed conjunctiva separated by connective tissue strands and where the tarsus shows some incurving.

According to MacCallan, Meyerhof and Peretz, there is no special treatment applicable to the cornea with the object of clearing up pannus. However peritomy may be performed. In this operation a collar of conjunctiva, 5 mm. broad, is excised round the corneal margin. The raw surface of the sclera should be seared with the galvano-cautery, the object being to destroy the vessels and prevent their reformation. Pannus seems to have two varieties or stages: One, in which the vascular granulation tissue between the epithelium and Bowman's membrane clears up under treatment applied to the eyelids, leaving only the attenuated vessels. Another in which Bowman's membrane has been destroyed in places, with invasion of the corneal stroma by trachomatous infiltration; here two things have resulted, first a permanent opacity, and second a destruction of the nutrient flow between the corneal corpuscles by the laying down of scar tissue. The absence of the normal nutriment renders necessary the persistence of pannus vessels.

#### Treatment of Stage IV

Theoretically no treatment is required in this stage, because all trachoma follicles and all subepithelial trachomatous infiltration have been absorbed and replaced by cicatricial tissue. But in between these cicatricial areas there are often islets of healthy conjunctiva which may again afford a bridge-head for trachomatous attack by a new brigade of contagion.

It is therefore advisable for all patients with healed trachoma, that is stage IV, to use daily some astringent drops as a prophylactic, such as solution of zinc chloride one fourth of one percent, or a solution of copper sulphate three percent. (J, 6)

#### OTHER METHODS OF TREATMENT OF TRACHOMA

The following list of methods of treatment have one used by one or more ophthalmologists, but have not been accepted by the greater percent of men to be as good as the preceding treatment. Because these methods do not seem to give very uniformly good results and have not been accepted as any standard of treatment they will just be listed with no discussion.

1. Collin and Schweisguth described the use of iodine vapour as a treatment for trachoma, mainly in the early stages.
2. Waele recommended the local application of arsenobenzol. The results were not striking, nor were many cases followed.
3. Gerard used comphorated oxide of naphthol.
4. Massage of the palpebral conjunctiva with Chaulmoogra oil is employed by Delance in Morocco. J.C. Hancock at the Fort Apache "Trachoma School" reports some good results with chaulmoogra oil. He believes that this treatment is of greatest value in stages I and II, particularly where there are many cases under treatment, for this method demands very little of the doctors time. The oil is massaged on the lids with considerable pressure, with no irrigation used following this treatment.

Zachert, in Poland, believes that the best treatment of stage IIa is the use of Chaulmoogra oil following mechanical treatment.

5. "Xysis" is used by Cuenod and Nataf. This treatment is rather drastic and its results are not very satisfactory. The patient often has to return for further treatment after the treatment has seemingly given good results. The conjunctival sac is cocainized and a hypodermic syringe containing 2 cc. of two percent cocaine solution is injected under the conjunctiva around the cornea. The whole area of the conjunctiva is then carefully curetted. A subconjunctival injection (volume not stated) above the cornea is then made with the following solution.

Cyanide of mercury -----	0.04	Grams.
Dionine-----	0.10	"
Cocaine hydrochloride---	0.20	"
Distilled water-----	20.00	"

Then, with the lids everted, boric acid powder is rubbed into the conjunctiva with the finger. Excess of boric acid is washed away with copper sulphate lotion. A drop of atropine sulphate solution is instilled, a little ointment applied to the lids and the eyes are occluded by a dressing.

The products of the curettage are then injected under the skin of the arm.

The dressing is removed after twenty-four hours, when marked oedema of the lids and face may be found. However, this soon passes away.

Symblepharon is likely to occur unless a glass rod charged with ointment is passed between the lids and the globe daily.

After three or four days drops of copper sulphate or nitrate of silver are instilled daily. The dressing is not reapplied after the seventh day.

At the end of six weeks or two months cicatrization is becoming established.

6. Cryotherapy or treatment with carbon dioxide snow was described by Harston of Hong Kong.

A pencil of carbon dioxide snow is applied to the conjunctiva, taking care to avoid contact with the cornea. An interval is allowed to elapse before replacing the everted lid for the cornea is apt to come into contact with the excess of snow. "At first the snow is applied to each part for fifteen seconds; later, when the patient is accustomed to the treatment, for as long as twenty-five, and thirty seconds. The disease is considerably shortened in its course, according to Harston, and the resulting scarring is considerably less than when other caustics have been used. According to Harson the most difficult cases to treat with this method are those that are acute, and that have a great deal of edema of the lids and conjunctivae with purulent secretion. The cases which respond the best are those that have become chronic. (J, 2)

7. X-Ray has been used by many authors with no marked results.
8. Radium has been used by many workers, and from their results it would seem that radium is of little benefit.

9. High-frequency currents or surgical diathermy are described by Monbrun, Casteran, Worms and Bidault. This treatment, used in itself, is of little value and has not gotten much further than the experimental stage.
  10. Inoculation with gonococcal pus must be mentioned, but with contumely. It is associated with infinite danger to the cornea. It was introduced because someone said that pannus cleared up after an attack of gonococcal conjunctivitis. MacCallan reports that he has seen innumerable eyes destroyed by gonococcal conjunctivitis in trachomatous individuals, but never noted any improvement of the state of the cornea in a trachomatous individual as the result of an attack of gonococcal conjunctivitis.
- II. Burr Ferguson of the United States Public Health Service injected 1 grain of mercury salicylate into the gluteal region of would-be immigrants to America who had trachoma. These injections were given at intervals of a week for four to six doses. This treatment was supposed to work by an induction of leucocytosis. This experiment was carried out in 1931, but no further work has been reported. Ferguson and Zorab believe that this method has some value, but until more proof and more cases are presented, it can not be accepted as a good form of treatment of trachoma.

(J, 8)



## SURGICAL TREATMENT OF TRACHOMA

Surgery is not usually advocated for the treatment of trachoma except in certain defined cases. Surgery, of course is used for the treatment of some of the complications of trachoma.

The Saunder's operation or Heisrath's operation is used in stage IIa where there is a thickened upper tarsus and perhaps entropion, and in those cases where there is no doubt that the conjunctiva of the upper fornix is cicatrized. This operation is a combined excision of tarsus and conjunctiva, in which you get rid of the diseased conjunctiva, and the thickened, incurved tarsus, and cure the entropion. (J, 6)

Rambo states that surgery is advised only for those patients who become discouraged and leave their treatment, and those who have severe, acute and chronic trachoma with pannus. Surgery is also recommended for severe cases of trachoma which are not improving under treatment, especially those wherein the sight is endangered by corneal irritation. (J, 7)

In the Rambo operation the tarsal plate is dissected from the muscle and other subcutaneous tissues. All diseased tissue is removed. A small mucous membrane graft is then sutured in the denuded area. This membrane may be taken from the lower lip.

Reports indicate that infections are very few in number and that the mucous membrane taken from the lip does not become trachomatous. Usually the pannus markedly improves, and in many cases the vision has been restored from the ability to see fingers to 6 / 10.

## SULPHANILAMIDE TREATMENT OF TRACHOMA

In 1937, Fred Loe and his associates, began using sulphanilamide in the treatment of trachoma in the Rosebud Indian Hospital. They used sulphanilamide on 140 cases of trachoma. On the basis of body weight they were given one-third grain of sulfanilamide, with an equal amount of sodium bicarbonate, a pound daily for ten days. Then the dose was decreased to one-fourth grain of sulfanilamide a pound daily for fourteen days. No other medication was allowed during this period. The following is the summary of the results on the 140 cases of trachoma: (J, 5)

### 1. Improvement of subjective symptoms:

- a. Cessation of lacrimation within twenty-four hours.
- b. Loss of photophobia within twenty-four hours.
- c. Improvement of vision within seventy-two hours in cases of pannus.

### 2. Improvement of objective symptoms:

- a. Paling of the conjunctiva.
- b. Paling of the trachomatous patches and flattening of the granules and follicles. At the end of three weeks of treatment a few flat-topped granules remained, and we found that only after several months did these disappear. The medication was not continued during these several months, however. The ninety-three patients treated in boarding schools were discharged as improved. These patients were examined at monthly intervals and showed improvement without further medication, with no exacerbations of any kind.

- c. In the cases in which there had been no scarring from instrumentation, the conjunctiva at the end of two months apparently resumed its normal velvety texture.
- d. The blood vessels of the conjunctiva become more visible on the fifth or sixth day of treatment, and daily thereafter they become more normal.
- e. In thirty cases of pannus treated in the hospital we noted that the opacity began clearing between the eighth and the fifteenth day, depending on the density of the pannus, with great improvement of vision.
- f. The granules on the lower lids were found to be the last objective symptoms to disappear."

Loe, and his associates, admit that it is too early to speak of the results as a cure, for it is not known whether or not recurrences will take place.

Harry S. Gradle of Chicago, after studying forty-one cases of trachoma under sulphaniilamide treatment at the Trachoma Clinics of Southern Illinois and the Illinois Eye and Ear Infirmary came to the conclusion that:

"1. Trachoma II and III responded fairly uniformly in a most surprising fashion in that the velvety patches and hypertrophies disappeared in short order. The thickened and hyperemic conjunctiva became thinner and pale, the individual vessels became visible, and the secretion disappeared in the majority of cases. The results of three weeks of sulfaniilamide approximated those of from three to six months of local treatment, but without scar formation.

2. Regardless of the stage, photophobia and lacrimation disappeared in short order. This subjective improvement was most striking and, to the patients, most gratifying. 3. In trachoma IIb and IIIa and IIIb there was a marked improvement in vision in cases in which the vision was decreased because of pannus. In the older and more malignant cases and those in which there were corneal scars due to old ulcers, the visual improvement was negligible. But in some instances the visual results were almost miraculous. 4. In trachoma IV and in malignant cases of trachoma IIIb, practically no improvement could be noted. It would seem that in the use of sulphanilamide we have a new means of combating the more acute stages of trachoma. " (J, 5)

Hirschfelder tried sulphanilamide on twenty-five white patients of the Southern Illinois Trachoma Clinics. These patients were selected because they showed signs of "active" trachoma. Each patient received one-third grain of sulphanilamide a day per pound body weight for a period of one week. In the second week the dose was reduced to one-quarter grain a day per pound body weight. The results are given below, the patients having been divided into four groups as to the type of trachoma present.

Group I. Patients ranged in age from 5 to 14, who had no, or only very slight, subjective symptoms and normal vision. Their conjunctiva showed no signs of acute inflammation, but there was dense folliculosis in the fornices. The pannus in this group was just developing. These cases, bord-

er line cases of follicular catarrh, did not show definite improvement after two weeks.

Group II. In this group there were 11 patients classified as "trachoma stage IIa with succulence". The patients complained of slight photophobia, epiphora, various degrees of blepharospasm, and diminution in vision. Objectively a velvety conjunctiva with imbedded small follicles was observed. There were various degrees of succulence. The appearance of the conjunctiva was somewhat muddy and indistinct. There were two to four millimeters of active pannus in most cases. This group showed improvement after treatment with sulfanilamide. The vision improved. The vision usually had been reduced to 20 / 40 to 20 / 200 and was improved about two lines on the Snellen chart. Objectively the conjunctiva looked dryer and paler, and the granules decreased in size. The velvety appearance was diminished on the sixth day. On the seventh day the presents of normal blood vessels was observed on the conjunctiva over the tarsal plate of the upper lid. The vessels of the pannus became thinner and less distinct on about the tenth day after the treatment was begun. However, they did not disappear completely during the course of observation. Seventy-five percent of the patients of this group felt unquestionable improved in their eyes.

Group III. This group included patients who had trachoma, stage three without too malignant sequelae due to the disease. These patients also showed improvement. Their lids looked paler and smoother after a course of two weeks, and

the vision improved, due to a slight clearing of the pannus. In this group the sulphanilamide seemed to moderate the course of the disease.

Group IV. In this group there were three patients, who, for the past years, had had very active and malignant forms of trachoma. They suffered repeatedly from flare-ups, and had vision of less than 20 / 200, due to marked scarring of the cornea, active pannus, and blepharospasm. These patients showed, aside from a slight paling, only little response to the drug, and their subjective symptoms, as well as the objective findings, did not clearly change.

After two weeks of observation and treatment, Hirschfelder believes that sulphanilamide has a paling and drying effect on the succulent conjunctiva of trachoma - stage II and milder cases of stage III. Further it seems to aid in the healing of pannus in cases that are not too old and not too malignant. (J, 3)

In a recent, single publication by Julianelle, Sory, Smith, and Lange it was brought to view that tartar emetic may be of great benefit in the treatment of trachoma. The possible value of this drug in the treatment of trachoma was discovered while Julianelle and his associates were experimenting with the action of various drugs and chemical agents on the virus of trachoma.

During an earlier study on the probable nature of the incitant of trachoma it was noted that tartar emetic (antimony potassium tartrate) is capable of inactivating completely the virus of trachoma, if the loss of its original capacity to infect monkeys be accepted as a measure of inactivation. Since then tartar emetic has been more widely studied as a possible therapeutic agent for the treatment of trachoma. "It is realized that the number of patients under observation is still too few to warrant more than an impression, the results nevertheless seem to be of sufficient interest to justify a preliminary report."

Tartar emetic was administered either by intravenous injection alone, or in combination with local application, while a few patients received only local treatment. Tartar emetic was used in 1 percent solution, in 5 cc. or 10 cc. quantities. When applied locally, it was applied once a day by massaging lightly the everted upper conjunctiva with a thoroughly moistened swab. Three other times during the day it was instilled into the conjunctival sac as drops.

The only other procedure adapted was the usual morning irrigation with saline and boric acid.

First Method of Treatment:

Intravenously only. Nine patients under treatment. Ages of the patients ranged from 14 to 59 years. The duration of their trachoma was from  $1\frac{1}{2}$  to 50 years. The planned course of their treatment was as follows.

Injection	Day	C.C.
1	1st	5
2	3rd	5
3	4th	5
4	7th	5
5	8th	5
6	11th	10
7	15th	10
8	18th	10
9	21th	10
10	25th	10

"It was not possible, however, to continue the injections as contemplated, since one by one the patients left the hospital for one reason or other. After treatment with tartar emetic seven of the nine patients showed definite improvement. Both the patients that showed no improvement received the smaller quantities of tartar emetic. It was felt, however, that the results were suggestive even though the treatment was insufficient."

Second Method of Treatment:

Intravenously only. Five patients under treatment. Ages of the patients ranged from 26 to 52 years. The duration of their trachoma was from 1 to 50 years.

Mon.- 5 c.c.)  
 Wed.- 5 c.c.) — 2 courses  
 Fri.- 5 c.c.)

Mon.- 10 c.c.)  
 Wed.- 10 c.c.) — 2 courses  
 Fri.- 10 c.c.)

Mon.- 10 c.c.)  
 Fri.- 10 c.c.) — 3 courses



Two of the five patients were discharged as arrested. One after fifteen injections and one after nine injections. The other patients are still under treatment, but the authors state that they show definite improvement.

#### Third Method of Treatment:

Eleven patients were under treatment. Their ages ranged from 12 to 40 years. The duration of their trachoma was from 2 to 30 years. Six of the patients exhibited a peculiarly stubborn resistance to treatment, one had been in the hospital 14 times, and another had been in the hospital 33 times with all types of treatments being tried with no avail.

6 successive days --	5 c.c.
8 th day -----	10 c.c.
10 th day -----	10 c.c.
12 th day -----	10 c.c.
15 th day -----	10 c.c.
19 th day -----	10 c.c.
22 nd day -----	10 c.c.
25 th day -----	10 c.c.
28 th day -----	10 c.c.
31 st day -----	10 c.c.

\* These injections were supplemented by daily local applications of the tartar emetic.

Two patients left contrary to consent and advice, with their condition improved but not arrested. The rest of the patients were dismissed greatly improved. The cornea became transparent, the pannus disappeared, and the vision was improved.

#### Fourth Method of Treatment:

Seven patients were under treatment. Their cases were of long standing. The local application of tartar emetic was the only treatment used. The treatment lasted from two to three weeks. In the three cases of very long standing there

was no improvement except for a slight improvement in vision. One patient was discharged as arrested. In the cases of three children the local application was supplimented by grattage. These cases were dismissed as arrested with smooth lids and glossy normal-appearing cornea.

#### Fifth Method of Treatment:

Five patients were treated by this method. These were primary cases with little previous treatment, characterized by marked follicular hyperplasia of the conjunctiva, -very suitable for grattage. In these case grattage was used along with intravenous injections of the tarter emetic. The patients received four injections of 5 C.C. on successive days, and on the fifth day a final injection of 10 C.C. was made. The edema of the lids was less, injection was not so marked, and rapid healing occurred without necrosis or sloughing in each case. Treatment was continued with local applications of silver nitrate and later with copper sulphate. The hospitalization was shortened to three to four weeks, and at the time of dismissal the conjunctiva had recovered its normal appearance, and it was difficult to realize an operation had been performed. The cornea was improved and the vision was better in those cases where vision had been impaired.

Out of 40 patients under treatment with tarter emetic intravenously or locally: 16 received their full quota and were discharged as arrested; nine left without receiving sufficient treatment but seven of these were improved.

Five were given tartar emetic plus grattage and all showed very good response and recovery. Four received local applications only, and the disease was checked in all cases. Six are still being studied. (J, 4)

## TREATMENT - CONCLUSIONS

In reviewing the treatment of trachoma it must be said that the old accepted treatment as outlined at the beginning of this chapter is the treatment of choice, until more proof as to the immediate and permanent benefit of some of the newer drugs and agents can be ascertained.

Chaulmoogra oil, would, from a few reports, be very adaptable to use in mass treatment of a number of cases of the early stages of trachoma. (J, 1)

Sulphanilamide seems to be, up to the present date, a very good treatment for certain stages of trachoma. It would seem that it is, however, of very little benefit in the catarrhal type of trachoma and in stage IV. It is too early to draw any hard and fast conclusion as to the permanency of the cure or as to the actual results received from treatment.

The use of tartar emetic in the treatment of trachoma must be kept in mind as a possible method of treatment. However, only one group of results have been brought forth and these are rather incomplete. So, until more work and further proof is presented this treatment should be viewed only with interest. (J, 1)

#

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