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# Trachoma : its etiology and treatment with sulfanilamide

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# TRACHOMA

## ITS ETIOLOGY AND TREATMENT WITH SULFANILAMIDE

by

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# INTRODUCTION

After seeing the end stage of several cases of the disease trachoma I was stimulated to investigate, through the medium of reading, the cause and treatment of the disease. Because it is the leading cause of blindness in various sections of the world and because the majority of students may practice medicine in those parts of the country where trachoma is prevalent I feel that any time spent on the subject is of great value.

I have limited this paper to the etiology of trachoma and its treatment with sulfanilamide chiefly because the literature on all phases of the disease is so voluminous that to cover it would take more time than is allotted, and because I feel that the causative agent and treatment go hand in hand, therefore, cannot be divorced.

## HISTORICAL BACKGROUND OF THE OCCURRENCE OF TRACHOMA

In the ancient Egyptian manuscript, the Papyrus Ebers (5), which dates back to the eighteenth dynasty or to a period of time estimated to be 1553 - 1500 B.C., is found the expression 'hetae m mrt'. This has been interpreted as referring to trachoma. So it is seen that trachoma is one of the oldest diseases known. Even though there is considerable literature on Egypt little or no mention of trachoma is found so it is reasonable to assume that the disease was not as prevalent or as severe as it is today or was in the comparatively recent past. In 1481 Rabbi Meshoolam Ibn Menahen referred to trachoma; a century later Prosper Alpinus, a Venetian physician, again referred to the disease and from this time on trachoma became permanently and commonly implanted in Egypt (24).

It is a well known fact that eye diseases have always been common in the Orient and trachoma undoubtedly was present in the ancient Orient. Mijaschita states that in Japan trachoma dates back as far as 1200 years ago (46).

Herodatus (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, the expression signifying trachoma. Aristophanes (444 - 380 B.C.) discussed in a summary fashion the cure and treatment

of the disease in Plutus and again refers to the affliction in Frogs. Hippocrates (460 - 377 B.C.) wrote a description of ophthalmia and trichiasis, and for treatment recommended applications of copper acetate and fresh grape juice. Also Plato, Aristotle, and Plutarch were aware of the disease (24).

The Aramaics or Syriacs knew of trachoma and pannus because they designated trachoma as 'garab' and pannus as 'sebel' and recommened scraping and scarification in the treatment. The book on ophthamology " Tadkirat-el-Kahhalin" written at Bagdad in the eleventh century by Ali Ibn-el-Aissa is probably the oldest book on diseases of the eye that has been preserved in it's original language. In this book is found an entire chapter on trachoma and the treatment is quite detailed for each of the four stages of the disease. So this may be judiciously accepted as evidence of the importance attributed to trachoma by the Arabic physicians (9).

From the material presented so far it is seen that trachoma was well-known in the old countries, however, it was not until the nineteenth century that Europe became fully aware of the disease. At this time under the name of Egyptian ophthalmia it was disseminated at a terrific rate of speed.

During 1798 Napoleon and his armies were invading the

land of Egypt and it is thought that this expedition was responsible for the spread of trachoma throughout Europe. Larrey, Vetch, and Eble, military surgeons of the French, British, and Prussian armies accurately described the disease and the disability it caused. On the return journey the soldiers spread the disease en route and carried it into their native lands. The Russian army did not incur the disease during the Napoleonic wars but it was not long afterwards that it began to appear sporadically in Russia. Consequently trachoma has become firmly implanted in Europe (43).

When the history of trachoma in the New World is considered nothing definite or tangible can be found. Some authorities believe that it was imported by the Spanish conquistadores (75). But other observers maintain that the Spanish probably contracted the disease from the Indians and contend that it is of more recent origin (15). Lewis and Clark comment a little on "sore eyes" among the Chopunish but it is uncertain as to whether or not they were describing trachoma. At the Flathead agency in Montana in 1868 McCormick reported "sore eyes" and Fox believes that the Blackfeet Indians contracted trachoma from the Indians at the Flathead agency. On inquiry to the Bureau of Indian Affairs Fox learned that the Indians thought that trachoma was introduced to them by employees of the Hudson's Bay Company. However, he presents sufficient evidence to relieve

this blame and states that the Celtic race was entirely responsible. By 1910 Hodge and Hrdlicka believed that the disease was permanently established among the Indians (15).

In view of the facts presented above it appears as though trachoma in the Indians was of fairly recent origin and probably was brought to them by the white man. However, Gifford (24) makes a statement that the disease existed among the Omawhaws in 1819 prior to the arrival of white men. According to J.J. Wall (74) the Canadian Indians believe that trachoma was brought to them from American tribes accompanying the early white traders.

Up to 1850 the immigrants coming to this country were mainly British, Irish, German, and Scandinavian and the incidence of trachoma was not so great. But after 1850 the immigrants consisted of Italians, Austrians, Slavs, Russians and Turks for the most part and the incidence of the disease increased tremendously. Cases and outbreaks of the disease, especially among school children and the alien population, were noted by numerous observers, and because of the contagiousness of the disease and the seriousness of it's sequelae it was regarded as a menace to the public health. Consequently in 1897 the Treasury Department, then in charge of immigration, classified trachoma as "dangerous contagion" and so prevented trachomatous individuals from entering this country (42,6).

In Canada the disease is found also among immigrants from Eastern and Southeastern Europe, as well as among the Chinese in British Columbia. An endemic focus exists among the Daukhobors and the incidence of trachoma in Manitoba and Saskatchewan is still a serious problem (74).

In Australia the disease appeared with colonization, however, it has never been a serious problem and has been eliminated except for foci in Northwest Queensland, West New South Wales, and the northern and eastern parts of the continent (40).

I was unable to find any statistics on the occurrence of trachoma in Nebraska. However, as a result of direct communication with several ophthamologists who have worked in the University of Nebraska Dispensary and outstate men I learned that although most of them have seen and treated the disease the incidence has not been high in their experiences.

# THE ETIOLOGY OF TRACHOMA

Since the time trachoma was first described a number of concepts have been advanced to account for the origin of the disease. Although most authorities of the present generation agree that trachoma is a specific infectious disease there are still some adherents to the numerous and varied theories. In the material to follow an attempt to review these theories will be made. Also the recent experimental work will be reviewed to try and make it possible to present the present day concept of the origin and the evolution of the disease.

## Various Theories as to the Causative Agent

Some observers have advanced the idea that the lymphatic constitution of an individual may be an important factor, either predisposing or causative. There are not many in this country adhering to this idea, in fact, it is disputed by some whosay that constituents of this theory are describing folliculosis and not trachoma (24).

Because trachoma has a high incidence in the lower income group of people, where malnutrition is seen, many authorities (16,58,63) believed that the state of nutrition played an important part in the development of the disease. But the occurrence in well-nourished persons such as wrestlers (49) certainly isn't in keeping with this idea.

Even though this concept was advanced before the specific knowledge of vitamins came into being (knowing that Vit. A plays an important part in the development of eye diseases), recent experiments have failed to show that either a defective diet or depressed physical condition is essential for the development of trachoma (31,73,22,55). In fact it seems as though the animals used in the vitamin deficiency experiments were less reactive and probably a little more resistant to trachoma than normal animals, that is, those on an adequate diet.

From time to time numerous observers have attempted to show that trachoma is a manifestation of various clinical entities, such as tuberculosis and syphilis. According to Pascheff (48) tuberculosis is the underlying and responsible factor in trachoma. He believes that the eye symptoms arise from an endogenous tuberculous source. This is not such an unreasonable concept since it is a well established fact that both trachoma and tuberculosis have a high incidence among the poverty-stricken and unsanitary groups of people. The only support for this idea is the differential leucocyte estimation and tuberculin skin tests which run parallel in both diseases. However, experimental evidence has failed to show any correlation between trachoma and tuberculosis (24).

Syphilis is another specific disease that has been

blamed for the initiation and development of trachoma. And some observers contend that symptoms of the disease are done away with under antiluetic treatment. But there is very little evidence to indicate more than a coincidental relationship, in fact, in the Trachoma Hospital at Rolla, Missouri it is found that trachoma very rarely occurs in syphilitic patients (24).

Some observers believe that trachoma is actually a local manifestation of a generalized disease and not a local disease per se. In these instances the disease is thought to be the result of malaria (30), an allergic phenomenon (35), a plasmoma, endocrine disturbance, a nasal infection, and capillary changes (24).

From time to time various men (11,12,44) have stated that they believe trachoma is transmitted by different insects. Also, Dr. Myles Standish (62) after observing immigrants for a number of years surmised that the acute cases must have contracted the disease while on board ship and so he advanced the theory of an intermediate insect host and named the bed-bug as the insect responsible. Standish also assumed that the cases of trachoma seen in loggers, who spent the winter in unsanitary camps, and in the Kentucky mountaineers was propogated through the bed-bug. And Dr. H.B. Young (77) in a direct rebuttal to Dr. J.M. Patton's report on the occurrence of trachoma in professional wrestlers

states that he believes an investigation of the wrestler's sleeping quarters for the bed-bug would probably reveal it's presence. However, I believe that Dr. Patton (49) has rightly assumed that the transmission of trachoma in his series of eight cases in wrestlers was through direct contact rather than through the medium of a bed-bug. Nicolle and Cuenod succeeded successfully in transmitting trachoma to monkeys with flies and lice but it is not unreasonable to assume that objects other than insects can absorb infectious material and so transmit the disease. This assumption is borne out by the fact that the usual method of spread is by coming into contact with infectious material on a towel or some other inanimate material used by a trachomatous individual. Nicolle and Cuenod allowed their insects to absorb infectious material then dissected their heads and feet and then inoculated animals. But because their experiments were extremely artificial not much weight is given to their results (24).

Infectious Nature and Transmissibility of Agent

There is little doubt in the minds of the majority of observers that trachoma is a communicable disease. Numerous experiments have been undertaken in which man was inoculated with trachomatous tissue. Suffice to say that all experiments from 1816 to 1937 prove that trachoma is transmissible to man,

reproduces itself experimentally as characteristically as when it occurs spontaneously, the duration of incubation following inoculation varies considerably from a few days to almost a month, and that epithelial cell inclusions occur and can be found when they are looked for. However, some have stated that the experimental inoculation of man with trachomatous material resulting in a clinically typical disease is not due to infection but a combination of trauma and secondary infection. But there is sufficient evidence of accidental transmission to man, as in doctors and nurses, to rule out such concepts (24). While on this subject one might wonder why the incidence of trachoma among the ophthamologists and attendants is not any greater than it is. The obvious conclusion is that trachoma although infectious is not so highly contagious.

Experiments (26,27) carried on in the United States Trachoma Hospital at Rolla, Missouri have shown that monkeys and apes may be infected with material derived from patients with trachoma, that human material is not infectious for other animals and is tolerated without visible effect even by monkeys when introduced into tissues other than the conjunctiva. The observers (27) also found that it was not possible to adapt the infection permanently to monkeys, thus indicating a high degree of tissue specialization by the infectious agent. They also found that

recovery from the experimental disease affords no measurable protection to subsequent inoculation with infectious tissues.

Microorganisms Associated with Trachoma - not Rickettsial

From the material presented so far it seems as though trachoma is an infectious disease experimentally transmissible to man, apes, and monkeys. So we find that as far back as 1881, when the science of bacteriology first came into being, a search for the specific microorganism was initiated. Since that time different biological agents have been pointed out as being directly related to trachoma. Eight different observers reported the presence of protozoan forms in trachomatous tissues but in only one instance was transmission attempted and the results indicated that the organism was without effect. Six different investigators reported that Blastomyces were seen in sections of trachomatous tissue but only one man succeeded in cultivating the the organism. Both Cryptococcus and Streptothrix have been cultivated from trachomatous tissue but the evidence that they are etiologically responsible for trachoma is sadly lacking. When it was proven that bacteria cause disease then many observers sought to demonstrate a bacterial agent as the exciting cause of trachoma. In 1881 Sattler announced he had found a Gram-positive coccus in both conjunctival

discharge and follicular material of trachomatous patients. In 1886 Michel found a diplococcus in the discharge and follicles of sixty-nine patients but it is very doubtful that he was dealing with trachoma. In 1887 on four different occassions cocci were reported as causative agents. In 1889 a motile coccus was isolated from trachoma patients. Numerous observers since have cultivated cocci from trachomatous patients. So it is quite obvious that cocci have been isolated on several occassions but the resultant experimental disease indicates that the conjunctival reaction was in general mild and corneal involvement was lacking and so cannot be designated as trachoma. Probably the most important observation of this group of investigations was that by Noguchi. He demonstrated a rod-shaped organism which he called Bacterium granulosis but neither he nor several other observers were able to produce orhtodox trachoma with this organism. On several occassions different investigators have observed a complete lack of specificity in the bacteria cultivable from trachoma (24).

## The Rickettsial Nature of Trachoma

With the generalized vagueness and doubt of the various organisms advanced investigations were directed toward some other kind of infectious agent. So in 1933 Busacca published the first account in regard to a rickettsial

organism. In 1934 he published two more papers on the same subject stating that in scrapings derived from the cornea during trachoma and stained with Giemsa, could be seen small red-staining bodies in masses and isolated pairs and that nondescript granules appeared blue. These bodies were found between, on, or in epithelial cells, as well as in follicles and in pannus and he considered these Rickettsiae because they were never observed in normal individuals, folliculosis, chronic catarrhal keratoconjunctivitis and several other non-ocular conditions. In view of these facts Busacca felt that they were specific for trachoma and so again in 1937 he reaffirms his belief in the rickettsial origin of the disease.

In 1935 Cuenod observed in Giemsa-stained preparations of follicular contents small particles stained pale blue or violet and aggregated in irregular masses between the epitheloid and mononuclear cells. He designated them as "plastilles" but did not classify them. Then in two publications in 1936, one by himself and the other in conjunction with Nataf, he says that the plastilles were actually rickettsia. Also they described several experiments to show that the rickettsial structures cause trachoma and multiply in the human body louse. In 1937 these men repeated their original observation and in addition produced infection in monkeys and a human after purifying the agent

by inoculation of guiena pigs intratesticularly. In 1936 Poleff found rickettsia-like corpuscles which he identified as those reported previously by Busacca and Cuenod. He also reported the successful propogation of the rickettsia-like bodies in tissue cultures and suggested the possibility that these bodies enter into the structure of the epithelial cell inclusion. Later in 1936 Poleff describes the technique of cultivation and considered the rickettsial forms as a phase of the inclusion bodies (24,1).

As stated previously, Cuenod and Nataf in 1936 and 1937 advanced the hypothesis that the louse may be the insect vector of trachoma. They also suggest that the theory of the rickettsial nature of trachoma was strengthened by the observation that maps showing the geographical distribution of the disease were superimposable on those of typhus, a definite rickettsial disease. They also suggest that the agent is identical with R. rocha limae or at least closely related (1). However, Weigl challenges this hypothesis on the basis that intra-anal inoculation of trachomatous material into normal lice gave negative results and R. rocha limae did not infect lice (1). In 1937 Foley and Parrot (13) confirmed the presence of rickettsial corpuscles in trachoma and identified them with inclusion elementary bodies. They also considered trachoma as a local infection with rickettsia. Also in 1937 Derkac suggested the theoritcal possibility of a positive Weil-Felix test in trachoma

and tested twenty patient's serum of which only five gave a positive test and he did not consider his results conclusive (1). In a publication by Postic (53) in 1938 he considers that there may be a relationship between the organisms of trachoma and those of typhus fever. He suggests that there may be several groups of trachoma rickettsiae and that each endemic area has a different variety, each giving a different agglutination titer. He states that he found a certain histological analogy between typhus exanthematicus and trachoma in the formation of small follicular masses around the blood vessels. He also believes that not counting possible interference with the result by former spotted fever, the Weil-Felix reaction is indisputably of importance in demonstrating the role played in trachoma by rickettsiae. Poleff (51,52) in two different papers in 1939 was convinced from his experiments with pure cultures of rickettsias that they are identical with the formations described by Cuenod and Nataf and were the cause of trachoma. He is also of the opinion that the rickettsia-like corpuscles described by Busacca and Cuenod, at any rate those which are not debri, cellular or otherwise, are identical with the inclusion bodies of Halberstadter and Prowazek at certain stages of their evolution.

So far, for the most part, the evidence has been in

favor of the rickettsial theory of trachoma. But in 1938, Thygeson (68), a most outstanding authority on the problem, examined trachomatous material from Tunis, Brazil, and the United States for the rickettsia-like bodies described by Busacca, Cuenod and Nataf. He found that no minute parasitic bodies other than the elementary and initial bodies of the epithelial cell inclusion of trachoma could be demonstrated. So Thygeson contends that the formations which these observers described as occurring in large numbers in the trachoma follicles are not parasitic but in all probability cell granules and cytoplasmic debri. Grüter, in a 1938 publication considers the rickettsiae of trachoma to be inflamatory proliferations and divisions of granules which occur normally in epithelial cells (24). In May, 1939 Braley (3) published a report and reached the conclusion that the bodies described and photographed by Busacca, Cuenod and Nataf, and others undoubtedly represent stained mitochondria and keratin granules rather than rickettsia. In October, 1939 de Rötth (57) was unsuccessful in repeating the experiments of Cuenod and Nataf and states that the appearance of the follicles does not prove the transmission of trachoma and so reaches the same conclusions as did Thygeson. In July, 1940 Bengtson (1) proposed that the question of the rickettsial nature of trachoma was a question of "what are rickettsiae?" She concludes that if the criteria is small,

bacillary bodies requiring Giemsa stain for demonstration, intracellular habitat, an arthropod host, and failure to grow on artificial media, it is questionable whether the organism of trachoma could be classified as rickettsial. She suggests that perhaps the definition of rickettsiae should be broadened to exclude the arthropod host. However, she believes that the louse might be an accessory factor. S.R. Gifford (17) in a review of the recent advances in ophthamology contends that Busacca, Cuenod and Nataf have inconclusive evidence for the rickettsial origin of trachoma.

From the material presented above one can rightly assume that there has been considerable work done in an attempt to prove and disprove the rickettsial theory of etiology. In my opinion the balance of evidence is against the rickettsial theory. However, the opinions of Cuenod, Nataf and others have raised a number of questions which are of certain prctical importance, such as the theory of louse transmission and the Weil-Felix reaction as a diagnosis of trachoma and cannot be entirely disregarded. Perhaps in the near future these questions will be answered.

## The Inclusion Body

The research done in this field dates back to 1907 when Halberstadter and Prowazek started investigating trachoma while they were on an expedition to Java to study

syphilis. Afte inoculating baboons with secretions from trachomatous patients they examined Giemsa-stained preparations of scrapings from their conjunctiva and discovered within the epithelial cells collections of granules that have since been known as inclusion bodies, epithelial cell inclusions, trachoma bodies, Halberstadter and Prowazek bodies, and Prowazek bodies. Because they saw similar structures in preparations of material taken from trachomatous patients they concluded this inclusion body was the infectious agent of trachoma. Even at this early date these two men put the infectious agent in the same class as smallpox, rabies, and molluscum contagiosum, diseases that are now considered as virus diseases. They also stated that the conjunctival epithelium is the portal of entry and chief source of dissemination of the incitant. At the same time Halberstadter and Prowazek's work was published Greeff described granules which he considered as the incitant of trachoma. His descriptions of them coincide perfectly with the elementary granules of the inclusion body. Later, however, he said that they played no part in the causation of trachoma. In 1908 Stargardt published a report on the inclusion bodies but he felt that other agents were able to stimulate epithelial cell inclusions and a year later Schmeichler confirmed this idea. Heymann observed inclusion bodies in ten of fourteen cases of gonorrheal

blenorrhea thereby seriously conflicting with the conclusions of Halberstadter and Prowazek (24). So whether the inclusion body was a reaction product of the epithelial cell in response to gonococcal infection or to the incitant of trachoma became a serious problem.

In 1910 Herzog considered trachoma the result of gonococcal infection occurring under special conditions. Then Halberstadter and Prowazek tried to answer the perplexing problem so they looked for inclusion bodies in genitourinary infections in men and women and were unsuccessful. And in three infants with gonococcus-free blenorrhea they saw many inclusions so they concluded that these inclusion bodies were independent of gonococcal infection. However, Jancke found inclusion bodies in urethral preparations of fifteen of sixteen patients with gonococcal infection. Then Lindner showed that the inclusion bodies were found in all cases of blenorrhea free of gonococcus so he said that there are two blenorrheal diseases, inclusion blenorrhea and gonococcal blenorrhea. He stated that the inclusion of blenorrhea was indistinguishable from that of trachoma. Halberstadter and Prowazek actually demonstrated cell inclusions in the genital epithelium of a mother giving birth to an infant with inclusion blenorrhea. They felt the inclusion was similar to but not identical with that of trachoma and designated it as Chlamydozoon blenorrheae. Later Lindner found

inclusions and free initial bodies in three instances of non-gonorrheal urethritis of man so he advanced the idea that trachoma and inclusion blenorrhea are manifestations of the same agent and in 1935 he classified them as trachoma and paratrachoma. Heymann considered the inclusion body as an unknown independent coexistent virus capable of multiplication and transmission to monkeys and apes. Lindner and Wolfrum felt that genuine trachoma followed inoculation of material from inclusion blenorrhea in man. But Gebb and Löhlein did not think it was trachoma (24). In 1934 Thygeson (65) demonstrated inclusion blenorrhea in adults was not trachoma but swimming-bath conjunctivitis. Sine then this work has been confirmed by Julianelle (24).

So the work done in this field indicates that in epithelial cells during trachoma there occurs a formation designated as inclusion body which certain authors regard as the infectious agent. Also inclusion bodies may be found in other follicular diseases such as inclusion blenorrhea and swimming-bath conjunctivitis. The occurrence of the inclusion body in experimentally infected humans has been accepted by Leber, Prowazek, and Thygeson (67) as proof of its viability. Still others (45,50) say that the inclusion body has no relation to trachoma. Szily, Stanculeanu and Mihail, Solovief, and the Duke-Elders (10) believe that

the inclusion body is the result of cytological degeneration. Herzog, Williams, and Bengtson (2) advanced the idea that the inclusion body was phagocytosed material.

In conclusion, it must be admitted that whatever its ultimate nature may be the inclusion body constitutes an integral part of trachoma, and, from the microscopical point of view it is still the only tangible evidence characteristic of the entire disease. In a later section the relation of the inclusion body, rickettsia, and virus will be discussed.

## The Virus Theory

As far back as 1905, antedating the discovery of the inclusion body by two years, Pfeiffer and Kuhnt reported on the infectivity of filtrates of human trachomatous material obtained by filtration through Berkefeld candles. They found the filtrates were not infectious and so concluded that the infectious agent was not filterable and so the viral concept indirectly came into being. In 1906 Baiardi, using Berkefeld filters, carried on similar experiments and reached the same conclusion. Hess and Römer using Berkefeld filters, also came to the same conclusion. In 1907, Fermis and Repetto in a series of four trials in filtration, only one of which used proper controls, also came to the same conclusion. In 1908, Bertarelli and Cecchetto

produced what they considered typical symptoms of experimental trachoma by filtrates. Nicolle, Cuenod and Blaizot in 1911 and 1912 reported that the agent of trachoma was a filterable virus. Then because everyone was concerned with the inclusion body and the advent of the first World War filtration experiments were forgotten until 1930. At this time Trapesontzewa concluded that the infectious agent of trachoma was not filterable (24). In 1931 Olitsky, Knutti, and Tyler (47) in a series of six filtration experiments had one successful inoculation thereby suggesting that the process of filtration may be irregular. In 1932 Cattaneo after carrying out four experiments on filtration concluded that lack of infectivity of filtrates may have been due to a loss of virulence during filtration rather than to an inability of the agent to permeate filters. In 1933 Lumbroso and Thygeson in a series of six experiments did not get any positive inoculations with their filtrates. In 1933 and 1935 Julianelle and Harrison in a series of eleven experiments on filtration obtained only one positive result (26,28).

In 1935 Thygeson and Proctor (70) conducted experiments in which four inoculations of baboons with bacteria-free filtrates of trachomatous materials resulted in a disease identical with that produced with unfiltered material and concluded that these results support the conclusions of Nicolle, Cuenod and Blaizot that trachoma is a filterable virus.

Also in 1935 Julianelle and Harrison (28) in a series of twelve experiments concluded that filtration of the infectious agent is extremely irregular and that such irregularities may be due to variations in the tissues as well as to the variations in the composition of the filters. Again in September, 1935 Thygeson, Proctor, and Richards (71) using a colloidion membrane, and thereby eliminating absorption of the agent as occurred in the filtration experiments using Berkefeld filters, confirmed the virus nature of the etiologic agent of trachoma. In the same month and year Thygeson (66) states that the evidence obtained from three different methods of attack on the problem of the etiology of trachoma indicates that trachoma is definitely a virus disease. The three methods of attack that he mentions are:-

1- Evidence obtained through a process of elimination---
   Julianelle and Harrison, Stewart, and Thygeson carried out extensive experiments using pure cultures or cultures of bacteria pooled in the proportions found on the trachomatous conjunctiva without results.
2- Evidence obtained by filtration experiments ---
   As previously mentioned above conclusive experiments have shown that the agent is filterable under certain conditions.
3- Evidence obtained by inoculation with bacteria-free trachomatous material ----
   Julianelle and Harrison using the method of testicular

inoculation which Noguchi developed to rid vaccine virus of contaminating bacteria were able to obtain active bacteria-free trachomatous material capable of inducing infections in monkeys.

I believe that Thygeson is correct in assuming that the infectious agent is of a virus nature on the basis of this evidence. In October, 1938 Thygeson and Richards (72) after a series of studies on the etiology of trachoma came to the conclusions that the causative agent is filterable under certain conditions, that it has the characteristics ofa virus (filterability, inclusion body formation, non-cultivability on non-living media), that it is identical with the elementary body of Halberstadter and Prowazek. They also believe, in this paper, that the virus of trachoma, with the viruses of inclusion blenorrhea and psittacosis, form a group transitional between Rickettsia and the typical viruses.

In my opinion the balance of evidence presented thus far indicates that the infectious agent of trachoma is of a virus nature but the definite category has not been adequately decided. In the next section the relation between the inclusion body and the virus nature will be pointed out and discussed because I believe that there is a definite relationship between the two.

## Relationship of the Inclusion Body and the Virus Nature

In 1934 Thygeson (64) reached the conclusion that the inclusion bodies of Halberstadter and Prowazek constitute intracellular colonies of the virus in various stages of development. He believed the small inclusions, made up of initial bodies, was the early phase of the virus while the large inclusion, made up of elementary bodies, is the late phase. In 1935 Thygeson (71) in an experiment, using the colloidion membrane for filtration, confirmed the virus nature of the etiologic agent of trachoma, and offers evidence to support the view that the trachoma virus and the trachoma elementary body (Halberstadter and Prowazek) are identical. Again in 1938 Thygeson and Richards (72) state that they believe the elementary body of trachoma represents the morphologic unit of the virus of trachoma because of the following findings:-

1- The identity in morphologic structure and staining reactions of the bodies of trachoma with the similar bodies of inclusion blenorrhea and psittacosis, established virus diseases.

2- The presence of the elementary bodies in an infective filtrate.

3- The presence of the elementary body in the lesions of trachoma with sufficient constancy to indicate etiologic significance,

4- Their multiplication in new hosts (man and baboons) when transferred directly or after filtration.

5- Their persistance in the lesions of trachoma through out the period of activity of the disease.

In January, 1941 Julianelle (25) published a paper in which is suggested an actual relation of the inclusion body to infectivity to the extent that the inclusion represents an agglomeration of virus particles. However, he feels that this opinion requires further study before it can be fully accepted.

In conclusion of this section I believe that the opinion stated by Julianelle substantiates the ideas of other observers but as is stated there will have to be further collaberation before anything definite can be decided.

## Conclusions

In the final analysis of the question of the etiology of trachoma I am of the opinion that the major portion of evidence originating from different laboratories designates a virus as it's causative agent. Among the chief characteristics indicative of viral activity is the cytoplasmic inclusion body identified with the epithelial cells of the conjunctiva and, occassionally even of the cornea. While opinion varies as to it's true significance, the majority

of observers, begining with Halberstadter and Prowazek, regard the inclusion body as actually the incitant itself or as a mass or colony of infectious units and more recently as agglomerations of virus particles. However, the evidence brought forward during all these years in support of these beliefs is essentially morphological, and as such it is subject to individual interpretation.

The successful treatment of trachoma, as shown in the next section, with sulfanilamide and the inability to curtail various other virus diseases with the same drug might be considered by some as concrete evidence that trachoma is not of the virus class. But since modern research has not yet determined the definite nature of viruses, one might speculate that the agent of trachoma is a part of the life cycle of the virus which can be affected by chemotherapy, in this instance sulfanilamide, or that there are various species of viruses that will respond to chemotherapeutic agents.

# THE TREATMENT OF TRACHOMA WITH SULFANILAMIDE

## Introduction

Until very recently the management of trachoma has been largely a surgical problem. In the history of this very interesting disease there has been only one procedure which has consistently persisted in spite of the various and numerous procedures advanced. The local application of escharotic drugs, especially some form of copper, has been used for at least three thousand years. With the advent of chemotherapy approximately three years ago a revolution in the management of trachoma has occurred, chiefly because it is so easy to use, much less painful to the patient than the old procedures, and good results are secured by its use.

In this section of my paper I propose to review the pertinent experimental work, which has been done during the last three years, in regard to the use of sulfanilamide and it's derivatives in the treatment of trachoma and subsequently evaluate the publications that have been published up to this time.

## Review of Experimental Work

The first report on the use of sulfanilamide compounds in the treatment of trachoma was published in August, 1937 by Heinemann (19). Although his series consisted of only three cases his results were so startling both to himself and the rest of the world that immediately other observers sought to determine the value of this miracle drug. And so we find that this was the begining of a problem which is not yet solved.

In July, 1938 Lian (36) reported his observations on the results of the treatment of trachoma with sulfanilamide. His series consisted of thirty patients and he found that the conjunctival and corneal complications responded well. However, he comes to the conclusion the sulfanilamide is a valuable aid in combination with mechanical methods and alone will not cure the disease.

In this country Dr. Fred Loe started to use sulfanilamide in trachoma at the same time Heinemann's report came out but he did not publish his work until October, 1938 (38). He states that in August, 1937 he selected two patients, one of whom had trachoma for two years the other eighteen months, and treated them by giving one-third of a grain of sulfanilamide per pound of body weight each day along with an equivalent amount of sodium bicarbonate for the first ten days. Then for the next fourteen days he gave them

one-quarter of a grain of sulfanilamide per pound and an equal amount of sodium bicarbonate. Five days after the treatment was started he noticed that the redness of the conjunctiva was disappearing, the granules and papules were decreased in size and the blood vessels became increasingly visible. As a result of his treatment he states that these two cases were apparently cured within one month. On January 6, 1938 he started treating thirteen patients sulfanilamide who had been under continuous treatment from one to seven years. Three of these patients were dismissed on Jan. 16, 1938 apparently cured, the other ten were greatly improved after eight days of treatment and were given sulfanilamide for two weeks longer. At the meeting of the American Medical Association in June, 1938 he reported the results of 140 cases of trachoma, as previously mentioned, and from the conclusions made it is assumed that all of the cases were arrested.

In 1938, at the same time Loe presented his paper to the American Medical Association, Gradle (18) read a report on the treatment of a series of 41 patients with sulfanilamide in which 25 percent did not respond to treatment and 75 percent, although not stated, are supposed to have been arrested. Even though his paper had been published before Loe's, Gradle gives all priority to him.

Also in 1938 in Great Britian Kirk, McKelvie, and

Hussien (33) proceeded to try out sulfanilamide. They based their trial solely on some research work which had shown the value of the drug in healing a meningitis induced in mice by the virus of Lymphogranuloma Inguinale and which showed Rickettsia-like bodies similar to those found in trachoma. They treated twenty-five patients using $22\frac{1}{2}$ grains of sulfanilamide daily in alternate seven day courses. They noted that the greatest improvement was seen where pannus and keratitis were present. From their results they concluded that the permanent effectiveness of the drug still had to be ascertained.

In a series of twenty-five patients, after two weeks of treatment and observation, Hirschfelder (23) got the impression that sulfanilamide has a paling and drying effect on the conjunctiva of trachoma stage II and milder cases of stage III. Also he noticed that it seemed to aid in the healing of pannus in cases that are not too old and not too malignant. He used the dosage and procedure recommended by Loe and reached the conclusion that the question whether or not the drug can completely arrest the disease or prevent recurrences is still not settled.

In April, 1939 Richards, Forster, and Thygeson (56) published a report of the treatment of twelve Indian children by the method of Loe. All of these children showed active

trachoma with follicular hypertrophy and pannus and all showed striking improvement. At the end of four and a half months the conjunctiva in each instance had become follicle free and smooth. In every eye, except one, there was a disappearance of corneal infiltrates and an apparent arrest of corneal activity. Also in every case the drug caused the disappearance of the epithelial cell inclusion so characteristic of active trachoma so it is assumed that all cases were arrested.

In August, 1939 a very interesting paper appeared in the literature. Brav (4) treated one case of recurrent trachomatous ulceration of the cornea with instillation of a two and one-half percent solution of neoprontosil locally. This ulceration cleared up and the pain was relieved by this procedure. This is the first instance of a sulfanilamide derivative being used locally.

In October, 1939 at a staff meeting of the Mayo Clinic Harley, Brown, and Herrell (21) made known their findings of treating trachoma with sulfanilamide and it's derivatives. In a series of eleven cases, four of which were treated with neoprontosil because they were intolerant to sulfanilamide, they found marked objective and subjective improvement in each case. All cases were grouped as stage II or III according to MacCallan's classification. In regard to neoprontosil they reached the conclusion that although the results were

not as dramatic they compare very favorably with those secured with sulfanilamide.

The use of sulfapyridine in the treatment of trachoma was reported for the first time by Spearman and Vandevere (60) in November, 1939. Their series consisted of two cases that had been intractable to all other methods, one with sulfanilamide. They were greatly impressed with the remarkable remission of pathologic signs and the improvement of vision secured.

In November, 1939 Julianelle, Lane, and Whitted (29) published their results on a series of 113 patients, all were Indians except for six white patients. They used the dosage recommened by Loe and found that twenty percent recovered, forty percent showed varying degrees of improvement and forty percent were not improved. So they reached the conclusion that the drug has marked and rapid effect on the secondary infections commonly associated with trachoma and that most striking results were seen in those patients with exacerbative disease.

Wilson (76) reported a series of eighteen patients that recieved one-third grain of sulfanilamide per pound of body weight each day for three weeks and then one-quarter of a grain per pound each day for three weeks. He also used a two percent ointment locally and secured an arrest of the disease process in all cases.

Lugossy (39) in a report published December, 1939 found that sulfanilamide preparations were of the greatest value in those cases of trachoma which were complicated by pannus and corneal ulcers. However, he concludes that sulfanilamide itself does not cure trachoma but hastens the curative effects of such remedies as injection of foreign proteins.

Another large series consisting of 100 patients was reported by Sie-Boen-Lian in December, 1939 (37). He reached the conclusions that the drug was effective in reducing secretion and diffuse thickening, papillary thickening influenced but little, the granules were not affected, and that the corneal complications (pannus, keratitis, corneal ulcer) responded best of all. He also found that recurrences of complications were rare.

In March, 1940 Spining (61) in Ganado, Arizona being stimulated by Loe's report and using the dosage outlined by him reports the treatment of fifteen adults with chronic trachoma associated with other acute eye conditions, such as bulbar conjunctivitis, phylycentular conjunctivitis, and corneal ulcers. He found that all of them recovered rapidly from the acute manifestations but in none of them could he find any evidence that the underlying trachoma was cured or even greatly improved. He also reports that seventeen children between the ages of eight and fourteen years with chronic

trachoma and little or no bulbar or corneal involvement other than slight pannus were treated with sulfanilamide for periods of seven to twenty-four days. In only one of these children was a clinical cure obtained, the other sixteen showed only slight to moderate improvement.

MacCallan (41) of the British school in March, 1940 published a report after using sulfapyridine. The report does not say how many cases were treated but the dosage used was three grams the first day and two grams on each succeeding day for nine days along with an equivalent amount of sodium bicarbonate. He concludes that up to the present time the drugs of the sulfonamide group have been found to be without effect on any virus disease and consequently has no effect on trachoma, since it is of the virus class. He believes that the good results obtained in the treatment of trachoma by these drugs have been procured by the elimination of superimposed bacterial infections.

The results secured in another large series was reported in May, 1940 by Forster (14). He used sulfanilamide in a dosage of one-half grain per pound of body weight daily, divided into four doses, for twenty-one days then if there was any evidence of trachomatous activity they were given a second course identical with the first. The disease, in 125 out of 167 trachomatous children became clinically

arrested following the one course. In the rest, the disease became arrested following the second course. He found that the effect of the drug on stage I was very striking, the conjunctiva and cornea returning to normal in ten days, but in the advanced cases the effect was slower.

Also in May, 1940 Kettler and Rutherford (32) reported a series of 63 patients out of which eight eyes were blind, one globe shrunken, and one enucleated. They used ten grains of sulfanilamide three times daily the first week and then ten grains twice a day for four to eight weeks and instilled into the conjunctival sac one drop of a two and half percent solution of neoprontosil four times daily. If the eyelid deformities were bad the patient was hospitalized and surgical correction done and during the time of hospitalization one-third grain per pound, maximum of forty grains, was given orally. They found that out of the 116 eyes capable of being improved the vision in 56 of them was improved. They concluded that improvement occurred in inverse proportion to the number and severity of complications, that the acute exacerbations of old trachoma with infective secretion are quickly controlled, that you can cure practically all in whom the infection has been recently acquired and where no complications have developed.

Thygeson (69) in June, 1940 reported a series of 31 cases of trachoma treated with sulfanilamide. Of these 16

were healed, 11 showed satisfactory improvement, and 4 exhibited little or no change. He concludes that his results confirm the claims of Loe and others that sulfanilamide exerts a definite curative effect in a high percentage of active trachoma cases. He also states that the effect is primarily on the trachoma virus rather than on the secondary invaders because of the striking results obtained in pure, uncomplicated cases and by the uniform disappearance of the epithelial cell inclusion bodies characteristic of the active disease.

As a result of work done by them in China, Lee and Rottenstein (34) reported a series of 95 cases in July, 1940. Seventy-five of these patients were treated by giving a daily dose of sulfanilamide of 0.02 gm. per pound of body weight for two to four weeks. Twenty of these patients were treated with sulfanilamide given intramuscularly in a dose of two to five grams per injection. Sulfanilamide was given every four days and sulfapyridine every seven to ten days, with a total of two to six injections being all that was necessary. They concluded that the treatment was effective in stages I,II, and III and that the intramuscular route was most effective.

In August, 1940 Hammond (20) reported a series of 12 cases of acute trachoma that were treated by giving sulfanilamide in doses of forty grains per day for two weeks,

thirty grains for three weeks, and twenty grains for two to six months, depending on how often the patients returned to have their prescriptions filled. He found that in every case there was marked improvement or complete arrest.

Also in August, 1940 Cosgrove (8) reported a series of 107 cases treated with both oral and local sulfanilamide. He reports that equal improvement of visual acuity was obtained by both methods individually and that the symptomatic relief of the patient with trachoma on local sulfanilamide is apparently as rapid and complete as that obtained from oral use. He also suggests that it may be possible to prevent the recurrence of trachoma after sulfanilamide therapy by the continued local use of the drug.

In September, 1940 Cooper (7) reported some observations which are entirely different from others and very interesting. In a series of 34 patients with trachoma treated with sulfanilamide, a recurrence of 62 percent was encountered within six to thirty months. Of those recurrences 16 were treated subsequently with iontophoresis and none had a second recurrence, a majority of them being followed for over two years. He suggests that routine treatment of trachoma consist of at least eight applications of quinine bisulphate by iontophoresis following apparent cure by sulfanilamide, as a prophylactic measure against recurrence. However, he warns that you cannot carry out iontophoresis until sulfanilamide

therapy has been completed because of the danger of producing a harsh reaction in the ocular tissues.

The latest report available was published in Feb., 1941 by Smith, Julianelle, and Gamet (59). In their series of 26 patients they used the dosage recommended by Loe. Their results show that two cases were arrested, 11 were improved but still clinically active, and 13 remained in a stationary clinical condition. In the final analysis they admit that 50 percent of the patients treated profited from the administration of sulfanilamide.

## Summary of Reports Reviewed

Twenty-four reports on the observations of various observers have been reviewed. Of these all but those of Heinemann (19), Brav (4), Spearman and Vandevere (60), and Lugossy (39) can be fairly judged as to the results of treatment of trachoma by sulfanilamide and it's derivatives.

Although all observers agree that trachomatous patients secure relief of objective and subjective symptoms, not all of them agree that the disease process is arrested. Julianelle, Lane, and Whitted (29), Spining (61), Cooper (7), Smith, Julianelle, and Gamet (59) had comparatively poor results but even at that I believe they had a fair enough percentage of arrestment of the disease

process to warrant the use of sulfanilamide in the future. Julianelle, Lane, and Whitted (29) and MacCallan (41) using sulfapyridine, believed that the good results they did secure was due to the effect on secondary invaders and MacCallan states it has no effect on trachoma.

All the observers not mentioned in the preceeding section had very good results, especially when the disease was of recent origin but in numerous instances long standing cases were cleared and arrested. Thygeson (69), in direct opposition to MacCallan (41), states that the drug has a direct effect on the virus and little effect on the secondary invaders.

Several observers have recommended that some other form of treatment be used in conjunction with sulfanilamide therapy, or that sulfanilamide or neoprontosil be used locally alone or in conjunction with oral use of sulfanilamide. Lian (37) believes that some form of mechanical treatment should be used with sulfanilamide therapy; Brav (4) secured excellent results in one case from local use of neoprontosil; Wilson (76) using sulfanilamide locally and and orally secured excellent results; Kettler and Rutherford (32) using neoprontosil locally with oral use of sulfanilamide had excellent results; Cosgrove (8) secured favorable results from the use of sulfanilamide both orally and locally; Cooper (7) by using iontophoresis in the

recurrent cases of trachoma following sulfanilamide therapy had excellent results.

It seems that dosage and treatment time are probably the two most important factors in explaining the varying response of trachoma to sulfanilamide. The importance of adequate dosage is well shown in the two series reported by Richards, Forster, and Thygeson (56) and by Forster (14) in which almost uniform healing was obtained on a daily dosage of one-half grain of sulfanilamide per pound of body weight continued for three weeks or longer, however, the toxic effects of the drug, especially in regard to the hemopoetic system, must always be kept in mind.

## Conclusions

The experience of innumerable observers in the treatment of trachoma with various methods during the entire history of the disease definitely shows that it is impossible to attain complete recovery in all patients and complete lack of recurrence in all individuals. So in the final analysis I believe that sulfanilamide has made a most prominent place for itself in the treatment of trachoma and that it will stand the test of time much better than previous forms of treatment except possibly the use of escharotic agents. Also the few reports that are available on the subject, indicate that the use of sulfanilamide or one of it's derivatives locally in

conjunction with oral therapy of sulfanilamide or some other local treatment such as that suggested by Cooper (7) may be of definite value but the literature is not sufficient enough to judge fairly.

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