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# THE ROLE OF ASSOCIATED AFFECTIONS IN TRACHOMA

by

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"It is a well known fact that bacterial infections are common in trachomatous patients though they widely differ from one region to another.

The varieties of bacteria involved have been thoroughly studied but it would be advisable to investigate further the effect of anti-trachoma agents on these bacteria.

In trachoma treatment it is desirable to use drugs active against both the virus and the usual pathogenic associated agents."

(Scientific Group of Research on Trachoma. London, Paris, Geneva (3-10 March 1952) (3-2-8).

The part played by associated forms of conjunctivitis (synonyms: superadded infections, trachoma-bacterium complex, superinfected trachoma, mixed trachoma) was stressed particularly by Dr. Victor Morax as far back as 1926. However, a résumé of medical literature shows a persistent tendency to group under the term of trachoma not only pure trachoma but also trachoma associated with bacteria.

Such an attitude is far from being scientific and nobody would deny today that the conjunctival flora of a given case of trachoma should be

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analyzed and that such analysis should be carried out as thoroughly as possible, in order to determine the part played by the trachoma virus or by the pathogenic bacteria in the clinical picture.

No therapeutic conclusion may be reliable if cases, the pathogenic agents of which are so widely different, are grouped under the same term. It seems, therefore, that one should consider PURE TRACHOMA on the one hand, and ASSOCIATED OR MIXED TRACHOMA on the other hand.

It is a fact that a careful analysis of the pathogenic flora would show that in certain countries pure trachoma is prevalent whilst in other countries an associated flora is almost always found. The eradication of the disease, which is the goal aimed at, should be considered as more difficult in the latter case.

Different items should be considered if an accurate account of the clinical picture is to be given :

1. Importance of the associated forms of conjunctivitis in the establishment of trachoma. First of all, do these associated forms pave the way for trachoma, as it was said (Morax, Cuenod and Nataf)?

2. Importance of the factor represented by the "associated forms of conjunctivitis" in the development of the disease :

(a) in respect of the eyelids

(b) in respect of the cornea

3. Importance of the "associated forms of conjunctivitis" as a factor acting on the visual acuity of the individual, i.e., on the significance of trachoma from the "social" standpoint. In other words, has the presence of bacteria associated with trachoma any influence as an aggravating factor?

## 1. Importance of the associated forms of conjunctivitis in the determination of trachoma

It has been proved that an acute or chronic conjunctivitis does not necessarily precede the appearance of trachoma. Contrary to the opinion advocated by some authors, a previous acute, sub-acute or chronic conjunctivitis is not necessary for trachoma to appear. But it may be said that conjunctivitis by bringing about an eye irritation, prompts the

patient to touch his eyes or to rub his eyelids and, thus, forms the onset of trachoma, due to the multiplication of infective contacts.

Some experiments made by Poloff and Viennot-Bourgin showed also that trachoma is more easily inoculated on an experimental basis when germs are present, as these seem to sensitize tissue culture to inoculation.

Conjunctivitis may therefore be considered as a factor in the spread and dissemination of trachoma.

Acute trachoma onset

The controversy on the acute or non-acute onset of trachoma is now closed. Authors such as Thygeson, Nataf, Biotti, Pagès, etc. showed that the acute onset of trachoma may exist, but that it is not a rule, contrary to the views expressed at a time by Mitsui.

However, it is possible to assert, as far as the countries bordering on the Mediterranean basin are concerned, that acute discharging conjunctivitis is mostly the result of an inoculation by a bacterium other than a virus (with the exception of "oculo-genital chlamidozoon", whose initial phase is always acute).

Therefore, with regard to trachoma virus, it may be said that the pattern of onset is mostly insidious.

2. Importance of the "associated forms of conjunctivitis" as a factor in the development of the disease

(a) with regard to eyelids (conjunctival mucous membrane) :

The analysis of several observations made in Morocco proves the very great importance of "superadded infections". If we refer to statistics, we find that the specimens and the analysis of smears indicated that eighty per cent of the examined individuals had "superadded infections". It often happened that several germs were present at the level of the same conjunctiva (Weeks bacillus, Morax-Axenfeld diplobacillus, Xerosis of Corynobacteria, Staphylococcus, Streptococcus, Pneumococcus). This gonococcus is of little importance and shows itself under the form of sporadic outbreaks.

It is beyond doubt that conjunctival hyperplasia, follicles or papillae and thickening of the chorion, are more frequent and more marked in the case of mixed trachoma and our research showed that their number and the extent of their hypertrophy, in particular with regard to "granulomas", depended on the virulence of the superadded flora and on the microbial associations.

Pannarale and Huet admit that the multiplication of the virus "may be induced by a simple inflammatory condition of bacterial origin, regardless of the type of micro-organisms which provoked it".

As I already wrote in our report in 1951, I am of the opinion that the two affections reflect on each other, and that bacteria and viruses associate in aggravating the lesions in the conjunctival tissues of the palpebral mucous membrane.

(b) With regard to cornea:

As Professor Bietti well demonstrated in his "considerations on the participation of the cornea in the trachoma process" (EURO 158.1/9, 8 sept. 58), the participation of the cornea in the trachoma process, especially starting with stage II of the disease, should be considered as a rule.

However, such a participation is far more frequent and far more severe in patients suffering from " associated conjunctivitis". A mixed infection increases in the proportion of fifty per cent the frequency, severity and persistence of corneal lesions, whether in the case of central ulcerations, transversally or horizontally elongated (Adiamantadès furrow-shaped keratitis) or diffuse epithelial keratitis or sometimes perforating ulcerations occurring at the lower limit of pannus.

The frequency of vascularization and its importance (shown in millimetres from the limbus) is far greater in mixed trachoma carriers.

Superinfection certainly plays a part in the production of pannus and the multiplicity of pannus localizations on the same cornea. It is mostly in patients with superadded infection that "pannus crassus" and "multiple pannus" are seen.

The marginal ulcerations in the shape of "nail scratches" and "paralimbal ulcerations" are also more frequent in superinfected patients than in patients suffering from pure trachoma.

At the static phase, it may be said that trachoma is always more severe on the corneas of superinfected patients than in other patients. Is the aggravating rôle of superinfection due to the microbial germ itself or to the toxins? It is impossible to answer with certainty.

In our report to the International League Against Trachoma (1951) we published a micro-photograph which conclusively proved that corneal cells may be invaded by Weeks bacilli in actual cell culture, and these germs penetrate the cell to its own detriment.

Therefore, the Virus + Bacterium combination intensifies the virulence of the infection and causes more considerable damage when trachoma is associated with pathogenic bacteria. It seems that the prevalence of conjunctivitis varies according to the different countries. Whilst conjunctivitis is very common in the area surrounding the Mediterranean basin, it seems less prevalent in Czechoslovakia, in Japan and in the United States.

2. Significance of associated flora according to each country

G. Akagi, J. Tsutsui, P. Nanba, H. Shimizu and H. Nishikiori, reported that the prevalence rate of Koch Weeks bacillus conjunctivitis was 6.7%, whilst in Morocco, we found it to be 45-50% according to the areas concerned. The Japanese authors consider that the influence of conjunctivitis on the development of trachoma is weak. They are perhaps right with regard to the bacterial infections, which are not numerous in their country; but such is not the case in North Africa, and the prevalence of Kock Weeks bacillus and the gonococcus (even more prevalent in Egypt and in Tunisia than in Morocco) presumably accounts for the difference noted in the percentage of severe cases in this country.

Again durin my visit to the United States, in the summer of 1957, I could ascertain that the prevalence of superinfected forms of conjunctivitis in Puma and Papago Indians, in Arizona, was extremely low, which, in my opinion accounts for the little number of severe trachoma cases found in the pupils of the schools visited by me.

According to R. Pannarale and M. Huet, the prevalence of "Haemophilus" in Tunisia is 47.6% in respect of discharging trachoma and 33% for apparently pure trachoma. These figures are pretty close to those found in Morocco.

But the Koch Weeks bacillus is not the only one involved, and like Pannarale and Huet, our investigations enabled us to note that in many cases the microbial associations were very frequent in conjunctivitis associated with trachoma (which we referred to as the "germs cocktail"). Pannarale and Huet noted the presence of a simple flora in 28.73% of the cases and a mixed flora in 49. 42% of the cases.

In Morocco, out of 17,000 slides examined, we found :

| | 1 | 2 | 3 | 4 | 5 | 6 | Rev. |
|---|---|---|---|---|---|---|---|
| Pure Kock-Weeks | 45,7 | 23.5 | 17,1 | 23.9 | 28.8 | 42.2 | 32,5 |
| Associated K-W. | 50,0 | 20,6 | 15,7 | 18,5 | 22.7 | 33,0 | 19,1 |
| K-W. (total) | 47,3 | 22,2 | 16,2 | 19,7 | 23.8 | 34.4 | 20,6 |
| Pneumococcus | 37.0 | 0,0 | 3,7 | 3,6 | 6.9 | 10,5 | 5,3 |
| Morax | 24.4 | 8,8 | 2,6 | 3.9 | 8.3 | 3.7 | 4,1 |
| Xerosis | 36,6 | 8,1 | 0,0 | 10,0 | 4.5 | 2,4 | 1,3 |
| Association (without K-W.) | 23,5 | 8,3 | 4.7 | 8,2 | 6.2 | 8,0 | 4.8 |
| Negative slides | 33,0 | 5.7 | 0.3 | 3,5 | 2.3 | 3.1 | 0,5 |

As it may be seen, these figures approximate to those quoted by the previously mentioned authors. On the basis of these data, we are therefore in a position to assert that the clinical aspect of the lesions which is always more severe in the countries where the microbial flora is very polyvalent, varies according to the flora, and that the complications are more severe and more frequent in trachomatous patients showing an important associated flora.

This applies also to trachoma in the Indians. Dr. Francis I. Proctor, who was then Indian affairs consultant in the United States, wrote me on 29 September 1934 the following :

"We do not have the mixed infections so common in Europe and especially in North Africa. I have examined 2,000 Indian children the last ten days, finding perhaps twenty-five per cent trachoma, most of them in stage III of MacCallan, with a few fresh cases and a good many suspicious, in which I cannot make a positive diagnosis. Among all these children, I have found six cases of mild conjunctivitis, one or two ulcers and a very few cases of pannus visible to the naked eye. Nevertheless, they have true trachoma, for I have seen much trachoma in Africa, as has Thygeson, and both Wilson and Lindner came here and said ours was true trachoma. We get cicatrization, some pannus, some entropion; but in general most of the cases are arrested without serious complications."

These findings by Dr. Francis I. Proctor were also made by myself in September and October 1957, during my mission in the United States, as I previously mentioned.

There is no doubt that in the Indians of America trachoma is less severe than in Morocco or in North Africa.

In our opinion, this should be ascribed to the absence of certain germs from the microbial flora of the United States.

MICROBIAL FLORA AND INCLUSIONS

In their valuable work, Pannaralo and Huet showed that there was no direct relationship between the bacterial flora and the presence of inclusions, and "that these were not found to be more often associated with Haemophilus than with other bacterial germs. In the inflammatory conditions of the conjunctiva, due to bacteria in trachomatous patients (forms of discharging trachoma), the intra-cellular inclusions were found *more numerous in cases without* superadded inflammation. The authors infer therefrom that the presence alone of certain associated bacterial specific species does not constitute a factor activating the virus multiplication, as this may rather be induced by a mere inflammatory condition of bacterial origin, irrespective of the type of pathogenic micro-organisms which caused it" (Pannaralo and Huet).

We consider it is regrettable that these authors carried out their investigations in winter, during which season the germs' virulence (both that of Koch Weeks bacillus and of the staphylococcus aureus) is at its lowest level, whilst in summer their findings could have been different.

It is to be pointed out also that the gonococcus is more often observed in autumn both in Egypt and in North Africa. But in Morocco it was very occasionally detected in the smears examined during the control of the mass campaign - it appears under an epidemic form only in some restricted areas. Like others, we have come across autumn epidemics, and, in a particular case (Gharb epidemic - 1956), we had among 1,483 examined individuals, twenty-five corneal perforations, of which eight were bilateral. Of these, sixty per cent were due to gonococcus and trachoma carriers. Furthermore, Koch Weeks and gonococcus were present as a mixed infection in this epidemic, which was not stopped until antibiotics instillatio. was made over a fifteen-day period by a team of specialized male nurses from Rabat.

The aggravating effect of the gonococcus on trachoma had already been noticed by the ancient authors, and MacCallan had set it in a separate category under the symbol Tr.II c.

## INFLUENCE OF MASS CAMPAIGNS ON THE INCIDENCE OF CONJUNCTIVITIS ASSOCIATED WITH TRACHOMA

Samples were taken in an area of the campaign site, during the whole duration of the campaign, on the following days: $D^0 - D^7 - D^{14} - D^{28}$, etc., with a view to following up the effect of aureomycin instillations. Curves were made for the four main cycles.

These curves show the spectacular influence of aureomycin instillations made over a three-day period (intermittent treatment) on the different germs and more particularly on the Koch-Weeks bacillus. It is to be noted that microbial associations respond to treatment to a lesser extent. Moreover, the statistical study proves that the germs promptly reappear (three to four days) after a total disappearance, and that the curves rise, but to a lesser index than in the previous cycle. This may be accounted for either by a re-infection from individuals having escaped treatment, or from flies, which are always numerous during the campaigns.

The assumption that a residual germ not reached by the antibiotic may persist on the conjunctival level is not acceptable, as in vivo experiments carried out at the hospital showed that the germ would disappear within three to five hours after aureomycin instillation, and that after three days, the conjunctivae could be considered as definitely freed from Koch Weeks and diplobacilli. This is an experiment we have been repeating for years every week, since all patients undergoing a major surgical operation are bacteriologically examined beforehand and put under observation during the few days preceding the operation.

INEFFICACY OF AUREOMYCIN ON CERTAIN OTHER GERM GROUPS

Some curves show that some germs only, such as the "Xerosis Corynebacterium", are little influenced by a day treatment, and it seems that when the "conjunctivogenous" germs (H. ., Koch, pneumococcus, staphylococcus or gonococcus) disappear, the xerosis corynibacteria become more and more numerous.

This fact led us to substitute other antibiotics for aureomycin, but we are not able to continue this research work, as the three laboratory assistants who were assigned to us were later on withdrawn. I was only able to try spiramycin, personally and on a small scale, and it seemed to me that it had a favourable invluence sumilar to that already obtained by aureomycin.

CONCLUSIONS

It results from my experiences that the part played by the forms of conjunctivitis associated with trachoma should not be disregarded, that the germ associations are extremely frequent, and that the mass campaigns should be maintained, even though they would only result in doing away with the forms of conjunctivit associated with trachoma. It is not my task in this paper to make statement on the outcome of these trachoma campaigns.