นิพนธ์ต้นฉบับ

Non-herpetic microbial corneal ulcers : a prospective study (demographic part).

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One hundred and twenty-five cases of non-herpetic microbial corneal ulcers were prospectively studied in various aspects during a two-year period at Chulalongkorn Hospital. Demographic data showed a ratio of 2.29 : 1.0, male to female, and bimodality in patients' age distribution was shown. 78.4% of cases were central and paracentral corneal ulcers. 88% were classified as moderate and severe grade. Over half (60.8%) of the cases received some form of treatment before persentation. In a higher number of cases (76%), compared with previous studies, we were able to identify predisposing factors through careful clinical approach. A change in the causative organism with increasing trend for Gram negative bacteria (28.2%) and anaerobes (14.6%) were discussed. Polymicrobial infection accounted for 13 of 125 cases and anaerobes constituted tha largest number in this group. Clinical alertness and significance were presented and emphasized.

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ได้ทำการศึกษาผู้ป่วยที่เข้ามารับการรักษาด้วยเรื่องแผลติดเชื้อที่กระจกตาดำชนิดที่ไม่ได้เกิดจากเชื้อเริม ที่โรงพยาบาลจุฬาลงกรณ์ในช่วงระยะเวลา 2 ปี โดยศึกษาแบบวางแผนล่วงหน้า ผู้ป่วยทั้งหมด 125 คน อัตราส่วนระหว่างผู้ชายต่อผู้หญิงเท่ากับ 2.29 : 1.0 ร้อยละ 78.4 มีแผลบริเวณกลางหรือใกล้เคียงตรงกลางกระจกตาดำ ผู้ป่วยร้อยละ 88 มีแผลระดับปานกลางหรือรุนแรง มากกว่าครึ่งหนึ่งคือร้อยละ 60.8 ได้รับการรักษาก่อนมาโรงพยาบาล คณะผู้วิจัยสามารถหาสาเหตุชักนำร่วมในการก่อให้เกิดโรคได้ถึงร้อยละ 76 ซึ่งสูงกว่าจากการศึกษาอื่น ๆ เชื้อซึ่งก่อให้เกิดโรคมีแนวโน้มของเชื้อกรัมลบ และเชื้อแอนแนโรปสูงขึ้น คือ พบร้อยละ 28.2 และ 14.6 ตามลำดับ ผู้ป่วย 13 รายใน 125 ราย เกิดจากเชื้อมากกว่า 1 ชนิด และเชื้อแอนแนโรป เป็นเชื้อที่พบร่วมได้บ่อยที่สุด รายงานฉบับนี้เป็นแนวทางสำหรับจักษุแพทย์ในการดูแลรักษาผู้ป่วยที่มีแผลติดเชื้อที่กระจกตาดำ

Microbial corneal ulcer is one of the major causes of blindness in Thailand[1,2] and other developing countries.[3] Despite many new development in antimicrobial agents and surgical interventions, microbial corneal ulcers still remain a significant problem in many nations of the world. Even with progress in immunology, cellular and molecular biology, our work is still far from complete.[4] In many places, specific etiological diagnosis are still problematic. Information obtained from literatures are very variable and connot be assumed to be representative of all microbial corneal ulcers in different regions of the world. Early demographic studies, especially from most of the developing countries, lacked a standardized clinical and laboratory data. This makes the interpretation and comparison of these data hard to evaluate and gives the impression that not much has progressed in this field.

In Thailand and many other developing countries, a relative scarcity of comprehensive and continuing information of this common discase exists. Lack of facilities in the diagnostic laboratory and trained personnel lead to imprecise data in etiological documentations. The worse part of this scene is the misunderstanding and mismanagement in certain cases which invariably lead to blindness. Previous reports in the country provided inadequate data and often yielded low postitive culture, especially in specific groups of organism such as anaerobes and polymicrobial infections. To help and contribute towards this worldwide problem, we designed a prospective study to look at various aspects of the disease and to objectively encourage a more comprehensive study in this field. In this report we will present the demographic part of the study.

Subjects and methods

We prospectively studied 125 patients who presented with non-herpetic microbial corneal ulcers from December, 1987 to November, 1989. All cases were seen at Chulalongkorn (University) Hospital by at least one member of our team. Most of the cases had been followed up at the specially organized corneal ulcer clinic. All data pertaining to the patients were filled out in a seperate form designed for the study.

Each patient underwent a complete history interview which included age, sex, occupation, present residential area, possible cause of the ulcer, date of onset, past medical history including ocular diseases, history of previous medication and treatment.

Data on eye examination included a record of the location, size (dimension of ulcer), depth and anterior chamber reaction. Corneal scraping was performed on every single case and directly inoculated onto blood agar, chocolate agar, Sabouraud's agar and thioglycollate broth for anaerobic bacteria (vitamin K and potassium iodide solution were used as reducing agents). Gram stain and KOH stain were taken at the same time. Any cases with the clinical suspicion of specific etiological agent would be specially cultured in specific media eg. fresh Escherichia coli-riched media for Acanthamoeba and Lowenstein Jensen media for mycobacterium. Beside Gram and KOH stainings, other stainings also applied in certain cases, such as Giemsa and AFB stainings. All specimens were sent to the microbiological laboratory and the Gram and KOH stains were reported by separate teams of specialized microbiologists who would inform us during the same period of time. Initial treatment was dependent on the staining report. Report on Gram stain included the type and amount of organism (S) seen by the microbiologist and arbitrarily graded into SLIGHT (S), MODERATE (M) and HEAVY (H). Inflammatory cells and KOH stain were also reported and graded in the same manner. Most culture reports were obtained by us within 2-3 days though a longer period was usually needed for fungus. Again, each postitive culture report was coded with SLIGHT (S), MODERATE (M) and HEAVY (H) which represented the degree of growth. Probable contaminants were also coded by the microbiologist.

Results :

125 cases of non-herpetic microbial corneal ulcers were studied prospectively within a 2 year period. Patients' age ranged from 1.5-84 years old. Age distribution is shown in Diagram 1. There were 87 males (69.6%) and 38 females (30.4%).

Data on patients' residential area shows that over half of the patients, 77 cases (61.6%) resided in Bangkok and Samutprakarn (a province, on the eastern side of Bangkok). The remaining (38.4%) came from other regions of the country Diagram 2. shows distribution of patients according to region.

Predisposing factors and associated ocular conditions were found in the majority of cases. Ninety five cases, or 76.0% have some identifiable associated ocular history or abnormal findings. of 125 cases, we could not find any related contributing factors in 30 cases. The frequency of identifiable factors are listed in TABLE 1. Note that the listed frequencies exceed the number of patients (95) this is because some patients had more than one related findings. Among these major categories, 'TRAUMA' is the leading cause in this study group and the history of foreign-body and vegetable-plant material account for a significant proportion.

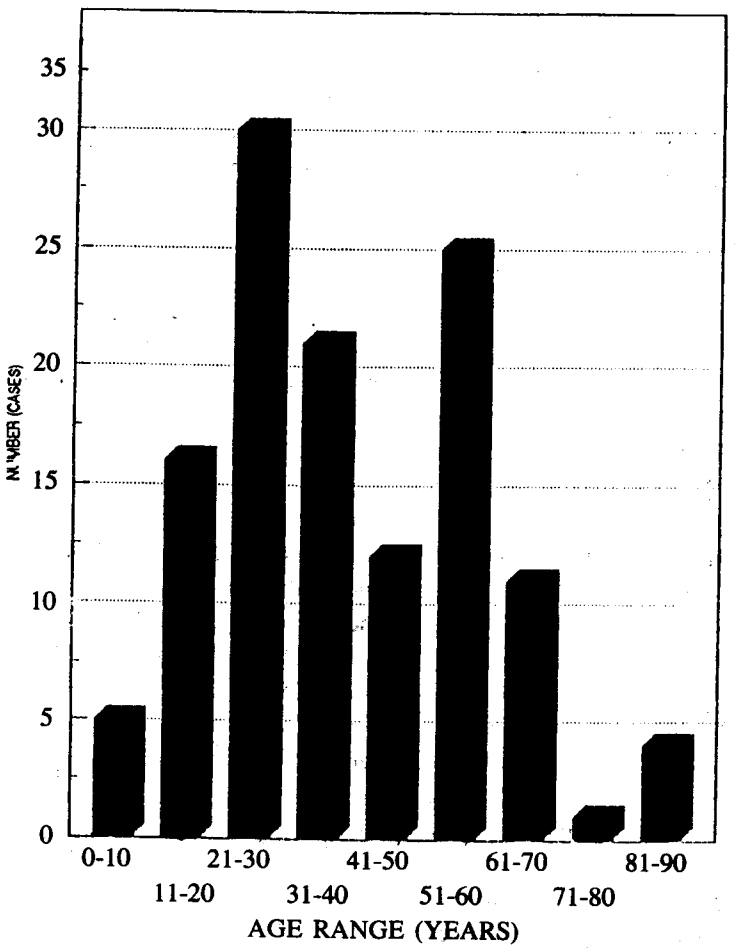

Diagram 1. Age distribution of the patients.

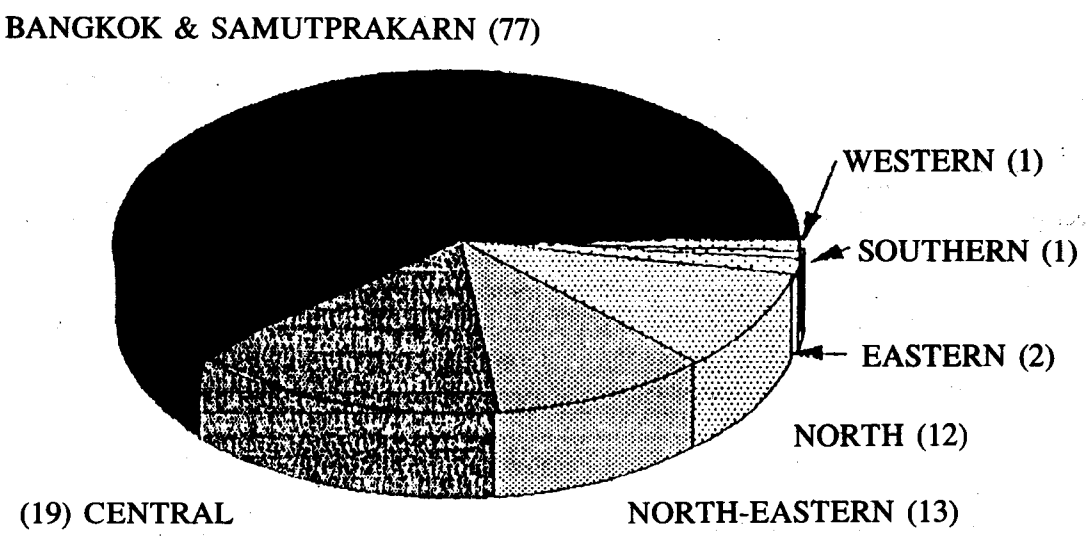

Diagram 2. Residential area of the patients. (At time of developing corneal ulcer) Number in parenthesis represent number of patient.

Table 1. Predisposing factors and associated ocular conditions.

Causes and predisposing conditions	Number
Trauma :	
Foreign body	45
Vegetable-plant contaminants	23
Direct trauma (larger materials)	10
Insect	4
Contact lens :	
Over wearing	2
Normal wearing	3
Corneal abnormalities :	
Previous herpes keratitis	8
Scar from previous ulcer	15
Bullous keratopathy	9
Eyelid abnormalities :	
Lagophthalmos with exposure keratopathy	6
Trichiasis and/or entropion	2
Lid mass	1
Lacrimal drainage system disease	
Chronic dacryocystitis	1
Post-surgical conditions :	
Post-penetrating keratoplasty	4
Post-glaucoma surgery	2
Dry eye state :	4
Prior use of topical steroid	1
Miscellaneous :	
Exophthalmos	2
Optic atrophy	1
Non specific red eye history	5

In this study group, 49 (39.2%) cases had not been treated and 76 (60.8%) had been treated by other medical centers or partially treated by general practitioners. Some treated themselves by purchasing eye medications from the pharmacy without prescription. The duration between symptoms and presentation to Chulalongkorn (University) Hospital are shown in Diagram 3. Seventy-nine cases (63.2%) presented to us within the first week. When looking at each group of ulcers with regard to the causative organism and mean time delay between the onset of symptoms and presentation to us, we found that, in TABLE 2. there is clearly a longer delay in the anaerobic group which took approximately 3 weeks for the patients to be seen by us. While most of the aerobic bacterial group were seen in less than 1 week and an intermediate period of time (1-2 weeks) in the fungal infection group.

Ulcer : clinical features :

The number of ulcers in each location are categorized in TABLE 3. Over 3/4 of cases in this study are central or paracentral corneal ulcers. 'Central' is defined as involvement of the center of the optical zone and paracentral, when ulcer involves part of the optical zone but spare the central 2 mm. area. There were 4 ring shaped ulcers which were due to nocardia (Fig 1) and acanthamoeba (Fig 2) infections. Right eyes were affected in 59 cases, and 66 cases in the left eyes. A comprehensive system of classification of the severity of ulcer into mild, moderate and severe was used as published elsewhere.[5,6] TABLE 4. shows the number of cases in each class of severity.

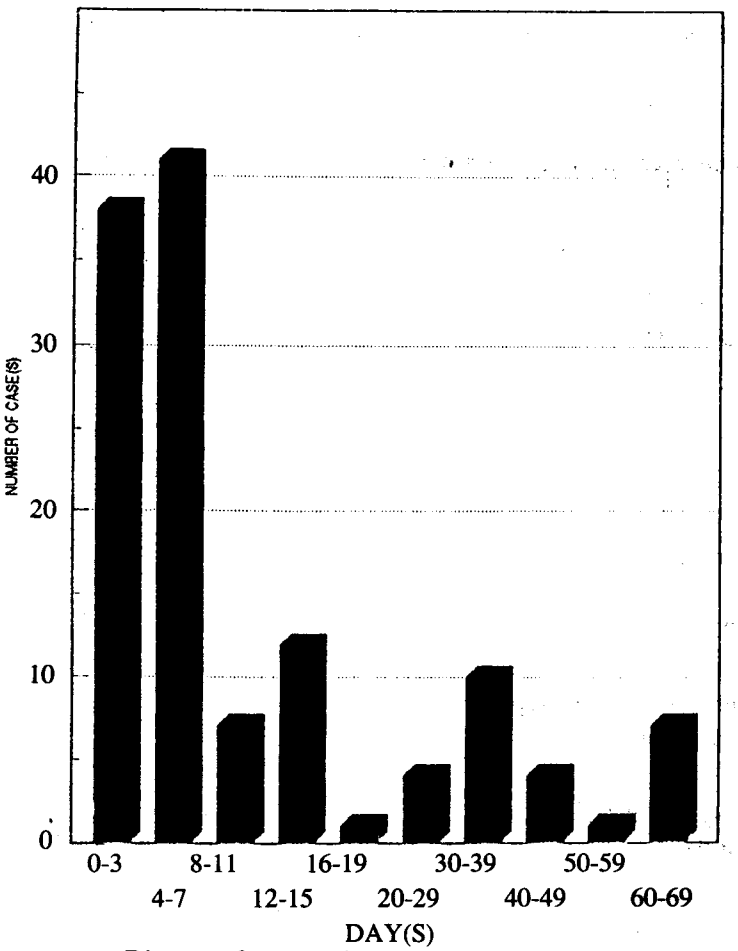

Diagram 3. Duration before presentation.

Table 2. Mean and median time delay before presentation at the hospital. (Central corneal ulcer group).

Causativeorganism		Mean (days)	Median (days)
Bacteria :	Aerobe	4.36	4
	Anaerobe	22.25	20
Fungus :		14.50	7

Table 3. Location of ulcers.

Location	Number of cases	Percent of patients
Central	53	42.4
Paracentral	45	36.0
Mid-periphery	17	13.6
Periphery	6	4.8
Ring shape	4	3.2

Table 4. Serverity of corneal ulcers.

Grading	Numbers	Percent (%)
Mild (grade 1)	15	12.0
Moderate (grade 2)	77	61.6
Severe (grade 3)	33	26.4

Microbiological study

Ninety-one cases (72.8%) were culture positive and 13 cases (14.3%) grew more than one organism. TABLE 5. shows the percentage of all isolates. Again, note that the total number of isolates in TABLE 5. exceeds 91 because there were 13 cases which had mixed or grew more than one isolate and is shown in detail in TABLE 6.

Of the culture positive group, Pseudomonas aeruginosa was the most common isolate, 12.8%. (see TABEL 7.) Staphylococcus aureus and staphylococcus coagulase negative eg. S. epidermidis and other less virulent staphylococci caused 10 cases or 8.0% S. pneumococcus accounted for 9 cases (7.2%), nearly equal to staphylococcus. Fungal isolates was obtained in 34 of 91 eyes or 37.4% overall. (see TABLE 8.) By far the commonest isolate in this group was Aspergillus sp. which accounted for 11 out of the 34. The second frequent isolate was Curvularia. Fusarium and candida were indentified in only 3 and 1 cases respectively.

Table 5. Organisms cultured from 125 cases.

Organism	Isolates	Percent (%)
Aerobic bacteria : Gram's (+)	24	23.3
: Gram's (-)	29	28.2
Anaerobic bacteria	15	14.6
Fungus	34	33
Acanthamoeba	1	0.97

Table 6. Mixed (poly-microbial) corneal infections.

Organism 1	Organism 2 (and 3)
Corynebacterium sp.	Branhamella catarrhalis
Corynebacterium sp.	Enterobacter sp., Neisseria
Propionibacterium sp.	P. aeruginosa
Propionibacterium sp.	P. aeruginosa
Propionibacterium sp.	S. aureus
Peptostreptococcus sp.	Acinetobacter sp.
Clostridium sp.	S. aureus
Clostridium sp.	Fungus (unidentified)
Enterobacter sp.	P. aeruginosa
Klebsiella sp.	S. aureus
H. influenza	S. pneumococcus
Aspergillus	Staph. coagulase-ve
Helminthosporium	Staph. coagulase-ve

Table 7. Bacterial organisms cultured positive.

Aerobic gram-positive:		Aerobic gram-negative:	
S. pneumococcus	9	Vibrio vulnificus	2
S. aureus	6	P. aeruginosa	16
S. coagulase test -ve	4	Acinetobacter	5
Corynebacterium	2	Moraxella	2
Nocardia sp.	3	Hemophilus sp.	2
Anaerobe :		E. coli	1
Propionibacterium sp.	6	Klebsiella	1
Peptostreptococcus sp.	4		
Clostridium sp.	4		
Fusobacterium sp.	1		

Table 8. Fungal organisms cultured positive.

Organism	NO	Organism	NO
Aspergillus fumigatus	4	Curvularia sp.	7
Aspergillus flavus	3	Fusarium sp.	3
Aspergillus sp. (?)	3	Helminthosporium	1
Aspergillus niger	1	Rhizopus	2
Cladosporium	1	Dermatiatious fungi	1
Acremonium kiliensis	1	Mold	1
Cephaliophora irregularis	1	Penicillium	1
Candida	1	Fungus to be	2
Emericella	1	identified (?)	

Stain and culture correlation

Gram stain results were positive in 69 cases (55.2%). 22 of these (31.9%) were correlated with the culture.

Of the 33 patients with positive KOH stains, subsequent culture confirmed the identity of these organisms in 24 cases (72.7%).

Discussion

Each year, the number of patients presenting with various etiological types of corneal ulcers at Chulalongkorn Hospital is high. To focus on the major causative agents, we studied non-herpetic microbial cornal ulcers which included bacterial (aerobic and anaerobic), fungal as well as protozoal ulcers in both the clinical and microbiological aspects.

Demographic data shows that there are two peaks in the age distribution. (Diagram 1.) The highest prevalence is at age 21-30, and the second highest prevalence is at age 51-60 years old. This is a consistent finding and can be compared to any other studies.[7,8] In the younger age group, there is a greater chance of exposure to various kinds of corneal injury while in the older age group, there is a decrease in the self-protection mechanisms of the eye. Not surprisingly, most of the corneal ulcer cases are males. The ratio of male : female is 2.29 : 1.0, which is slightly higher than 2.1 : 1.0 in another series taken from a study in the north-eastern part of the country.[9] Two other studies, one from South Africa[10] and another from New-York[11], showed 80% male predominance while another two studies[7-8] showed no notable excess of males. This serves as a reminder that there are differences in the demography data in these different groups. However, we all know that males are at a greater risk of eye injury in their occupation and

life style. Older people also have the additional factors such as lid abnormalities and post-surgical conditions. (see TABLE 1.) A case with post couching bullous keratopathy had repeated ulcers and Pseudomonas sp. were isolated in both cultures. A case with lid abnormality which thus leads to repeated trauma and tear film disturbance, and so easily develops ulcer.

A careful interview and examination often reveal some evidence of the predisposing or etiologically related factors. In our study, over 3/4 cases had some contributing factors and this should be emphasized to those who care for these patients with corneal ulcers. Treating only the ulcer without looking for a related problem may result in certain cases becoming prone to repeated infections and eventually to lose their vision. Indeed our study is an example of this effort while many other studies have overlooked this point.

As with other studies, the most common predisposing cause was trauma-related but there was also a larger percentage of our patients who had a history of vegetable-plant contaminants compared with other studies. This may only reflect the difference in geographic and occupational aspects of the study subjects.

One of the predisposing causes that we should be increasingly aware is contact lens wearing. We found 5 cases in this study. It is well-known that contact lens wearers have an increased risk of corneal trauma. Even without any abrasion, the cornea may suffer from hypoxia. The decrease in tear exchange under the contact lens also cause a compromise in the clearing function of tear film and lid.[12] Two out of 5 cases of contact lens wearers had culture positive for Pseudomonas sp. but the cultures of both contact lenses and solutions had not been done. There was a case of a young boy student whose contact lens case and saline solution were cultured positive for fungus and KOH stain revealed positive for hyphae but the culture was negative from the ulcer itself. We started treatment as for a fungal ulcer and it healed within 5 days. The isolation of organisms from the ulcer together with contact lens, carrying case and all the solutions are well documented elsewhere,[13-15] and this should not be overlooked. Since one may not be able to obtain positive culture from just the corneal ulcer itself in this specific group, so, in such cases, we would recommend that the possible source of infection also be cultured. However, it is not always the case that organisms will be grown from contact lens, saline solutions and/or carrying case as described in another study.[16] The possible explanations for such cases could be referred to in other studies[17] where sources of infection are not clear.

An important point in the epidemiological pattern is the changing ratio of causative organisms. Increasing reports of Pseudomonas and other Gram negative bacteria as major causative agents in developed countries especially in United States and Europe[18,19] makes us wonder whether this is a real trend of all corneal ulcers or just only true in those developed countries. Data from Katz et al.[20] from a study in Bangladesh showed that Pseudomonas was the most common isolates but seemed to contradict with the laboratory data of Mahajan which was done in India. Mahajan[21] showed 35% positive culture of Staphylococcus and much less for Pseudomonas. Other reports from Nepal[22] also showed that 31% of culture positive were S. pneumoniae and 23% were Stahpylococcus while Pseudomonas accounted for only 10% of 398 cases. Another report from South Africa also stated 38% culture positive for S. pneumococcus.[10] Our study showed 29 of 103 isolates were Gram negative aerobes and one case of Gram negative anaerobe, while 24 of 103 isolates were Gram positive aerobes and 14 of 103 were Gram positive anaerobes. We conclude that in our study, Gram-negative bacteria account for nearly 80% of Gram-positive bacteria. Though there are discrepancies among studies, one can see a definete trend toward a greater number of Gram negative cases and a smaller number of Gram positive cases. As can be shown when Thygeson reported the incidence of S. pneumoniae to be 70% in his 1947 study.[23]

Reports from studies in this country, even the recent one,[8] did not show a positive culture for anaerobic bacteria, while it now generally recognized that many cases of corneal ulcers are caused by anaerobes. Scattered reports have been published.[24,25] We detected 15 out of 125 cases of anaerobic organisms in our study which is different from other local reports. We believe that the actual anaerobe recovery would be more if we had used prereduced media in all cases and also kept the culture specimen for a 5 day report rather than 48 hours. This is because early exposure to oxygen may effect the more fastidious anaerobes including Propionibacterium acne.[26] However, we hope that our study may bring attention to the anaerobic methodology in the future.

We also found that cases with anaerobic bacterial infection (Fig 3 & 4) usually presented late, even later than fungal ulcers. Most of the cases had already moved into the advanced stage which left a dense scar when healed. This again serve to emphasize the significance of an anaerobic culture and its relevance in clinical practice.

There is another important point we would like to point out, and that is to stress that the concept of

"one infection -one organism" is no longer true with corneal ulcers. We found 13 of 125 cases had mixed microbial infection. Anaerobes were the most comnon isolates involved in these polymicrobial infections, and occurred in 6 of 13 cases. Staphylococcus was less frequent, 5 of 13 cases. However, Strep. pueumococcus was involved in only one case, which was a mixed infection with H. influenza. This correlates with Jones' findings that polymicrobial infections usually involve non-pneumococcal streptococcus.[27] As a clinician, one should be aware of the possibility of polymicrobial infection in every case which fail to respond to a given therapy.

Chronic corneal ulcers also deserve some attention. We had a previous case of Acanthamoeba polyphaga which was the first case in Thailand with positive culture, histopathological finding and electron microscopic documentations. In this study, we discovered another case of culture positive acanthamoeba. Beside acanthamoeba, Nocardia and mycobacterium are two other agents which may mimic others and usually run a chronic course. At present, We have found up to five cases of Nocardia sp. (unpublished data) in Chulalongkorn Hospital in this three-year period. All of our Nocardial cases are characterized by a ring-like ulcers and had considerable lag period prior to presentation.

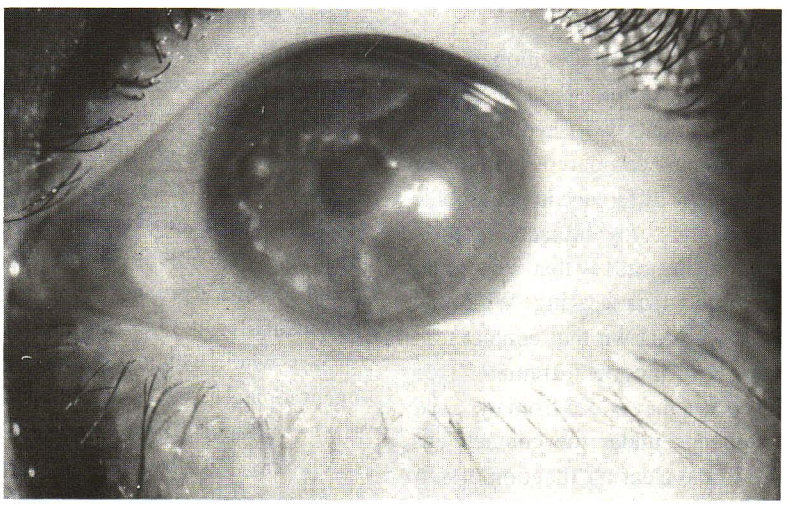

Figure 1. Nocardial keratitis characterized by ring lesion with elevated nodules.

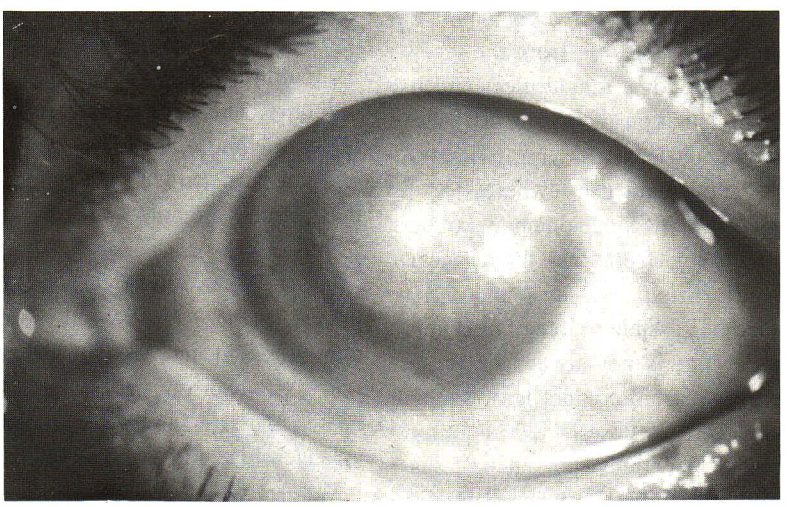

Figure 2. Chronic progressive ulcerative keratitis of Acanthamoeba infection.

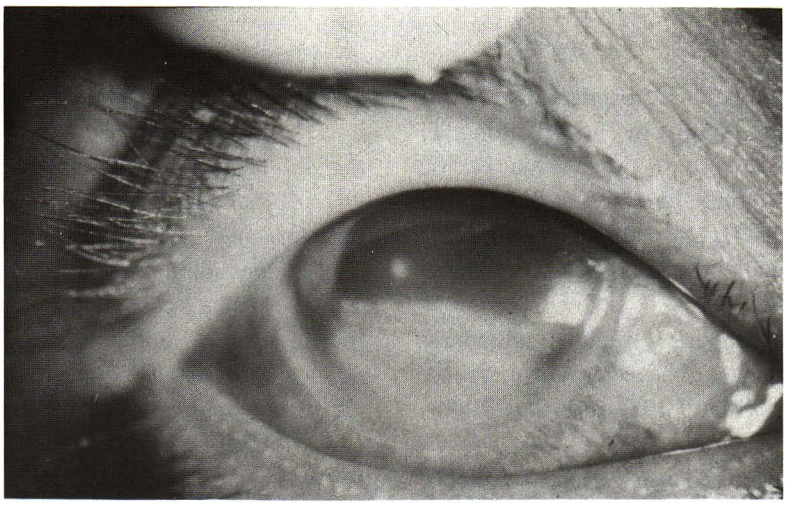

Figure 3. Keratitis caused by clostridium.

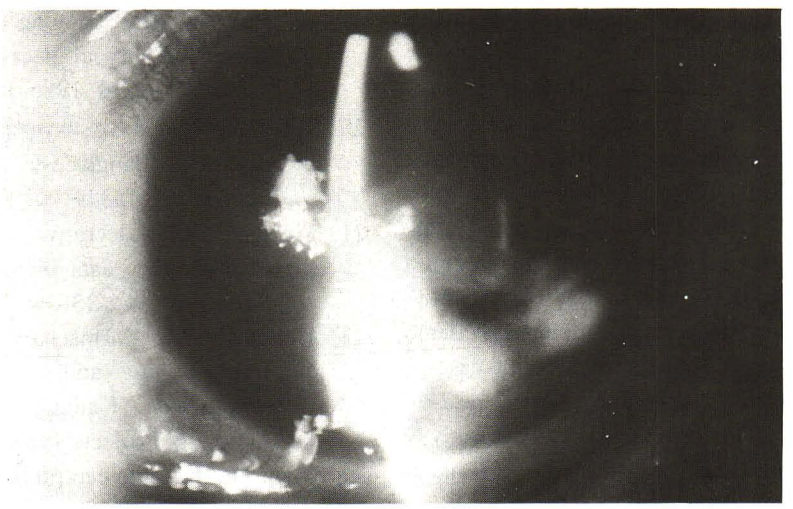

Figure 4. Corneal ulcers caused by peptostreptococcus.

In summary, we have studied this very common eye problem but which still need more data in demographic, clinical and microbiological aspect. We also showed that a significant number of predisposing factors could be learned by comprehensive history interview combined with careful ocular examination which have beneficial effects in the preventive measure of the health care program as well as in each individual case, to diminish the chance of re-infection. The change in microbiological studies and the increasing significance of Gram negative organisms must be emphasized. The importance of anaerobic and polymicrobial infections should not be overlooked. Also rare cases of acanthamoeba and nocardia should be kept in mind when managing these patients. Precise data on this common 'CORNEAL ULCER' condition are needed and can be obtained from local and international study groups.

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