

EFFECTS OF PHOTOCHEMICAL AIR POLLUTION ON THE HUMAN EYE —CONCERNING EYE IRRITATION, TEAR LYSOZYME AND TEAR pH—

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ABSTRACT

This paper is presented to make both ocular symptoms and signs clear, by means of some experiments on the eye affected by photochemical air pollution.

This paper summarizes three experiments, these results and discussion. The first series of experiments were performed in order to research eye irritation caused by photochemical synthetic irritants. They proved the threshold of eye irritation and the grade of irritable pollutants. Effects of photochemical air pollution on the human eye were epidemiologically investigated in the second series of experiments. Tear lysozyme and tear pH were chiefly traced as factors of the affected eye. In the third series of experiments, hen egg lysozyme was examined under various synthetic pollutants to seek what substances reduce the tear lysozyme. As a result, it has been suggested that ozone(O₃) was primarily responsible for its reduction under photochemical smog. Finally in this paper, it has been discussed why ocular symptoms and signs occurred in photochemical smog.

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INTRODUCTION

It was in the summer of 1970 that an attention was paid to the damage to human bodies caused by photochemical smog for the first time in Japan. The incident happened at the playground of a certain senior high school in Tokyo on 18th July, 1970. Some 40 females

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students on the playground suddenly complained about a slight difficulty in breathing, dizziness and irritation of their eyes and throats, and all were taken to the hospital by ambulance. At their subsequent examination the hygienic department of Tokyo Metropolis ascertained that this incident was caused by photochemical smog. As a result of this incident wide-range studies on the effects of photochemical smog upon the human body were initiated in Japan.

In the United States, where the development of motorization took place about 20 years earlier than in our country, it is reported that the city of Los Angeles experienced the problem of air pollution due to photochemical smog as early as the late 1940's. In 1950 Haagen-Smit¹⁾ reported the this new type of air pollution was the gas which was produced in the atmosphere, when the exhaust gas emitted by automobiles reacted to the sunlight. The pollutant gas resulted in doing harm to plants, and causing irritation of the eye and even the cracking of tires.

We have carried out a series of experiments on the eye affected by photochemical air pollution, since the simple survey of the affection to the eye under environmental pollutions was presented in 1974.²⁾ Subsequent researches on the affection to the eye were done to make both subjective and objective signs clear.

At first, one experiment was made for research on the relationship to eye irritation by irritants in synthetic oxidant from 1975 to 1976. Examined irritants were formaldehyde, peroxy acetyl nitrate (PAN), peroxy benzyl nitrate (PBzN). Thresholds and grades of eye irritation were studied with each of a single irritant gas and compound irritant gases, because an air pollution was composed of various irritants.

Another epidemiological study was made throughout two summer seasons (1975–1976) in Tokyo. Those subjects studied were students of a senior high school. When photochemical oxidant was higher, the value of lysozyme in tears decreased significantly and besides there was a tendency that the pH value of tears also decreased. Corneal changes were frequently observed on the day when the oxidant level proved the highest during the 76' investigation period.

Some experiments using the smog chamber were carried in order to trace what substances decreased the lysozyme activity. As a result, it has been suggested that ozone (O_3) was primarily responsible for its reduction under photochemical smog.

A] EYE IRRITATION IN PHOTOCHEMICAL SYNTHETIC OXIDANT

Photochemical oxidant is a secondary pollution produced in the air when the nitrogen oxides (NO_x) and hydrocarbon (H·C) emitted largely by automobiles react to the ultraviolet rays of the sunlight. An oxidant is the general term of the substances which have the potential of oxidizing those which are unoxidizable in the atmosphere. Ozone, aldehyde and PANs are the main ingredients of the oxidant, and then are colorless and non-smog. The incident of the photochemical smog contains other factors as shown in Figure 1.

1) Materials and methods We tried experimentally to observe the effects of each irritating substance in the eye, which consisted of formaldehyde, PAN and PBzN. Furthermore the effects of the mixed gases with formaldehyde, PAN and PBzN on the eye were investigated.

Figure 2 presents the way we exposed pollutants in our experiment. A bag was arranged

THE INCIDENCE OF THE PHOTOCHEMICAL SMOG

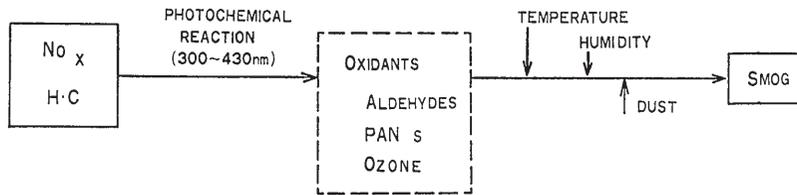


Fig. 1. Photochemical oxidant is a secondary pollution produced in the air when the nitrogen oxides (NO_x) and the hydrocarbon (H.C) emitted largely by automobiles react to the ultra-violet rays (300–430 nm) of the sunlight. Photochemical smog are produced from oxidant and aerosol.

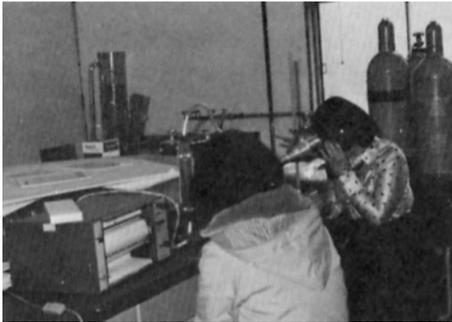


Fig. 2. A bag, seen at the left edge of the photo, was arranged in a such manner that when it was pressed, the gas could flow out of an opening at a rate of 400 ml/min. The testee's eyes were applied to the opening during 300 seconds (see the right edge of the photo).

in such a manner that when it was pressed, the gas could flow out of an opening at a rate of 400 ml/min. The testee's eyes were applied to the opening during 300 seconds. The irritant concentrations were measured through the flowing gas in this way. The testee's eye was observed with the slit-lamp before and after the experiment. The numbers of testees were a range between 10 and 22 and there was the range of age from 19 years old to 32 years old. The gases used in this experiment and their measurements^{3)~5)} are shown in Table 1.

Eye irritation was evaluated as Response Delay Time (RDT) in seconds. Eye Irritation (EIL) was classified in 4 grades as shown on Table 2.

2) *Results* Threshold values of eye irritation (represented with RDT) were indicated in the concentration of 0.2 ppm for formaldehyde and 0.05 ppm or more for PAN and 0.01 ppm or more for PBzN. The relation between EIL and the concentration of each

Table 1. The gases used in this experiment and the methods of their concentration measurements

substances	concentration measurements
H·CHO	Acethyle acetone method
PAN	Gas chromatography with ECD
PBzN	Gas chromatography with ECD
O ₃	Ethylene chemiluminescence method

Table 2. Quantification of eye irritation

Grade	Complain
0: None	
1: Barely noticeable	Light windy Touch, Dry Feeling Conscious Blinking
2: Light (Strange Feeling)	Itching, Light Tingling Frequent Blinking
3: Moderate (Foreign Body Sensation)	Foreign Body Sensation Smart Feeling Oppressive Pain
4: Severe (Pain Reflex)	Sting Pain Tearing Not to open The Eye

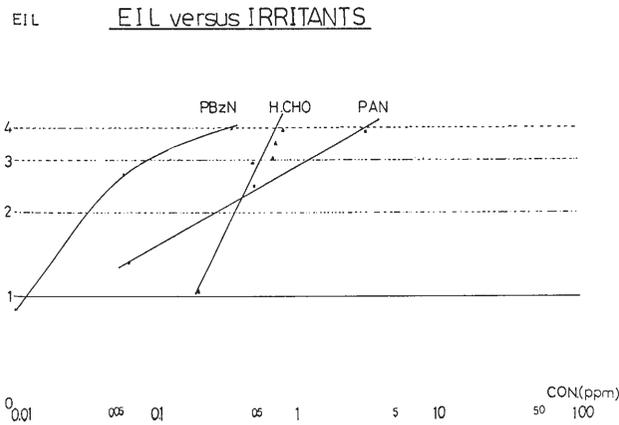


Fig. 3. Formaldehyde and PBzN have a steep inclination at the point from “barely noticeable” to “severe” level. On the contrary the curve of PAN shows a gentle slope and reaches the “severe” level at the point of 3 ppm.

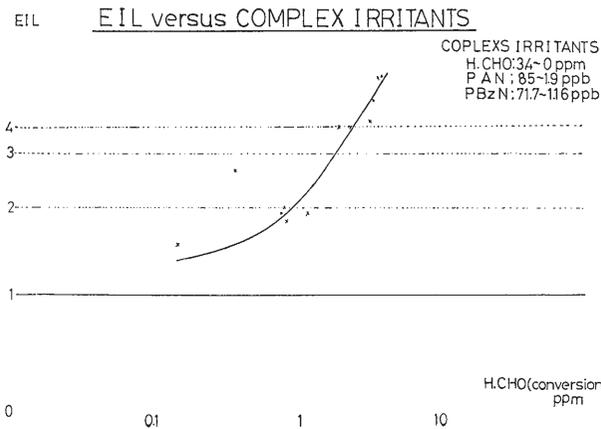


Fig. 4. EIL of the mixture of formaldehyde, PBzN, PAN and O₃ indicated the steep inclination. Threshold value of the eye irritation (represented with RDT) was indicated in the con. of 0.14 ppm for the mixed gas.

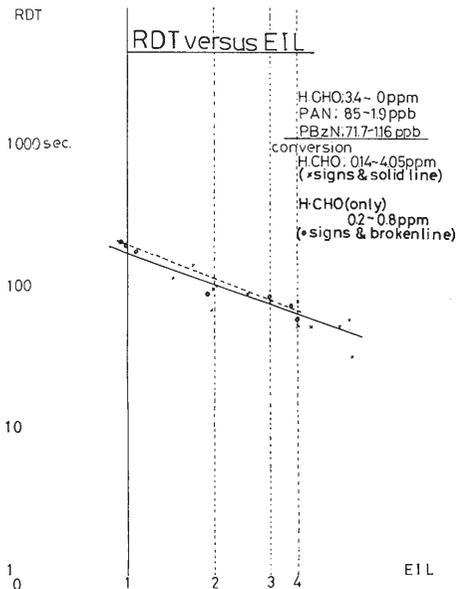


Fig. 5. The relations between RDT and EIL were indicated as regard to formaldehyde and the mixed gas. Until EIL reaches "severe" level it takes 62 seconds in case of formaldehyde, while in case of the mixture gas the same fact occurred at 58 seconds. On the contrary, "barely noticeable" level begins at 153 seconds in the former case and then in the latter case, at 121 seconds. Both results are almost similar.

pollutant gas shown in Figure 3. Formaldehyde and PBzN have a steep inclination as the point from "barely noticeable" to "severe" level. On the contrary the curve of PAN shows a gentle slope and reaches the "severe" level at the point of 3 ppm.

As shown in Figure 4, EIL of the mixture of formaldehyde, PAN, PBzN and O₃ indicated the steep inclination. Threshold value of eye irritation (represented with RDT) was indicated in the con. of 0.14 ppm for the mixed gas. It has been revealed that in the mixed gas the concentration can be obtained by making an arithmetical summation of those for each irritant, when they converted to formaldehyde's concentration. The same results were represented in the relation RDT and EIL as shown in Figure 5. Until EIL reaches "severe" level, it takes 62 seconds in case of formaldehyde, while in case of the mixture gas the same fact occurred at 58 seconds. On the contrary, "barely noticeable" level begins at 153 seconds in the latter case and then in the former case, 121 seconds.

The results of experimental corneal epitheliopathy are shown in Table 3. It is remarkable that superficial keratitis occurred in the very low concentration of PBzN as a common experimental condition.

Table 3. It is remarkable that superficial keratitis occurred in the very low concentration of PBzN as common experimental condition

Irritant	Con. (ppm)	Exposure time (sec.)	K.S.D. (No. of cases)	Incidence (%)	Monitors (No. of cases)
H-CHO	0.5	300			
PAN	0.5	300	4	22	18
O ₃	0.4				
PBzN	0.01 ~ 0.05	300	5	31	16

B] THE EFFECTS BY PHOTOCHEMICAL SMOG ON LYSOZYME AND pH IN TEARS

In 1968, Sapse⁶⁾ reported that the lysozyme activity in tears decreased when photochemical smog took place. We conducted an research on following factors of tear lysozyme, tear pH, the damage of the corneal and eye irritation.

1) *Materials and methods* In order to investigate the human eye affected by photochemical smog, epidemiological examinations were carried out 7 times during two summer seasons. The subjects studied were students who belonged to a senior high school in the southwestern area of Tokyo. The numbers of subjects were from 43 to 28 as shown in Table 4 and all subjects were 16 or 17 years old. On a typical summer afternoon between 1 and 4 o'clock prone to photochemical smog, each of examined items were performed, which consisted of the concentration of oxidant at the testing place, eye irritation, the tear lysozyme value, the tear pH and the slit-lamp examination (only in 1976).

Measurements of air pollutant gases were carried out by the conventional methods in Japan. Subjective symptoms of eye irritation were asked in all. The tear pH was measured by both colorimetric method in 1975 and a glasselectrometric method in 1976.⁷⁾ The lysozyme values were measured by the lysoplate method as previously reported.⁸⁾

Table 4. The subjects studied were students who belonged to a senior high school in the southwestern area of Tokyo. The numbers of subjects were from 43 to 28 and all subjects were 16 or 17 years old boys.

Subjects			
1975		1976	
	n		n
June, 4	39	June, 9	43
June, 9	37	June, 23	43
June, 19	28	July, 8	35
July, 4	39		

2) *Results* The investigations of 1975 and 1976 are presented collectively in Table 5. The value of the tear lysozyme decreased significantly in both years on a day when the oxidant concentration was the highest.

Both $1700 \pm 599 \mu\text{g/ml}$ and $1165 \pm 397 \mu\text{g/ml}$ show a statistically significant decrease as compared with those on each of control days. Each significant "p" value was shown on Table 5. While the mean value of the tear pH was 7.13 on the control day, it was 6.98 at the highest oxidant level in 1975. There is a significant decrease ($p < 0.01$). In 1976, the similar tendency was observed but there was no a statistical significance.

On a slightly rainy day as a control there were none at all who complained of any irritation of the eye, but when the oxidant level increased above 0.01 ppm, 2-22% range of all testees complained of eye irritation.

As shown in Table 6, those two factors of the human tear lysozyme (HTL) and the tear pH were varied by means of eye irritation and the corneal epitheliopathy. When HTL activity with corneal erosion was compared with that of no corneal changes, a statistical significance ($p < 0.05$) was obtained between the two mean values of HTL activity. However, the mean value of the tear pH in cases of the corneal epitheliopathy was a higher level than that without it.

Table 5. The results of 1975 and 1976 are presented collectively. The value of the tear lysozyme activity decreased significantly in both years on a day when the oxidant concentration was the highest. As regard to the tear pH, the same tendency was observed in 1975, but in 1976 the similar tendency was obtained.

Mean value & S.D. of lysozyme & pH in the tear (1975)

Date	Oxidant (ppm)	N	Lysozyme ($\mu\text{g/ml}$)	pH
6/ 4	0.135	39	2117 \pm 426	6.99 \pm 0.25
6/ 9	0.165	37	2037 \pm 712	7.15 \pm 0.32
6/19	0.210	28	1700 \pm 599*	6.98 \pm 0.21*
7/ 4	0.033	39	2166 \pm 700	7.13 \pm 0.23

* P < 0.01, compared with July, 4.

(1976)

Date	Oxidant (ppm)	N	Lysozyme ($\mu\text{g/ml}$)	pH
6/ 9	0.02	43	1671 \pm 713	7.24 \pm 0.23
6/23	0.10	43	1774 \pm 518	7.24 \pm 0.19
7/ 8	0.175	35	1165 \pm 397*	7.16 \pm 0.21**

* P < 0.001, compared with June, 9 & 23.

** P < 0.1, compared with June, 23.

Table 6. Those two factors of the human tear lysozyme and the tear pH were varied by means of eye irritation and the corneal epitheliopathy. When HTL activity with corneal erosion was compared with that of no corneal changes, a statistical significance ($p < 0.05$) was obtained between the two mean values of HTL activity. However, the mean value of the tear pH in cases of the corneal epitheliopathy was a higher level than that without it.

Date	Items	No. Cases (or Eyes)	Lysozyme ($\mu\text{g/ml}$)	pH
7/8	Eye irritations	+ 4	826 \pm 271*	7.14 \pm 0.17
		- 31	1208 \pm 389	7.16 \pm 0.22
	Corneal erosion	+ 16	931 \pm 231**	7.25 \pm 0.23
		- 54	1234 \pm 409	7.13 \pm 0.20

* P < 0.1

** P < 0.05

C] HEN EGG LYSOZYME (HEL) IN SYNTHETIC AIR POLLUTANTS

1) *Materials and methods* HEL activity was examined under various air pollutants in the smog chamber. The concentration of HEL was 5 mg/ml and then 3 μl of this solution was absorbed in the filtrating paper, which were punched out at 6 mm diameter. 10 sheets of this paper were exposed with one air pollutant in the smog chamber under 100% humidity. HEL activity in exposed sheets was measured by lisoplate method. The value of HEL activity at non-exposure was defined as 100%. 10 experiments for one pollutant were repeated, and then the average values were picked up.

2) *Results* Figure 6 shows that HEL activity remarkably decreased with ozone in 40 minutes. Under exposure to 0.1 ppm of ozone, HEL activity decreased down to 68% in 20 minutes and then still down to 65% in 40 minutes. Under exposure to it (0.2 ppm),

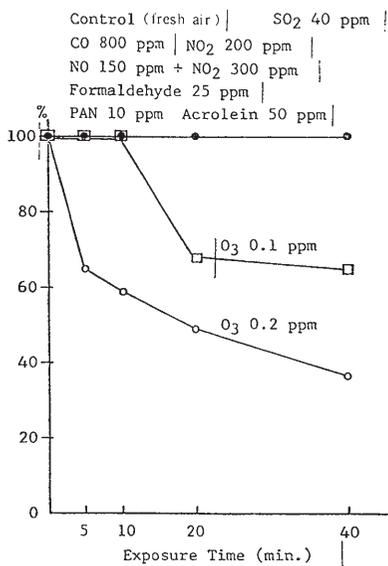


Fig. 6. HEL activity remarkably decreased with ozone in 40 minutes. Against other air pollutants, no decrease occurred at all.

HEL activity much decreased to 65% in 5 minutes and then decreased further down to 39% in 40 minutes. Against other air pollutants, occurred no decrease at all.

D] DISCUSSION

Since the shocking episode of Rissho High School on July 18, 1970, the authorities in protecting against photochemical smog have advocated that those who suffered from respiratory symptoms, eye irritation, headache and others are requested to report. They have announced a photochemical smog warning whenever oxidant level exceeds 0.15 ppm.

Accordingly, human health disturbances by photochemical smog must establish themselves on their criteria, causes and effects.

1) *Eye irritation in laboratory experiments* Most laboratories that measured eye irritation from synthetic smog also tested the responses of their panels to formaldehyde, acrolein and other irritant gases. Threshold concentrations in Table 7 were summarized by Wilson⁹⁾ and seemed to be in a relative wide range. Probably, this concerns the measurement of irritant gases, quantification of eye irritation and sensitivity of testees.

Threshold value of formaldehyde in our experiments is similar to that reported by Stephens.¹⁴⁾ Threshold values of PAN and PBzN are slightly lower than those previously reported.

Furthermore, threshold value of mixed gases with formaldehyde, PAN, PBzN and O₃

Table 7. Threshold concentrations were summarized by Wilson and then seemed to be in a wide range.

Estimated eye irritation threshold values

Irritation level	Irritant concentration, ppm					Reporters
	O ₃	Formaldehyde	PAN	PBzN	Acrolein	
Barely noticeable	—	1.5	—	—	0.6	SCHUK, E. A., <i>et al.</i> : 1959 ¹⁰⁾
Threshold	> 1.8	3.0-10	—	—	0.6-1.3	JONES, M. H.: 1962 ¹¹⁾
Light	—	0.1	—	—	—	SCHUK, E. A., <i>et al.</i> : 1966 ¹²⁾
0.5 on 0-3 scale	—	1	—	0.05	—	HUESS, T. M., <i>et al.</i> : 1968 ¹³⁾
No irritation	—	0.25	—	—	—	HUESS, T. M., <i>et al.</i> : 1968 ¹³⁾
Threshold	—	1	0.5-1	—	0.5	STEPHENS, E. R., <i>et al.</i> : 1968 ¹⁴⁾
Threshold	—	—	0.25	—	—	RAVEN, P. B. ¹⁵⁾
Threshold	> 0.75	—	—	—	—	BATES, D. V., <i>et al.</i> : 1972 ¹⁶⁾
Threshold	> 2.2	—	—	—	—	HINE, C. H., <i>et al.</i> : 1961 ¹⁷⁾

Table 8. Eye irritation degree and eye irritation threshold are as shown above. Threshold value of formaldehyde in our experiments is similar to that reported by Stepehn. Threshold values of PAN and PBzN are slightly lower than those previously reported. Furthermore, threshold value of the mixed gas with formaldehyde, PAN, PBzN and O₃ was found to be 0.14 ppm. It is first reported that eye irritation of compound irritant gases was researched, in so far as it is known.

Eye irritation degree	Eye irritation threshold values		
	Irritant	Con. ppm	
PBzN > PAN > H-CHO	Simple	H-CHO	0.2
		PAN	>0.05
		PBzN	>0.01
	Complex	H-CHO	
		PAN	0.14
		PBzN	

was found to be 0.14 ppm. It is first reported that eye irritation of compound irritant gases was researched, in so far as it is known. Previous studies have shown that the intensity of eye irritation from synthetic smog correlates reasonably well with measured level of formaldehyde, acrolein, PAN and PBzN. And then we had also the same results as shown in Table 8.

2) *Epidemiological investigations in photochemical smog* By means of epidemiological investigations over two years, there was a significant decrease in HTL activity and human tear pH when oxidant level exceeded 0.17 ppm. Generally, the higher the oxidant level was, the less HTL activity was. In 1968, Sapse⁶⁾ reported that the mean values of HTL activity of those who complained of eye irritation decreased to 60%, in comparison with those of normal persons when they investigated at the middle oxidant level. In 1972, Pietsh¹⁸⁾ reported that the decrease of HTL activity occurred at the oxidant level of 0.19 ppm, but not at the level of 0.16 ppm.

Our studies may also suggest that activity and tear pH decreased altogether when the oxidant level was kept continuously between 0.15 ppm and 0.2 ppm for 2 hours. In this condition, there were significant decreases of two factors in comparison with those of control day. The similar results were obtained when its level continued to change from 0.15 ppm to 0.17 ppm for 1 hour.

Shimizu¹⁹⁾ too described that the measurements of HTL activity and the tear pH could make parameters for the eye damaged by photochemical smog.

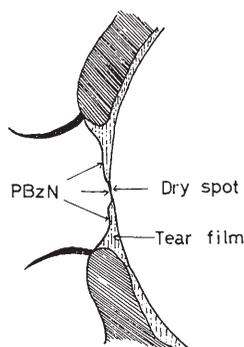
Kabayama²⁰⁾ previously reported that acute superficial keratitis was observed under higher oxidant level. Its clinical findings have been confirmed in our results.

3) *Ocular signs and symptoms in photochemical smog* —containing also their mechanisms— The ocular findings that are obtained from a series of our experiments on the eye affected by photochemical smog are found to be eye irritation, acute (or subacute) superficial keratitis, the decreases of HTL activity and the tear pH. Although each of them had already been prescribed by many authors, four ocular findings have not yet been discussed together. This paper will be the first in which the eye damaged by photochemical smog is integrally discussed.

Table 9. Polluted chemical substances are the smallest and their size is about from one a thousand to one a ten thousand in comparison to that of bacteria. Human may have partially controlled them but for the most part of them, let them loose.

The alteration of host-parasite relationship			
Kind	Size	Character	Research stage
Bacteria		Independent life cycle	Almost hunted. Already overcome.
Virus	*1/10 ~ 1/100	Dependant life cycle	Battle is half over.
Chemical substances	**1/1000 ~ 1/10000	Diffusion & accumulation	Partially controlled. But for the most part, let those loose.

*, **; Those values are comparative versus bacteria.



Schema: the epitheliopathy caused by PBzN.

Fig. 7

Structure and Composition of the Tear Film

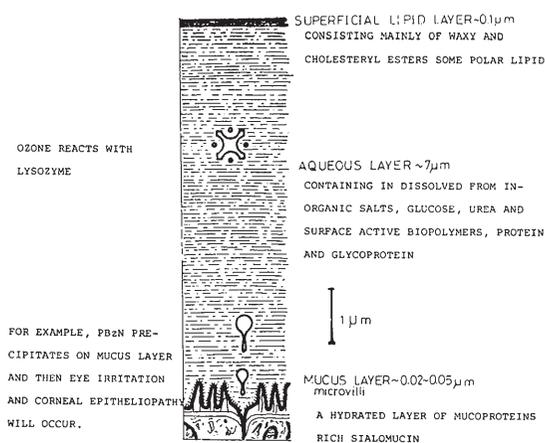


Fig. 8

- Fig. 7. Air pollutants which consist of both irritant and non-irritant gases conflict the eye continuously, where the average speed of them seems to be as fast as that of the pellet but the free pathway of them is as tiny as 10^{-7} m or less.
- Fig. 8. Air pollutants can be soluble in the tear film. First, the tear pH is inclined to be acidic by oxidant. Secondly, as like the tear lysozyme, the enzymatic system in the aqueous layer may be disturbed by both irritants and non-irritants. Thirdly, for example, PBzN will be precipitated into the mucus layer and then can cause the eye irritation and the corneal epitheliopathy. (The schemata of the tear film shown in Fig. 7, and 8 are quoted from Holly and Lemp^{2,1)})

Generally speaking, environmental pollution will expand itself widely still in future, since polluted chemical substances have been covering in the earth. As shown in Table 9, our ophthalmologists must bring an action against the very small substances because we are coexisting with environmental pollution.

The mechanism which caused the ocular symptoms and signs by photochemical smog is almost unknown. But the effective reasoning can be offered on the basis of scientific aspects. Air pollutants which consist of both irritant and non-irritant gases conflict the eye continuously, where the average speed of gases seems to be as fast as that of the pellet.

Of course, the free pathway of them is as small as 10^{-7} m or less. As shown in Figure 7 and 8, air pollutants can be soluble in the tear film. First, the tear pH is inclined to be acidic by oxidant. Secandarily, as the tear lysozyme activity was found to be inactivated by ozone, the enzymatic system in the aqueous layer may be disturbed by both irritants and non-irritants. Thirdly, for example PNzN will be precipitated into the mucus layer and then can cause the eye irritation and the corneal epitheliopathy.

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