Severe eye burns. pH changes? Nothing more to treat? Foundation of new approaches in research and clinical treatment in eye burns

Schrage NF, Blomet J; Tombach- Frentz M., Reim M
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Abstract:
Eye burns up to now have been understood as contact of the eye or skin with irritants and aggressive chemicals. Mostly the pH is used to estimate damage capacity of chemicals. This concept has been argued to be insufficient and clinical gradings were added to give prognostic hints. Moreover irritants used in cosmetics have been tested since 50 years with the Draize test without any chemical concept of knowing what is harmful and which substance not.
Due to a lot of clinical experience, cooperation with chemists and new concepts in research we want to elucidate the role of chemical dissociation pK, acid and base on the pH, the concentration and dissociation dependent effects on osmolarity and the current treatment concepts fromthis pointof view. Why do chemical corrosives interfere with cells and live processes? An answer to this question might be the amphoteric character of amino acids under physiological conditions. To preserve this and to keep amino acids far from their inactive salt forms must be one concept in treating chemical burns.

Exept Mr. J. Blomet all authors declare that they have no financial interest in this publication
Mr. J. Blomet is chemist. He is the president of PREVOR company which owns the
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CHEMICAL UNDERSTANDING OF EYE BURNS

Chemical ocular burns are the direct result from the action between the aggressive chemical products and the physiological environment. The clear understanding of the mechanism of action enables to anticipate the efficiency of first aids.

1. Anticipation of the reactions: Released energy

The reactivity of an acid or a base is bound to its aptitude to split up. This capacity of dissociation is measurable on a pKa scale. When an acid reacts with a base, the released energy depends on the difference between the pKa. More precisely, the acid (or the base) will react with the base (or the acid) which will have the most extreme pKa value.
To anticipate the reactions,the face to face products are placed on a pKa scale. The most extreme acids and bases will react. We talk about the longest diagonal that will firstly react (Diagram 1). The more an acid or a base is dissociated, the more it will react with another base or acid.

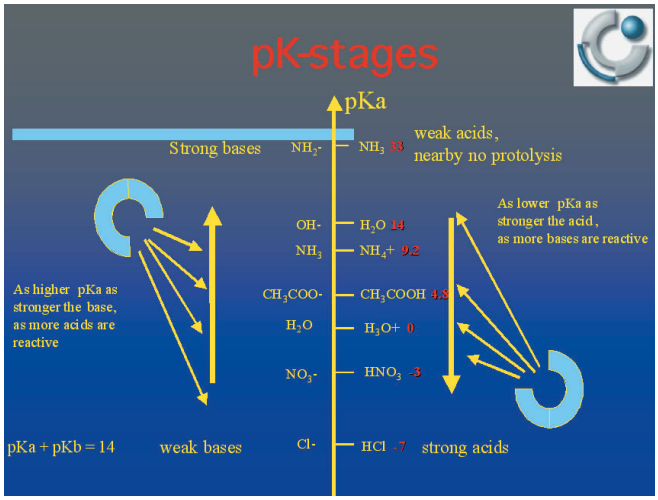

Fig. 1: pKa scale with chemical possible ways of reaction. Examples of Fig 2 illuminates the reaction pathways

2. pH and pKa

The pH depends on the quantity of free H^+ or OH^- ions. The difference between the present amount of dissociated H^+ or OH^- ions and the total available quantity of H^+ or OH^- ions during continuos release can be very high. This total and fianally available real quantity of the chemical agent decides on the amount of tissue that consequently can react and therefore may be chemically damaged, i. e. be burnt.
For instance, ammonia has a pH less high than soda for the same concentration, because it is less dissociated. But despite that, the burn with ammonia is as severe as with soda because ammonia will be as well in contact with the same tissues (as we will see that later).
A very low or very high pH is always an unfavourable pre-

dictor of chemical burns, but neutral pH does not indicate harmless substances due to the possibility of non-dissociated active products.

3. Properties of the physiological environment

Water can react as an acid (pKa = 14) or as a base (pKa = 0). This means that no acid with a pKa value inferior to 0 and that no base with a pKa value higher than 14 can exist in water. It is dissociated right away. This is why all the active bodies have inevitably a pKa between 0 and 14. Therefore, they are generally very little dissociated. Thus the glycine will be in an physiological environment (7) under the form NH^+_3 - CH_2 - COO (or NH_2 - CH_2 - COOH) stable by resonance:
(The formulas should be checked to be correct, may be more extensively explained)

NH^+_3 - CH_2 - COOH ➔ NH^+_3 - CH_2 - COO + H^+ pKa = 2,35

NH^+_3 - CH_2 - COO ➔ NH_2 - CH_3 - COO + H^+ pKa = 9,25

Most of the amino acids (see table) are a little dissociated at the physiological pH except for the acids that have a $pKa_1 < 7$ or a $pKa_2 > 7$

4. Evaluation of the chemical action according to pKa and concentration

The physiological environment of Skin, tears, conjunctiva and cornea consists of molecules that can act as acids or as bases and others that are weak acids or weak bases.

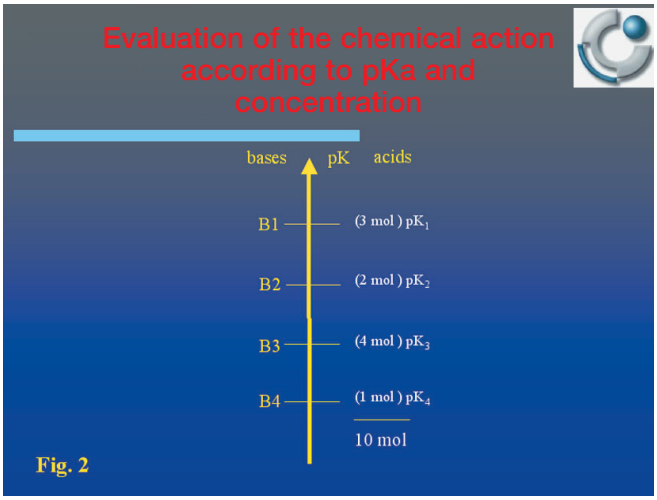

Fig. 2: To faciliate understanding we assume simplified that action of an acid acts on a total group of only four bases as our "physiological environment" The possible reactions of this acid acts in the way Fig 3 explains

Nevertheless, they all have distinct pKa between 0 and 14. Each of these bodies may be placed on a pKa scale with its respective concentration. In the following section we explain on a simplified example how reactions take place and that, dependent on the reactive partners, pKa decides on the amount and way of reactions.

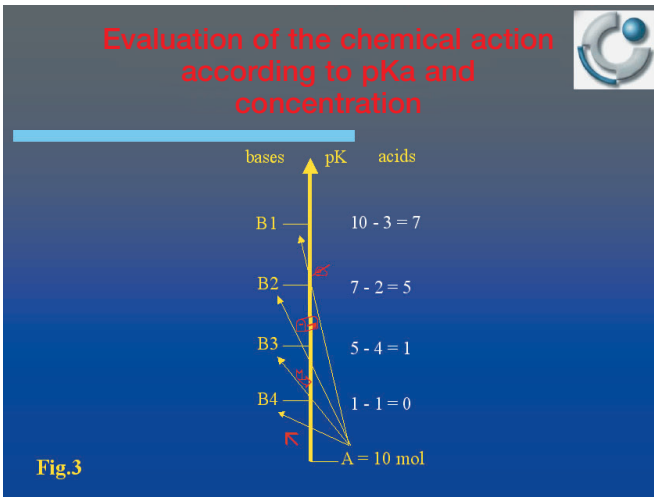

Fig. 3: One acid "A" with an assumed rather high concentration of 10 mol and a pKa < pK4. "A" will attack in the following order B1, B2, B3, B4 and therefore will change the molecules totally and destroy our physiolgical system. This equals a total burn.

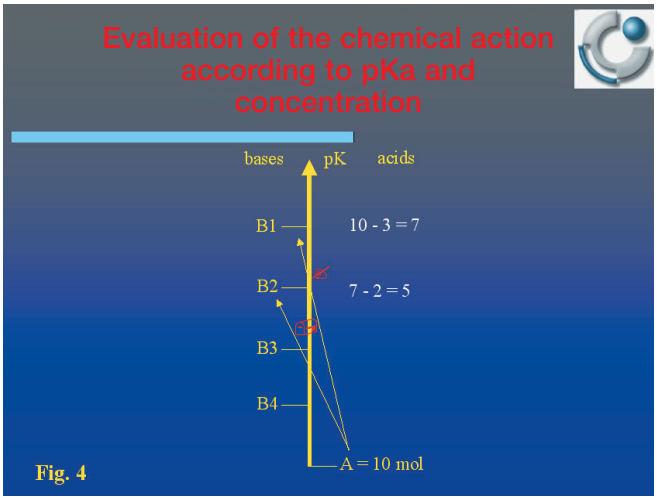

Fig. 4: If A is still present in an amount of 10 mol, but with a pKa between those of Base 2 and 3, pK2 and pK3, then Acid A will attack B1 and B2. Because their pKa´s are superior, these two reactions are possible. But if the amount of A exceeded that of Base 1 and Base 2, the reaction will stop even ifthere is still an amount of e.g. 5 mol of Acid A present. Consequently, the damage will be less than in Fig. 3 The mechanism of Fig. 4 will probably resemkble only an irritating agent, damaging less severe than that in Fig. 3..

(I suspect, that in Fig. 4 is an error. Why did you not place the Acid A more up between bases 2 and 3??)

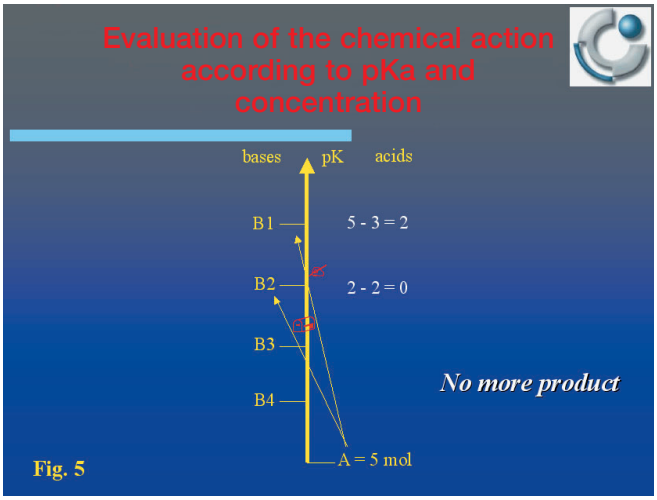

Fig. 5: If the acid A is present in a smaller amount than in Fig 3 and 4, e.g. of 5 mol with a pKa < pK4, this acid A will react with the bases B1 and B2 having the extremely low pKa untill acid A is totally consumed. Then the reaction will stop. We should have an effect of an irritating agent. This is why strongly corrosive products may become, at a weak concentration, irritating agents.

5. Chemical burn and first aid therapy.

Following our examples of the previous section we know that the attack of a chemical product will modify the pH as result of diagonal reactions defined by specific pK of the reactants. To treat a chemical emergency the need is to prevent the chemical product from acting by introducing a chemical reactive product which will react in priority on the aggressor and will release the amino acids of the native tissues in order to re-establish their amphoteric properties.
The problem in therapeutic intervention normally is that we do not know and there is no time to decide which type of intervention antic-acid or anti-base to take. Therefore, we believe that a therapeutical system should manage both situations.

A buffer solution will react by a acido-basic reaction in producing the opposite acids or bases which do not fundamentally solve the problem. Actually, the buffer solution will mainly readjust the pH changing molecules within the tissues but this re-establishing of pH does not re-establish physiological pKa of tissue molecules. This is the chemical reason of corneal calcification after rinsing with Phosphate buffer shown by Schrage et al.[2].
In case of normal pH this will mean that all amino acids are present in the dissociated form of weak aminic and carboxylic dissociation as real amphoters except asparaginic acid which under normal conditions of pH of 7 will be completely acidic and aminic dissociated. On Tab. 1 there is a very interesting observation to be seen. In the third column, there is a gap in the aminic acid dissociation constant pK between 4,8 and 9. This describes (does this mean: "corresponds to a pH of 7.0 to 7,6, in which cells survive in tissue cultures and describes the limits between which human beings survive in alcalosis or acidosis"?) by means of pH the concentration of maximal surviving of cells in tissue culture and in much narrower limits of 7.0 to 7.6 the conditions of surviving of human beings in extreme acidosis or alcalosis.
The background of this is the supposed capability of proteins and aminic acids to act as real amphoteric moleculse and not as salts. This describes the underlying mechanism of biological reactive systems and leads to a concept of treatment with excess of ions of higher pKa than the biological tissues offer.
Diphoterine® is a molecule with a pKa I = 5,3 and pKa II = 9,1. It covers the total span of biological susceptible tissues, and therefore is able to protect them from chemical reactions. Diphoterine® will interfere in reacting first (in modification of the diagonal of Fig. ??) and protect the physiological components such as amino acids.[3] (What is second?)
Interestingly Tab. 2 shows the dissociation constants of the different dissociation steps of the commonly used first aid buffer solutions. Always the first dissociation step lays within the span of the amino acid gap of dissociation between... This is meaningful concerning our (?) chemical concept being introduced before. Nevertheles in contrast to real (natural?) amphoteres (what does that mean???), Diphoterine® that behave only with these two pKa and pKb without salt formation the type of buffering action is different forming salts. The further dissociation steps interfere with those of

pK a	Acid	Base (plus Proton)	pKb	
6.52	H_2CO_3	$HCO_3^- + H^+$	7,48	bicarbonate buffer
10.4	HCO_3^-	$CO_3^{2--} + H^+$	3.6	
7,12	H_2PO_4	$HPO_4^- + H^+$	6,88	phosphate buffer
12.32	HPO_4^-	$PO_4^{2-} + H^+$	1.68	
4,75	CH_3COOH	$CH_3COO^- + H^+$	9.25	acetate buffer
9.28	H_3BO_3	$H_2BO_3^- + H^+$	4.72	boric buffer[5]
12.74	$H_2BO_3^{2-}$	$HBO_3^{2-} + H^+$	2.04	
13.79	HBO_3^{2-}	$BO_3^- + H^+$	0.21	

Tab 2: pK a values of currently and possibly clinically used buffer solutions[4].

amino acids and might produce new reactive partners into the tissues with extreme pKa and pKb dissociation constants. We doubt that this concept of buffering has one major obstacle in interfering with the equilibrated amphoteric gap of the aminoacids between 4.8 and 9. This gap and its functionality for biological actions under physiological conditions is essentially to maintain or to restore. Otherwise amino acids are present as salts and biological - chemical action stops. (Was wollen Sie hier zum Ausdruck bringen?)

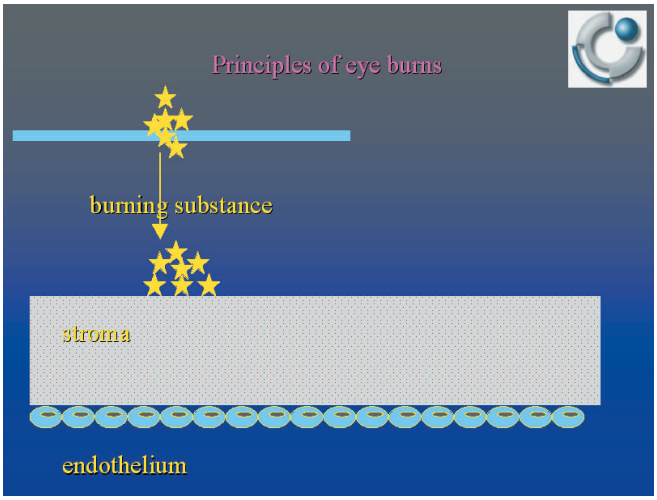

Fig 6: burning substance touches the corneal surface

ACUTE EYE BURNS:

If a highly concentrated agent touches the eye it attracts water from tissue and tears by osmotic forces. The dilution process of the agent begins into the tissue overwhelming protective mechanisms. The pH buffers (bicarbonate, proteinbuffers, phosphatebuffer system) exhausts and changes (what does it change?). The cellular redoxsystems cannot any longer protect the tissue from radicals (Glutathione oxidises, tocopherols and ascorbic acids disappear).[6]
Different zones of damage appear to be evident: total necrosis, subletal damage, touched tissues without overwhelming damage and untouched tissues[7]. Aim of all therapies must be to stop damage by removal of foreign body mechanically by scraping (in lime burns) and by rinsing[8]. Other aims are to maintain as much of surviving tissues as possible. This requires specific properties of fluids to be used.
The tissues touched by highly concentrated fully dissociated burning agents are highly loaded with electrolytes meaning that the osmotic pressure is quite high. We measured this in corneas being exposed to 1 mol NaOH for 30 seconds. The osmolarity assayed by cryoscopic freezing point depression in a Osmomat 300 (Gonotec) was 420 ± 45 mOsml/kg for 1200 pooled homogenized healthy pig corneas with a hydration of 3,125.[9] After exposure of 20 healthy pig corneas to 1 mol NaOH their mean osmolarity rose to 1380 mOsm/kg (Please add standard deviations!). This gives an impression of the osmotic forces that act when using hypotonic solutions in first aid of eye burns. There is a tremendous upload of water for cells if they survive high osmotic trauma rinsed with tap water. This will lead to cellular disrupture by means of water uptake by osmotic forces through semipermeable membranes.
We demonstrate this uptake in images of cell cultures of fibroblasts being exposed to tap water.

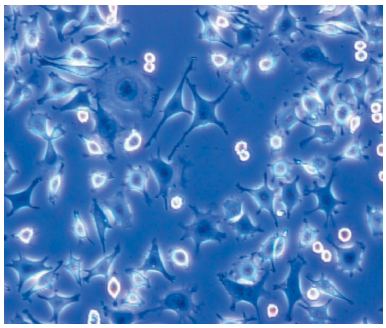

Fig. 7: cells alive before rinsing with aqua bidestillata.

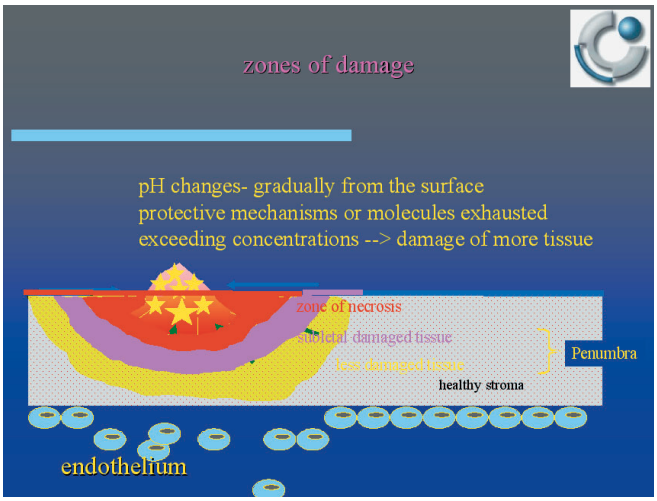

Fig: 8: The burning substance invades the cornea by diffusion, at first hyperosmotic disruption of cells, and by attracting additional water from the surrounding tissue the protective mechanisms of the tissue are exhausted. The devastating situation is: Zone of necrosis close to the burning agent, zone of subletal damage and surviving zone.

The rinsing solutions have to be adapted to the tissues to be treated and their state after burns. Therefore we recommend in all cases of hyperosmolar trauma (and those are nearby all traumata of this type) hyperosmolar solutions in initial treatment directly after eye burns.[10] This must not mean that we would not rinse with any other available solu-

tion if the specific type is not available. Every type of solution that can be drunk without harm is possible for emergency eye washing. Beverages of higher concentration of alcohol or acid drinks should be avoided, but from warm coffee up to milk, coke and tap water should be used to rinse as fast as possible in emergency[11]. Hyperosmolar solutions like "Diphoterine®" or "Previn®" should be supplied if secondary prevention is organized, to protect the penumbra from additional disrupture of cells by hypoosmolar cellular trauma.

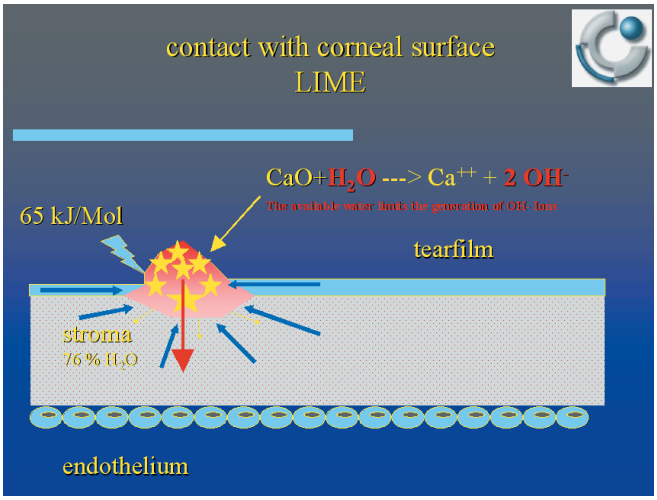

Fig. 9: Especially lime produces heat and invades the tissue by hydrolysis and water attraction. Therefore removal of particles is essential to stop the trauma.

After rinsing with hyperosmolar solution an isoosmolar rinsing should follow to normalize the osmotic pressure of the tissues.

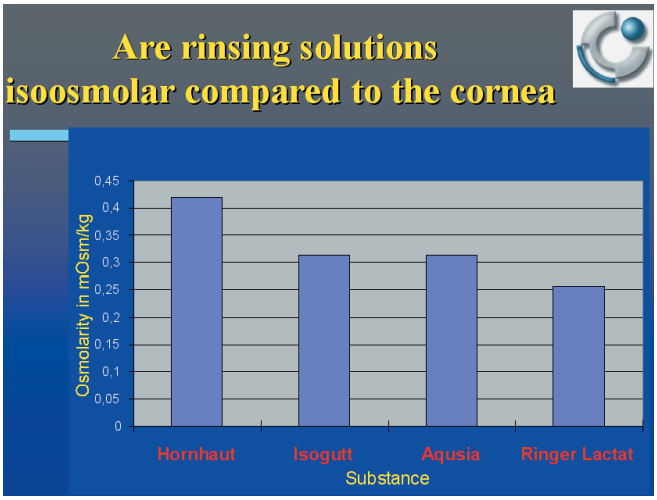

Fig 10: Direction of osmolarity changes after eye burns. From 1 molar NaOH returning to normal corneal osmolarity. Tap water is nearby 0 to 20 m/mOsm/Kg meaning severely hyoposmotic

Mechanism of hyperosmolar rinsing:
Hyperosmolar rinsing is able to remove water and solutes from the tissue. Thereby the osmotic pump of hyperosmolar rinsing solution is used to move the aggressive substances out of the cornea. Further osmotic disrupture of highly ion loaded cells is avoided. Thereby less damage will appear after eye burn.
Hypo - osmolar rinsing with tap water results in a high concentration difference between rinsing fluid and tissue, which is mainly corneal stroma. With hypo-osmotic rinsing, ions are renoved by means of dilution. But under these conditions, abundant amounts of water diffuse into the tissue. The uptake of water by injured cells will explode the cell body by osmotic forces. (Fig 7)

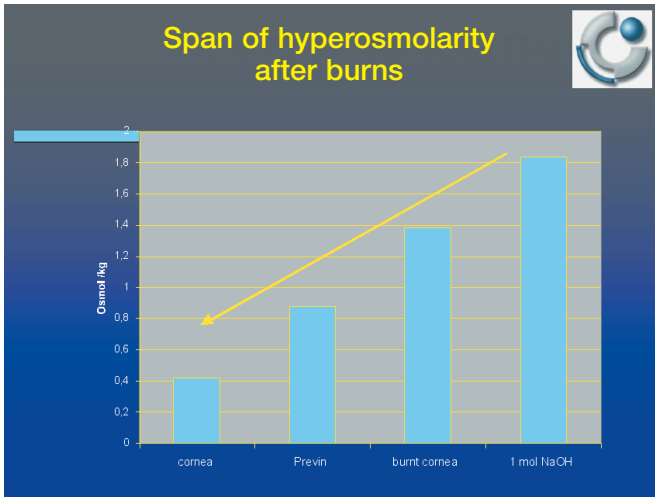

Fig. 11: Osmolarities of commercially available "isoosmolar" rinsing solutions. In fact those are isoosmolar to the blood-serum but not to the cornea. On the corneal stroma and keratocytes, these solutions are hypo-osmolar.

PARTICLE REMOVAL

In lime or concrete burns particles and deposits of CaO may be retained in the fornices and under thze lids. It is essential to remove these particles. , because Calciumoxide (CaO) in lime and concrete reacts with tear fluid and tissue water and produces new hydroxyl-ions This continueing burning process must be stopped. It is essential to remove all particles. In severe cases, ectropionizing is not sufficient. Therefore, Calciumoxide particles and other burning substances should be removed from the deep fornices under retrobulbar or general anesthesia.
pH measurements as indicator for unexpected remnants of burning agents
Remnants of particles with ongoing action of burning are indicated by simple measurement of pH in tears by pH indi-

cator paper (for example Merck). In the case of Fig. 12 a tubing of a concrete pump exploded and concrete under high pressure hit the workman standing aside on both eyes. After immediate rinsing and cleaning with q-Tips the pH of the fluid rinsed out of eye began to increase as soon as rinsing was stopped. Therefore, under general anaesthesia the lower deep fornices were examined, and huge deposits of concrete were found subtarsally and removed surgically.

EXHAUST OF OXIDO- REDUCTIVE EQUILIBRIUM

A third factor in corneal disease is the constitution of redox systems. Ascorbate, tocopherol and glutathion are reductive and oxidative partners being involved in scavenging of superoxide and hydroxyl radicals.[12] The exact function of these systems is yet poorly understood, But there there is some evidence, that redox system may be exhausted in specific eye burns, following other laws than those known from acid or alkali burns.
From clinical observationtwo common types of delayed action of burning substances are known. in. First are the hydrogenperoxide eye burns of contact lens wearers suffering from oxidative stress. This type of eye burns is specifically delayed in development of pain and damage. There is a slow evolution of corneal damage. fter exposure with hydrogenperoxide, when the error is noticed,the eyes were first rinsed. After more than 3 to 12 hours increasing symptoms were noticed. Punctate superficial keratitis and later deeper stromal edema develop with descemets folds up to a late endothelial damage.

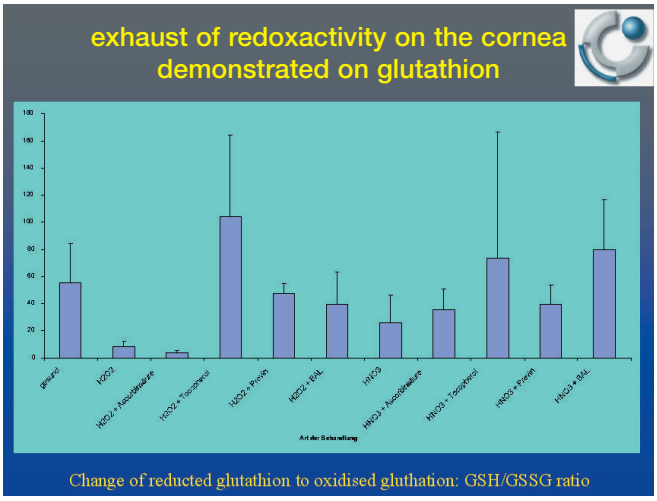

Fig 13: Redox state of the glutathione system after treatment with different substances being known as oxidising or reductive. Especially HNO_3 changes the oxidised fraction extremely. Addition of Previn and British Antigen Lost (Dimercaprol) to the treated corneal homogenates re-established normal redox properties of the system whereby the total available amounts of glutathione

Another typical example of exhausting the corneal oxido-reductive "buffering " system is the keratitis electrica. Here by UV-radiation peroxides and free radicals are generated within the cornea. As mentioned above for hydrogenperoxidic eye burns, from the time of UV light exposure the onset of symptoms more than 4 hours elapse. Other newer types of eye burns with delayed reactions were seen in accidents with radicalic or oxidative chemical compounds acting as starters of plastic polymerisation.
There seems to be a different mechanism of action because of the structural integrity of the tissues and the nonexistence of tissue lysis as known from acids and alkali. The agressive chemicals act by successive reactions with single molecules fixed in the connective tissue structure and continuously moving with reactions from molecule to molecule through the tissue. In the cornea, this chemical reactions run from the epithelium downwards to the endothelium like a "domino" game. Exhaust of reductive forces of the cornea will allow to damage the functional proteins top-down. In lighter cases a complete regeneration is achieved. Severe cases end with permanent corneal edema and endothelial necrosis.
(Why did you not discuss tear gas injuries?)
In vitro we tried to measure the existence of this mechanism by means of oxido-reductive potenial changes with a platinum microelectrode (Microelectrodes, Inc.) and failed to get reproducible results. Therefore we continued to measure the levels of the individual redox partners by means of enzymatic analysis of the oxidised and reduced Glutathion[13]. Here we found reliable results and found that different oxidizing agents changed the ratio of oxidized and reduced glutathion in homogenates of corneal buttons as shown in Fig. 13.

Conclusion:

In chemical injuries of the eyes, details of chemical biological are still unkown. Several factors like pH and thermal conductivity have been identified in the past. New concepts are proposed that include further physico-chemical properties of living matter, and to take into account the specific structure of proteins and the amphoteric character of amino acids. In this context, the osmolarity of tissues and fluids, dissociation constants pK and redox potentials were taken into consideration. More detailed understanding these parameters may lead to new chemical and physical treatment options in eye burns, such as, preventing formation of amino acid salts, changes of osmolarity and changes of the ratio of redox metabolites, reversing penetration of burning agents, and late progressive reaction of chemicals in the eye tissues. Nevertheless, these considerations do not replace immediate first aid. The most important treatment has to be, to

rinse a burnt eye without delay.. But it is to be expected, that newer treatment concepts taking into account osmolarity, pK and redox systems will prove their special value. Eye burns by other chemicals than alkali or acid are evaluated in current research projects to investigate the diversity of concepts presented here.

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