TOXICOLOGY OF THE EYE

FOURTH EDITION

TOXICOLOGY OF THE EYE

Volume I

Effects on the Eyes and Visual System from Chemicals, Drugs, Metals and Minerals, Plants, Toxins and Venoms; also, Systemic Side Effects from Eye Medications

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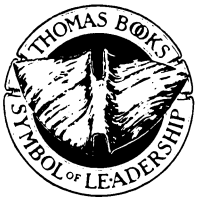

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PREFACE TO THE FOURTH EDITION

This Fourth Edition has been prepared with Joel S. Schuman, MD as an extremely thoughtful and helpful co-author.

The three previous editions of this book were published in the 1960s, 1970s, and 1980s respectively. Now in the 1990s our objective for the Fourth Edition has been to incorporate the large amount of new information on ophthalmic toxicology that has become available by the end of 1991.

Many methods have been employed to determine the toxic effects of various substances, and great attention has been paid of late to *in vitro* methods of analysis. However, this is far too broad and political a topic for discussion here, and is beyond the scope of this text. The toxicology of the substances that we describe in this book has been arrived at through a variety of techniques, including both *in vivo* and *in vitro* methodologies.

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In preparation of the First Edition, the author gave thanks to Charles J. Snyder, former librarian of the Howe Library of Ophthalmology, and to those others who helped in the laboratory and literary research, in particular Harold L. Kern, Sc.D., Helen Pentz Nardin, Myra Rolston, Elizabeth Cushing Kolm, and Hellen L. Crewe.

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In the Third Edition it was made clear that the whole undertaking was made feasible by the kind and understanding support from Mr. Edward V. French and Mrs. Caterine L. French.

For both the Third and Fourth Editions the authors thank Patricia (Fitzgerald) Basler for her invaluable help in transforming handwritten text, via word processor to typescript, ready for the publisher. We are grateful for her valuable suggestions, and her efforts beyond the call of duty to see the job done.

The authors also are grateful to Chris Nims, Kathleen Kennedy, and Carol David of the Howe Library for their interest and help in obtaining necessary publications. Combing of the ophthalmic toxicology literature for the Fourth Edition has been facilitated by use of the periodic publications "Ocular Resources" and "Current Contents."

We thank Dr. David L. Epstein for his encouragement and initial support to undertake the Fourth Edition. Valuable support has been given by Tufts University School of Medicine, thanks to Professor Carmen A. Puliafito, M.D. The authors of this edition are duly grateful.

Throughout this project, from 1940 to the 1990s, Professor David G. Cogan has given his most deeply appreciated encouragement.

CONTENTS

TOXICOLOGY OF THE EYE

CHAPTER I

INTRODUCTORY OUTLINE OF TOXIC EFFECTS ON THE EYES AND VISION

Chapter I provides a systematic, anatomic outline of disturbances of the eyes and vision produced by toxic substances either by direct contact or by systemic routes. Substances that cause specific toxic effects are cross-referenced in the Index by effect and by name.

Chapter II discusses the toxic properties and effects of individual chemicals, drugs, plants, toxins, and venoms with bibliographic references.

A. CORNEAL AND CONJUNCTIVAL DISTURBANCES

1. Contact Action on Cornea and Conjunctiva, Immediate Effects

Accidental splashing or squirting of substances into contact with the eyes is the most common cause of toxic eye injuries. Some substances produce serious injury or pain almost immediately. Others produce superficial reversible damage, and others induce injury that may appear unimpressive at first, but becomes progressively worse after a latent period. It is important to recognize these different types of toxic action, because of their bearing on prognosis and treatment. The following discussions will stress these differences.

Unger (1990) has published an exhaustive review of the *immediate* response of the anterior segment of the eye to noxious stimuli, with particular concern with changes of permeability in blood vessels and changes in intraocular pressure. The chemical, toxic substances specifically considered as noxious stimulants were: formaldehyde, N-mustard, bradykinin, prostaglandin, and alkali/acid.

a. Lacrimators (tear gases), Immediate Effects

In the Index under "Lacrimators" is a list of substances that at low concentration in air have the special property of causing immediate stinging and smarting sensation in the eyes, with tearing. The lacrimogenic sensation is produced by selective stimulation of sensory nerve endings in the cornea, but with certain exceptions there is very little organized information on the relationship of lacrimogenic discomfort and physical or chemical properties of the lacrimators. Substances that have the most intense lacrimatory action tend to be very reactive chemically, and may stimulate the nerve endings through specific chemical mechanisms.

Most of these chemically reactive substances which produce stinging and lacrimation without evident injury to the cornea at low concentration can, at high concentrations, cause severe damage and opacification of the cornea. These severe reactions are described in Chapter II under *Tear gas weapons,* and under the individual names of the *tear gases.*

In examining the mechanisms of action of lacrimatory agents on the eye, the first problem is to explain the stimulatory effect on the sensory nerve endings of the cornea. The second problem is to explain the injurious actions at higher concentrations. What relation one may have to the other is unknown, but it is clear that injury to the cornea and conjunctiva is independent of stimulatory effect on nerve endings. Investigators have so far been much more intrigued with trying to explain how lacrimators may stimulate the sensory nerve endings than with explaining the basis for serious injury.

Bacq (1946) has pointed out that representative lacrimatory agents as well as nonlacrimatory vesicants react with sulfhydryl groups and reduce the activity of

sulfhydryl-dependent enzymes. Mackworth (1948) reported having tested several lacrimators *in vitro* for inhibitory effect on a variety of enzymes. Mackworth reported that lacrimators which he tested were selectively toxic to sulfhydryl or thiol enzymes, whereas enzymes such as cytochrome oxidase and lactic dehydrogenase, which were known to be insensitive to thiol reagents in general, were also insensitive to lacrimators. Mackworth hypothesized that lacrimators acted *in vivo* by combining with sulfhydryl (thiol) enzymes, but reported no actual tests on eyes or eye tissues. Dixon (1946, 1948) similarly concluded that lacrimator action was due to reaction with sulfhydryl enzymes, and that this involved either a positive halogen or a carbon-carbon double bond which was made reactive by neighboring ketone, ester, aldehyde, nitro, or other groups. Dixon also indicated that the site of action must be in the corneal nerve endings, and noted that similar molar concentrations were required for stimulating the nerve endings as were required for poisoning enzymes. Dixon acknowledged that the relationship between sulfhydryl groups in the nerve ending and the production of nerve impulses was unknown. Dixon also called attention to the fact that lacrimators were strong inhibitors of cell respiration and glycolysis, and that on the skin they could cause vesication if in sufficient concentration. Peters (1963), reviewing the subject, pointed out difficulties in the concept of lacrimatory action being based on reaction with sulfhydryl groups in the nerve endings. One problem was that most of the inhibitions of sulfhydryl enzymes by lacrimators had been found to be essentially irreversible, whereas the stinging sensation induced by low concentrations of lacrimators obviously and characteristically disappears when exposure of the eye to the lacrimator is terminated. Peters commented in 1963, "If it is an -SH group in the eye with which the lachrymator combines to produce the irritation, where is this -SH group in the eye? Is it the nerve itself or is it some sensitive nerve ending? Since the lachrymatory effect wears off, the combination could not be irreversible unless there can be some rapid regeneration of the group in question."

Fleckenstein (1967) in a series of biochemical studies on lacrimators confirmed that they were very active inhibitors of cellular respiration, often more effective than cyanide. However, concentrations of lacrimators necessary to interfere with tissue metabolism or respiration *in vitro* were often several hundred times greater than the concentrations in air that would produce distinct discomfort of the eye. As a possible escape from this dilemma, Fleckenstein postulated that there might be an adsorptive and selective concentrating effect in the superficial layers of the corneal epithelium and nerve endings to produce a locally higher concentration of lacrimator than in the surrounding air. Fleckenstein postulated that the concentrated lacrimatory agent caused depolarization of the nerves and drop of the resting membrane potential by local inhibition of oxidation.

Castro (1968) studied the inhibition of cholinesterase by several alkylating agents, including some lacrimators, and obtained evidence of an inhibitory effect that involved reaction through some group other than sulfhydryl, and which was reversible *in vitro.* Although there was no direct evidence that cholinesterase itself was involved in lacrimatory action in the cornea, the demonstration that a lacrimator, such as chloracetophenone, could have an inhibitory action on an enzyme through reaction

with groups other than sulfhydryl, and that this type of reaction was reversible, seemed to provide a new possibility for explaining the transitory nature of the sensory response when the eye is exposed to a lacrimator. Inhibition of cholinesterase itself in the cornea can hardly be involved in the lacrimogenic action, since some strong lacrimators (bromoacetone and chloropicrin) do not inactivate cholinesterase, and powerful anticholinesterase drugs, such as echothiophate, produce no lacrimatory sensory stimulation when applied to the cornea.

Treatment is not ordinarily required for the lacrimatory action, since it is self-limited when exposure is discontinued. Potentially it could be suppressed by local anesthesia. When treatment is needed after exposure to lacrimogenic substances, it is for corneal and conjunctival injury which may be produced by concentrations greater than those that are simply lacrimogenic. No specific antidotes or effective countermeasures are known at present. (This aspect of lacrimators is discussed in Chapter II under *Tear Gas Weapons* and *Chloroacetophenone.*)

Bacq ZM: Thiol-binding substances. EXPERIENTIA 2:349–354, 1946. (French)

Castro JA: Effect of alkylating agents on human plasma cholinesterase. BIOCHEM PHARMACOL 17:295–303, 1968.

Dixon M: Reactions of lachrymators with enzymes and proteins. BIOCHEM J 42:xxvi--xxvii, 1948.

Dixon M, Needham DM: Biochemical research on chemical warfare agents. NATURE 158:432–438, 1946.

Fleckstein A: Absorptive concentration of substances with mucous membrane irritating action in the respiratory tract. EXPERIENTIA (Suppl. 13):117–125, 1967. (German)

Mackworth JF: The inhibition of thiol enzymes by lachrymators. BIOCHEM J 42:82–90, 1948.

Peters RA: Biochemical Lesions and Lethal Synthesis. New York, Macmillan, 1963.

Unger WG: Review: Mediation of the ocular response to injury. J OCUL PHARMACOL 6:337–354, 1990.

b. Caustic Chemicals, Immediate Injuries

Rapid, deep penetrating injuries of cornea, conjunctiva, sclera, and even lens and iris are most notoriously produced by alkalies and acids. (Detailed descriptions are given in Chapter II.) Injuries produced by alkalies and acids are principally a result of extreme change of the pH within the tissues. This has very rapid, almost immediate, action on the tissues which can be prevented or minimized only by very rapid emergency action. Some physical changes in the tissues are immediately evident, such as dissolution of epithelium and mottled clouding of corneal stroma from alkalies, or coagulation of epithelium by acids, but many other changes appear later, including edema, loss of mucopolysaccharide from the corneal stroma, further opacification and vascularization and degeneration of the cornea. (A comprehensive review of angiogenesis in the cornea has been published by Klintworth (1991).)

Research is being aimed toward reversing the initial physicochemical changes and toward anticipating and preventing the secondary changes. At present, the main principle in initial treatment has been prolonged irrigation with water or

saline solution to remove excess alkali or acid, hoping that this might interrupt the process.

There is a paradox to be noted, that the most serious chemical burns may produce little pain, because severe chemical injury destroys the sensory nerves of the cornea and renders the cornea anesthetic; whereas injuries that are relatively slight, superficial, and reversible, involving principally the corneal epithelium, may cause great discomfort, apparently by exposing corneal nerve endings to irritation rather than destroying them. (A review of studies of corneal sensation has been published by Martin (1988).)

Klintworth GK: *Corneal Angiogenesis. A Comprehensive Critical Review.* Springer-Verlag, New York, 1991.

Martin XY, Safran AB: Corneal hypoesthesia. SURV OPHTHALMOL 33:28–40, 1988.

c. Solvent Splashes, Immediate Effects

A splash of a chemically inert solvent usually causes immediate stinging and smarting pain, and it may cause loss of some or all of the corneal epithelium, particularly if it is a good fat solvent. Even if all the epithelium is lost from the cornea as a result of splash of ordinary organic solvents, it generally regenerates in a few days without residual permanent damage. While the epithelium is missing, the corneal stroma may be slightly swollen and the posterior surface of the cornea may appear wrinkled.

Most organic solvents that are employed mainly for their physical solvent properties have no strongly acidic or alkaline character, and have little or no tendency to react chemically with tissues. Fortunately, many organic solvent splashes are well tolerated by the eye. Descriptions of the properties of individual solvents can be found in Chapter II. Ratings from tests on rabbit eyes can be found in the Index.

The first aid treatment of solvent splashes is immediate irrigation with water. Since these substances do not bind chemically with tissues and are readily eliminated by the irrigation, it seems that a brief irrigation, for a minute or two, should suffice. The very prolonged irrigations that have been recommended for acid and alkali burns should not be necessary.

d. Detergent or Surfactant Splashes

Contamination of the eye with surfactants and detergents presents a complex problem that is discussed in more detail in Chapter II under *Surfactants.* A great many of these substances are listed there in cationic, anionic, and nonionic categories, pointing out some related differences in type and severity of injury. It is noteworthy that there are practical differences and species differences in the dangers to the eyes presented by these substances. Some detergents that are used industrially and in the household rarely cause serious eye injuries in the people using them, though tests on rabbit eyes commonly show serious results. Some surfactants, such as ordinary soap, cause immediate stinging or burning with little or no injury. Other surfactants have produced corneal edema and loss of corneal epithelium with no warning

discomfort, as described in Chapter II, particularly under *Ointments.* Some surfactants have delayed effects after a latent period, which will be described below.

In first aid treatment of eyes contaminated by surfactant or detergent liquids or powders immediate irrigation with water is appropriate. How long this irrigation should be continued has not been established, and this seems to deserve experimental investigation.

2. Contact Action on Cornea and Conjunctiva, Delayed Effects

a. Corneal Epithelial Painless Edema, after Latent Period

In the Index under *"Corneal epithelial (painless) edema, with delayed onset of haloes, from contact action"* is a list of chemicals, mostly amines, which in vapor form, after several hours of exposure, induce swelling of the corneal epithelial cells. People exposed to this effect may then see colored haloes about lights because of diffraction effects from the myriads of swollen cells. This peculiar reaction to the vapors of these substances has in most cases occurred in workmen who have been exposed for several hours to concentrations of the vapors that were not unduly unpleasant at the time of exposure, and they have usually noted no disturbance of the eye during the working day, but in the evening on the way home from work they have seen colored haloes around lights. Usually there has been no discomfort such as results from death or loss of epithelial cells, and the condition has been spontaneously reversible, sometimes by the next day, and at least within a couple of days. The mechanism by which these substances produce reversible corneal epithelial edema with a delay in onset after exposure is unknown.

With excessive exposure, it is possible to develop eye discomfort or pain as a result of more severe injury of the epithelial cells, as will be discussed in following paragraphs.

No special treatment except avoidance of excessive concentrations appears indicated, since the condition has characteristically been spontaneously reversible.

b. Corneal Epithelial Injury, Painful, after Latent Period

In the Index under *"Corneal epithelial injury (painful), with delayed onset, from local action"* is a list of chemicals, drugs, and plant materials which have the striking feature of a delay or latent period before onset of symptoms. These substances several hours after exposure cause injury, with death or loss of corneal epithelial cells and associated discomfort. (It is notable that some of these substances at lower levels cause only epithelial edema with haloes, but without pain, as described in preceding paragraphs.) When exposure causes delayed onset of discomfort, it appears to be similar to the reaction to excessive exposure to ultraviolet (in so-called ultraviolet keratitis, sun lamp keratitis, snow blindness, or welder's flash), and analogous to the delayed reaction of the skin in sunburn. Typically, during exposure these substances cause essentially no discomfort or irritation, but several hours later the