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MARIJUANA AND THE EYE – A REVIEW

KEITH GREEN, Ph.D. *
Departments of Ophthalmology and Physiology
Medical College of Georgia
Augusta, Georgia

Abstract

A review is given of the basic and clinical effects of marijuana and its constituent compounds on the eye. Brief accounts of the chemistry, metabolism, and other medical effects are provided as well as a brief discussion of glaucoma. Available toxicological data are presented with reference to drug effects on the eye, especially as these relate to comprehension of the mode of action. A perspective is presented on the use of marijuana and its constituents in the treatment of glaucoma, concluding that although it is undisputed that smoking of the raw material causes a fall in intraocular pressure, continued use in this mode leads to substantial pathological changes. Development of drugs based on the cannabinoid nucleus or derived from newly discovered water-soluble compounds appears to be an area worthy of future investigation.

History of Marijuana

Various forms or extracts of *Cannabis*, or marijuana, have been used for many centuries as medicinal compounds. Studies of the Chinese literature[1,2] indicate that *Cannabis* was used as long as 2000 to 3000 years ago as a sedative

*Address reprint requests to: Keith Green, Ph.D., Department of Ophthalmology, Box 3059, Medical College of Georgia, Augusta, Georgia 30912.

and all-purpose medication ("tonic"). Several books on the subject of marijuana have traced its historical use as a medicant and relaxant in several cultures, primarily in India and the Near East, indicating the connection between its use and religious rituals.[3,4]

Widespread use occurred in the Middle Ages where it was used as an anesthetic, analgesic, and "cure" for many ailments. Its euphoric-inducing capabilities were readily recognized, although the excessive, intoxicating effects were warned against. The Dispensatory of the United States of America of the mid-nineteenth century[5] describes the extract of hemp as "a powerful narcotic, causing exhilaration, intoxication, delirious hallucinations, and, in its subsequent action, drowsiness and stupor." Various uses are described, including increasing uterine contractions in delivery, and relief from the symptoms of gout, rheumatism, tetanus, hydrophobia, and uterine hemorrhage. Attention is drawn to the fact that the influence of the extract only occurs in a certain proportion of cases.

Extracts of *Cannabis* were used throughout Europe for many years as patent medicines during the late eighteenth and early nineteenth century, but the highly diverse nature of the potency gave extremes in therapeutic efficacy and, as more specific medications became available, the preparation fell into disuse in the mid-1930s. In the United States, passage of the Marijuana Stamp Act in 1937 virtually abolished the use of *Cannabis* extract and almost completely halted research on the material. The plant extract is still used in some cultures for its purported medical benefits and as a relaxant. Use of the material as a pleasure-inducing, mind-altering drug did not spread to the United States and Western Europe until the latter half of the twentieth century, a move that accompanied significant sociological changes in both the United States and Europe. Its more widespread use at that time was associated with wide-ranging social changes and was symbolic of freedom from established society, rebellion, or anything controversial.

Research in many countries was performed only at a low level until about 1960 because medical interest in *Cannabis* was purely esoteric until that time, with only a few drugs derived from *Cannabis* being studied. With the increased widespread use of the material in various groups in Western civilization and the parallel, although not necessarily associated, increase in the use of heroin[6] and other drugs of abuse, various governments instituted both scientific and epidemiological studies of the effects and use of *Cannabis*-derived material.[7,8] These were the first contemporary attempts to summarize the state of scientific knowledge and review the societal implications of *Cannabis* use.

Marijuana is now the third most widely used recreational drug after alcohol and tobacco. A very low toxicity is ascribed to the material and, in controlled settings, the available evidence indicates that it is questionable as to whether or not any deaths can be directly attributed to its ingestion. Such statements

have been interpreted by some as being "pro-pot," but these are facts based on a purely scientific evaluation of the data. There is little question that deaths can be attributed to the use of marijuana, but these are as the result of judgment errors on the part of the person using marijuana, not as a direct result of a pharmacological consequence. Ingestion of multiple drugs also adds to this confused area, yet it appears that marijuana use per se induces such a marked state of intoxication that other activities become physically impossible when used at high doses.

The research output on marijuana, as measured by the number of publications, has increased dramatically since the mid-1960s[9] and considerable knowledge has been accumulated regarding its biological effects. Despite the increase in the number of publications on marijuana, little is known with confidence in humans because much of human experience is purely anecdotal and is dependent on both the quality of the raw material and prior frequency of use; thus, controlled studies are difficult to find. Reports do exist, however, of the early phases of clinical studies of the acute pharmacological response to several primary constituents of marijuana, the cannabinoids, which reveal that the primary effects are euphoria/dysphoria, tachycardia, conjunctival redness, and at high doses, orthostatic hypotension.[10-12] Each cannabinoid appears to evoke its own typical range of responses, especially with regard to psychoactive effects, as characterized to date by the limited number of cannabinoids tested in humans.

There are about 360 compounds extractable from the plant material, of which about 60 are cannabinoids[13] that are specific to *Cannabis*, and many of which are common to other plants (e.g., chlorophyll, sugars, etc.). Whereas the pharmacological effects of many of these compounds are known, large gaps in our knowledge of their effects exist in both clinical and preclinical studies of these compounds.

Medical Effects

Various areas of clinical concern have been identified in chronic marijuana users, including alteration of cellular metabolism, changes in the immune response, emphysema-like changes in the lungs, and modification of hormone levels.[14] These, and more, have become areas that are of extreme concern among marijuana researchers, and many studies have attempted to answer these questions. There are differences in the content of the study groups, however, with some groups containing prior users and others not so. The degree of prior use appears to influence the data and the results thus far appear somewhat equivocal. The overall clinical significance of several preclinical and clinical laboratory observations is not clear at the present time, and despite

the increase in published information in this area, considerably more sound epidemiological and clinical laboratory work is needed to unambiguously provide answers to many remaining questions.

Equivocal data exist on T-cell suppression, with an apparent initial impaired immunity that ultimately returns to normal levels.[15,16] Inhibition of DNA, RNA, and protein synthesis has been noted in tissue culture cells exposed to marijuana smoke,[17,18] but the evidence for chromosomal changes is weak.[19] Inhibitory effects on thymidine uptake have been noted in cultured lymphocytes,[20,21] an effect ascribed to the nonspecific change in membrane conformation.[22] Data also exist indicating the effect of Δ9-tetrahydrocannabinol and other cannabinoids on the synthesis of macromolecules in cultured HeLa cells,[23] and effects on membrane-bound ATPases have also been noted.[24,25]

Decreased circulating testosterone levels have been ascribed to marijuana users, but the values appear to be within normal limits.[26,27] Interference with normal growth and development in adolescents has been noted, as well as abnormal sexual development in the male fetus of females who are classified as heavy marijuana smokers. In Rhesus monkeys, the incidence of abortion and neonatal mortality is four times higher in recipients of Δ9-tetrahydrocannabinol (vide infra) than in control groups[28] and male rat pups from litters of mothers treated with Δ9-tetrahydrocannabinol show significant retardation of development.[29]

In the reproductive system, inhibition of ovulation has been noted in Rhesus monkeys, as well as an increase in pregnancy loss rate and decreased levels of circulating leutenizing hormone and follicle-stimulating hormone.[30] In males there is an impairment of spermatogenesis in humans[28,31] and the production of abnormal sperm in experimental animals.[32-34]

The initial bronchial response to marijuana smoke is one of bronchodilation,[35] which may ultimately prove to be of therapeutic benefit in the treatment of asthma. However, inflammation of the lungs has been noted, with emphysema-like pathology showing macrophage infiltrates with associated cholesterol deposits and bronchitis symptoms after chronic marijuana use.[36,37] In addition to these physiological changes, alterations have been found in short-term memory, learning skills, motor coordination, driving ability,[38] and many other psychological and coordinative tests indicating a wide-ranging spectrum of effects of marijuana on a multitude of different physiological systems.[39]

Cannabinoids have been shown to inhibit the incorporation of precursors into protein and nucleic acid of rat brain slices, being most marked in 3-day-old rats compared to older animals, as well as inducing morphological reductions in nuclear membrane-bound ribosomes in rat brain and showing preferential binding of labeled Δ9-tetrahydrocannabinol to mitochondrial brain fractions.[40] Other ultrastructural studies indicate pathological changes

in the brain, including the morphology of the synapse and volume density of the rough endoplasmic reticulum and the nuclei.[41] Tolerance to repeated administration has also been noted,[42,43] indicating that increasing concentrations are needed with continued use to elicit the same pharmacological response.

Chemistry

Many of the chemical ingredients of marijuana have been identified, with Δ9-tetrahydrocannabinol (Δ9-THC; molecular weight 302 daltons) being the compound found in greatest amounts in most plant materials. However, the absolute amount is variable, depending on the genetic strain of the plant, the environment in which the plant grew, and the part of the plant from which the extract is prepared. Colombian and Mexican material contains a high proportion of Δ9-THC, whereas Turkish and Czechoslovakian material tends to contain a low amount of Δ9-THC. Flowering tips often contain the highest quantities of psychoactive material, as distinct from the stalks.[44,45]

Delta-9-THC was first isolated and identified in 1964,[46,47] and was shown to account for most of the activity of the parent plant material or its crude extract.[48] The cannabinoids, of which Δ9-THC is a representative, are highly lipophilic, and therefore, although they are soluble in various organic solutes, precipitate readily in aqueous solutions unless bound to proteins. The absence of a nitrogen atom combined with the material's lipophilic character and the absence of any ionizable group are the factors responsible for lack of water solubility. Organic solvents are usually used for solubilization of the cannabinoids, and frequently the solvent itself has been implicated in affecting both the mode and the manner of action of a particular cannabinoid.[49,50]

There are small differences in the basic molecule that distinguish one cannabinoid from another,[10,51,52] but these small changes, such as the position of a double bond, opening of a part of a ring structure, or an addition onto the side chain (see Fig. 1 in Ref. 52) impart widely varying characteristics to the molecule. Some specific structural requirements have been identified as inducing specific psychogenic responses in monkeys.[53]

Metabolism

The metabolism of the cannabinoids has become better understood with the availability of synthetic parent compounds, improved detection methodology, and the availability of radioactively labeled cannabinoids. Although Δ9- as well as Δ8-THC cause the same effect as marijuana extracts, it is still uncertain whether the effects are caused by the parent compound or metabolites.[54-56]

Delta-9-THC is known to undergo a complex transformation, producing both psychoactive and nonpsychoactive metabolites that may be mono-, di-, or tri-substituted,[57] some of which appear to be more active than Δ9-THC in certain tests whereas others are inactive relative to Δ9-THC in other tests.[58-60] The metabolic pathways have been traced using radioactive Δ9-, Δ8-, or 11-OH-Δ9-THC, as well as by chromatographic analytical procedures. This has been done when marijuana is smoked or specific cannabinoids are given by various routes.[61-65] The conversion of Δ9-THC to the 11-hydroxy compound was identified as a key metabolic step, followed by conversion to the carboxilic acid. This pathway was followed irrespective of the route of administration of the parent drug. Certain metabolites, such as the 11-hydroxy compounds, are excreted in the feces, implying passage via the liver and gallbladder whereas the acid forms predominate in urine.

Correspondence has been sought between the peak plasma levels of various compounds and the euphoric "high" and other physiological effects.[61] Despite the appearance of various metabolites, time course studies indicate that the tachycardia and other psychotomimetic effects more closely parallel the levels of Δ9-THC rather than other metabolites.[66] The parent compound, therefore, as well as metabolites, undoubtedly contributes to the pharmacological activity of marijuana.

Ocular Effects

The eye may be considered, in general terms, as a fluid-filled sphere that has a clear portion, the cornea, on the anterior surface and is encompassed by the sclera over the remainder of the surface. Within the eye are, passing posteriorly from the cornea, the fluid-filled anterior chamber, the iris, the lens and posterior chamber, the vitreous humor, and the component layers of the retina and choroid. The fluid between the posterior surface of the cornea and the anterior surface of the lens, known as the aqueous humor, is constantly exchanged at a rate of about 2% per minute or 2 to 3 μl/min. This fluid is formed at the ciliary processes of the ciliary body, located at the periphery of the posterior chamber immediately behind the iris, and flows between the iris and lens through the pupil into the anterior chamber.

Regulation of either the inflow of fluid or its egress from the eye, the latter via the trabecular meshwork and Schlemm's canal (located in the interface between the peripheral iris margin and the extreme edges of the cornea), controls intraocular pressure. Pharmacological or surgical manipulation of either site of aqueous passage affects intraocular pressure,[67] thus drugs affecting intraocular pressure may have either one or both sites of action. Furthermore, there are several means by which drugs can affect either inflow or outflow, including direct effects on enzymes located in the ciliary

epithelium, regulation of blood flow in the ciliary processes, effects on the trabecular meshwork per se or on vessels carrying aqueous away from the eye. These mechanisms have not been fully elucidated and much remains to be determined regarding the intimate details of these steps. The studies with marijuana and its derivatives have offered a means of investigating these basic processes as well as determining the specific drug effects on the various regulatory components.

One of the more obvious features of marijuana use is the redness or hyperemia of the conjunctiva. A feature that has been erroneously attributed to marijuana in the past has been pupil dilation. The latter appears to be a response noticed by persons usually associated with law enforcement who arrest drug users and is a concept adhered to by law enforcement personnel. The response is more likely the product of fear than of drug use because pupil dilation has not been noted to occur in laboratory or clinical settings during acute[68] or chronic marijuana use.[69]

Conjunctival hyperemia, noted in a broad-spectrum controlled study of marijuana use, lead to the involvement of ophthalmologists in examining the ocular response to marijuana smoking, and it was noted by Hepler and Frank[70] that an associated fall in intraocular pressure occurred about 1 hr after smoking 2% marijuana through a water-cooled pipe. A wide variation in response was found, with a range between +4 and −45% of initial intraocular pressure in the 13 individuals in this study, with an average fall in intraocular pressure of −25% from the baseline values. This initial observation was further documented and expanded with further measurements of other ocular parameters.[68] Noted in this latter study was a decrease in tear flow by about 50%, and a decrease in ocular pulse pressure during tonography. The former observation related to the anecdotal information of a "dry eye" reported by marijuana users.

These results following the acute smoking of marijuana have been substantiated in several studies and are reviewed elsewhere.[52,71] Smoking of marijuana and oral or intravenous administration of cannabinoids leads to a dose-dependent fall in intraocular pressure. Although relaxation has been implicated by some[72] to be associated with the fall in intraocular pressure, this is not a common finding among other workers.[68,69,73-75]

Purnell and Gregg[75] and Cooler and Gregg,[73] in groups of 4 and 14 volunteers, respectively, found a dose-related fall in intraocular pressure following the intravenous administration of Δ9-THC. The peak euphoric effect was completed yet the intraocular pressure remained decreased, thereby indicating a temporal separation of these two phenomena. Although Perez-Reyes et al.[74] found that the maximum fall in intraocular pressure was correlated with the degree of euphoria-induction caused by intravenously administered cannabinoids (Δ9-THC, Δ8-THC, 11-OH-Δ9-THC, cannabinol, and cannabidiol), there was a lack of correlation when the temporal effects were compared.

The euphoric effects had disappeared whereas the intraocular pressure fall was sustained beyond this initial event.

Merritt and co-workers[76-78] have shown that intraocular pressure falls after either marijuana smoking or oral ingestion of Δ9-THC in both normal and open-angle glaucoma patients. They also noted a corresponding decrease in systemic blood pressure, an effect also noted with one of the systemically administered compounds, Nabilone,[79] and large amounts of Δ9-THC (12 mg in cigarette form).[72]

The first data on glaucoma patients was reported by Hepler et al.[69] Of the 11 patients studied, 7 showed a fall in intraocular pressure that averaged 30% after smoking 2% marijuana cigarettes. Further studies[80] with either smoking or oral (capsule) Δ9-THC showed an average fall in intraocular pressure of 20% with 1% THC (0.5 mg) and 34% with 3% THC (1.5 mg) when measured 30 min after initiation of smoking. After oral ingestion, the fall in intraocular pressure was 14, 23, and 24% with 5, 10, and 20 mg Δ9-THC, respectively, indicating a peak response with the 10-mg dose level that was not enhanced by additional drug. Greater quantities were required via the oral route than by smoking, presumably because of the poorer absorption by the former route. In those patients who could not be taken off their normal antiglaucoma medication, the effects of marijuana were additive to these drugs (epinephrine and pilocarpine) because an additional fall in intraocular pressure was caused by Δ9-THC. Intraocular pressure increased in some patients, however, indicating the variable response of individuals. Merritt and co-workers[77,78] have substantiated these observations.

A total of approximately 250 volunteers, either normal or open-angle glaucoma patients, have participated in studies to determine the acute effects of marijuana smoking or cannabinoid use (oral or intravenous administration). This constitutes a reasonable population for drug evaluation, especially because the largest single group was only about 40 persons, indicating that the observations are reproducible. The confirmation of effects, therefore, is widespread and occurs in a variety of groups with similar concentrations of material and with very similar time courses.[52,71]

In addition to the acute studies of marijuana effects, some long-term studies have been undertaken with both smoking and oral ingestion. In one study[81] the ingestion of large oral doses of Δ9-THC lead to the suppression of an evoked fall in intraocular pressure following the smoking of a marijuana cigarette. Marijuana cigarette smoking induced a fall in intraocular pressure prior to the oral intake of Δ9-THC, but after 70 to 210 mg every 24 hr over a 1- to 5-day period oral intake of Δ9-THC lead to suppression of the intraocular pressure fall induced by a marijuana cigarette.

Studies with long-term use in a controlled clinical setting with 29 physiologically normal subjects for 94 days showed a repeated fall in intraocular

pressure after marijuana cigarette smoking.[69] The only other ocular change was the decrease in ocular pulse pressure during tonography, although total outflow facility remained constant. Lacrimation was not determined in that series, thus making comparison with the earlier study impossible. A long-term retrospective study was undertaken in Costa Rica[82] with an analysis of persons who had smoked marijuana regularly over a 10-year period. These individuals were matched for age, sex, and physical and socioeconomic status, as well as for cigarette versus marijuana smoking. Various aspects of visual discrimination related to color vision were the only differences noted between the groups.

Glaucoma

Glaucoma is one of the leading causes of blindness in the world and describes a group of ocular diseases characterized by an increase in intraocular pressure that damages the optic nerve and leads to an eventual loss of vision. The disease affects over 2 million persons age 35 or older in the United States and approximately 300,000 new cases are diagnosed each year. The most prevalent form of glaucoma is primary open-angle glaucoma, in which an insidious rise in intraocular pressure occurs, leading ultimately to blindness if uncontrolled. It is this form of glaucoma that is most responsive to treatment by pharmacological agents or surgery.

Treatment of glaucoma may be pharmacological or surgical (e.g., trabeculectomy, trabeculotomy, cyclodiathermy). Surgery is useful in many cases, but there is a high incidence of failure and serious complications can occur. Therefore, pharmacological methods are important for the therapy of this disease. Antiglaucoma drugs are effective in regulating intraocular pressure to desirable levels (usually less than 21 mm Hg) in many patients, but adverse effects have been well documented with all current therapies.

Miotics, such as pilocarpine, cause a constricted pupil that reduces light passing through the eye to the retina, and in an older population with cataracts, adds to the loss of vision already present. Brow-ache and accommodative spasm caused by severe contraction of the ciliary muscle also become a problem in younger persons in whom the ciliary muscle is more capable of responding to the drug because of the greater plasticity of the younger lens: This accommodative problem decreases with age as the lens nucleus becomes more rigid.

Mydriatics, such as epinephrine, cause a dilated pupil and can also cause reactive hyperemia of the conjunctiva in some patients as well as conjunctival and corneal deposits of adrenochrome material. Systemic effects, such as tachycardia, are also seen with a high degree of frequency, especially in elderly patients. Beta-adrenergic blocking agents are effective in reducing intraocular pressure but cause many other side effects, such as corneal anesthesia,

decreased lacrimation, and systemic effects (decreased pulse rate, bradycardia) resulting from systemic absorption. In addition, many patients show adaptation (refractoriness or tachyphylaxis) or decreasing effectiveness with time, despite continued drug use. Systemically administered carbonic anhydrase inhibitors are effective in reducing intraocular pressure but cause a sequence of undesirable side effects, including parasthesias, decreased appetite, loss of libido, renal calcium deposits, a feeling of malaise, and alterations of potassium metabolism. These systemic effects require considerable management or alteration of drug therapy in order to retain control of intraocular pressure.

All of the side effects in each of these groups of medications contribute to a lack of patient compliance and patients may have irreversible loss of vision as the disease progresses. There is, therefore, a great need for the development, or discovery, of alternative drugs to lower intraocular pressure that have minimal ocular and systemic side effects, retain efficacy over long periods of time, and can be delivered in an acceptable form.

The knowledge that marijuana use caused a fall in intraocular pressure provided a starting point for investigations on the possible use of compounds derived from marijuana as antiglaucoma medications. The mere fact that the material is a widespread drug of abuse has provided a certain degree of public impetus to research efforts, although, fortunately, this has been tempered by a scientific approach. Further impetus arises because of the widespread occurrence of glaucoma in the population and the need for better and more effective medical therapy.

Basic Studies

Our initial data in the rabbit,[83] showing a fall in intraocular pressure after intravenous administration of Δ9-THC, has been confirmed by several authors. Dose levels were used similar to those found in human plasma after smoking a marijuana cigarette[84] and concentrations of pure cannabinoids used by ourselves. Cool et al.[85] described a 30% fall in intraocular pressure after a dose of 100 to 200 μg Δ9-THC per kilogram body weight, with a time course showing a maximal fall in intraocular pressure at 1 hr and return to baseline at 3 hr. Elsohly et al.[86] found that Δ8-THC, Δ9-THC, cannabinol, and Nabilone were active in reducing rabbit intraocular pressure when given intravenously, but cannabidiol was inactive. Hepler et al.[69] designed a delivery system for the intoxication of rabbits with marijuana smoke. They also found a 30 to 40% fall in intraocular pressure with the maximal fall occurring at 1 to 2 hr. Topical solutions of 1 and 2% Δ9-THC in sesame oil also reduced intraocular pressure in rabbits,[69] as well as when Δ9-THC was suspended in carboxymethylcellulose.[87] Mechoulam and co-workers[88] have described the effects of some cannabinoid derivatives in a rabbit glaucoma model. Eyes

pretreated with α-chymotrypsin in the posterior chamber show a lens dislocation and a resultant elevation in intraocular pressure. This model is a secondary glaucoma, however, and the only relationship to open-angle glaucoma is an increase in intraocular pressure; the usefulness of the model is lessened because of this lack of a direct relationship.

In addition, the treatment regimen in these studies was not as a drop but rather as a conjunctival bath using the eyelids as the sides of the corneal reservoir. This approach utilizes a large volume of solution, with a larger mass of available drug, which further allows a high level of systemic absorption. Nevertheless, these authors identified that both Δ8-THC and cannabinol acetate induced long-standing falls in intraocular pressure that compared very favorably with epinephrine in the same model system. This finding correlated with that of Perez-Reyes et al.[74] who showed that Δ8-THC, which has reduced psychoactive activity relative to Δ9-THC, also caused a substantial intraocular pressure fall in humans following intravenous administration. Topical Δ9-THC was also found to reduce intraocular pressure in dogs.[89]

Some studies have been made with structural modifications of the Δ9-THC molecule, including additions to the side chain and adding a nitrogen[90-92] to the molecule.[93,94] These compounds were found to have activity in normal rabbit eyes after topical application,[87] causing a fall in intraocular pressure which was similar to that caused by Δ9-THC. Some other compounds, which contained a variety of structural modifications, induced severe side effects, including keratitis and corneal ulceration. This was especially true of one compound tested in female dogs that contained a fluoride atom, although it was determined that this response was species-specific because neither rats nor Rhesus monkeys of either sex were similarly affected.[95]

The animal studies have allowed the site of action to be discerned of both the cannabinoids, at least as exemplified by Δ9-THC,[96-98] which has been used primarily as a model cannabinoid, and of the newer, extractable water-soluble compounds.[99] It is of interest that the cannabinoids appear to act by increasing outflow facility, that is, the ease with which fluid exits from the eye, whereas the water-soluble compounds act by decreasing the inflow of fluid into the eye.[99] Thus, although arising from the same plant material, these diverse chemicals influence aqueous humor flow rate and intraocular pressure by diverse mechanisms.

Studies using various cannabinoids, administered either topically[96,100] or intravenously,[101,102] indicated that the basic structure-activity relationships seen in other test systems[53,103,104] appear to apply. There are some variations, however, in that cannabigerol, which has an open-ring structure[102] has been found to have an intraocular pressure-reducing activity greater than Δ9-THC.

We have been able to determine that the action of the cannabinoids is mediated through the adrenergic nervous system and its synaptic mediator,

norepinephrine. One aspect of this interaction was found between Δ9-THC and arachidonic acid metabolism[105] whereby intravenous THC prevented the pharmacological consequences that normally accompany arachidonic acid instillation onto the ocular surface. The characteristic features of this response, namely, the increases in intraocular pressure, aqueous humor protein, and total outflow facility, were all markedly reduced in Δ9-THC-treated eyes after arachidonic acid treatment compared to non-THC-treated rabbits. The topical administration of prostaglandin E_2, one of the cyclooxygenase products of arachidonic acid, results in ocular changes similar to those seen after arachidonic acid, but these responses were unaffected by THC, implying that THC antagonized the in vivo ocular production of prostaglandin from arachidonic acid rather than prostaglandin action per se.[106] This action of Δ9-THC may provide a means by which the drug can influence the adrenergic nervous system in a less dramatic manner, because a feedback has been identified at the adrenergic synapse involving norepinephrine modulation of prostaglandin release (or conversion) that in turn modulates norepinephrine release.[107] One effect of THC could be to interfere with this process by blocking prostaglandin and other cyclooxygenase product formation, enabling more norepinephrine to be released. This action of THC might be accomplished by effects on the phospholipases, which are responsible for conversion of arachidonic acid to prostaglandin, or by inhibition of a specific pathway. The former is, however, more likely because once the cascade is initiated there are several metabolic pathways that can be followed from arachidonic acid and it is unlikely that THC would be capable of inhibiting all of these simultaneously.

A more substantial involvement of the adrenergic nervous system in the mediation of ocular cannabinoid responses was obtained after a specific surgical procedure. Removal of the superior cervical sympathetic ganglion interrupts the adrenergic nervous supply to the eye, leading to the degradation of nerve terminals within 2 weeks[108] and rendering the eye supersensitive to endogenous catecholamines. Intravenous administration of Δ9-THC in animals subjected to unilateral sympathectomy resulted in a decrease in response of both the intraocular pressure fall and the change in outflow facility on the operated side, whereas the opposite eye showed a normal response. Both aspects of aqueous dynamics were affected by the alterations in sympathetic status of the eye, indicating the role of the sympathetics in the regulation of intraocular pressure.

Use of a ganglionic-blocking agent, hexamethonium chloride, induced similar changes in terms of blockade of the THC effect, implicating THC as being mediated by the adrenergic nervous system with a primary effect on the central nervous system transmitted to the eye via the sympathetic chain.[96,109-111] A complete understanding of this complex interaction requires further pharmacological testing in other model systems to fully elucidate the mode of action of the cannabinoids.

Related to our observations in the rabbit on adrenergic interaction with the cannabinoids were some clinical studies using adrenergic antagonists. The conjunctival hyperemia associated with marijuana smoking in humans markedly reduced by pretreatment with propranolol.[112,113] Inhibition of the tachycardia and rise in blood pressure also occurred, indicating an effect of the β-adrenergic antagonist at either peripheral or central sites. This, and other evidence indicating blockade of central marijuana effects with adrenergic antagonists, indicates that marijuana acts on central pathways, although it does not delineate the ocular response. There appears to be, therefore, both a locally and a centrally mediated effect of the cannabinoids in inducing a change in both intraocular pressure and outflow facility. The central component appears to be related to the adrenergic nervous supply and requires an intact innervation for a complete expression of the response. The local component also involves the adrenergic nervous system and appears to relate to the presence or absence of an intact adrenergic nervous system in the eye.

Systemic absorption of the drug was indicated in studies where topical administration occurred, as unilateral drug delivery in drop form resulted in bilateral responses.[114] These findings indicated, from a pharmacological measurement, that absorption of drug occurred from the eyedrop as it passed through the lacrimal canaliculi and into the nasal passages. The systemic concentration must have been sufficiently high to induce a response in the contralateral eye as intraocular pressure was found to decrease there. The time course was the same in the non-drop-treated eye compared to the contralateral-treated eye, although the quantitative response was reduced. Calculations revealed that even if drug placed onto the surface of one eye was absorbed into the circulation, then a sufficient amount was present systemically to induce a significant effect in the nontopically medicated eye.[96] From a 50-μl drop of a 2% Δ9-THC solution the total available material for systemic absorption would be 1 mg, which is sufficient to induce a large fall in intraocular pressure when administered intravenously.[52]

Use of radiolabeled Δ9-THC allowed this finding to be substantiated when radioactive material (which was not chromatographically characterized as the parent compound or a metabolite) was found in the eye opposite that receiving drug. In the aqueous humor of the eye not receiving the drop the levels of radioactive tracer reached slightly less than 20% of the concentration in the aqueous humor of the eye receiving the drop, whereas the iris showed a concentration that was almost 70% of that in the drop-receiving contralateral eye at 1 hr after administration.[98] Systemic absorption undoubtedly occurred and contributed to the bilateral ocular response that resulted from a unilateral application. The small body weight (< 3 kg) of the rabbit and low blood volume (< 150 ml) would assist in sustaining high systemic concentrations. The high degree of absorption of labeled material by the iris indicated that

cannabinoid was probably concentrated in this tissue by a mechanism related to that seen in iris, choroid plexus, liver, and kidney for a number of organic solutes.[115] This finding was substantiated by studies on Δ9-THC uptake in isolated iris[116] where it was shown that the uptake was a metabolically dependent process.

Radioactive material also allowed a comparison of different vehicles for topical drug delivery in terms of drug penetration into various ocular tissues. The greatest intraocular concentrations (in the iris, aqueous humor, and cornea) were found after light mineral oil was used as the vehicle, although the amount of drug entering the eye from any solvent compared to that administered onto the ocular surface was small.[98] These studies permitted preparation of Δ9-THC in a suitable dosage form for human use, with the incorporation of parabens for the maintenance of sterility and the use of glass bottles to prevent loss of the parabens and solubilization of plastic containers by the oil. The parabens are one of the few bactericidal agents that are compatible with mineral oil.

The determination of the optimal delivery system led to the determination of the subchronic ocular and systemic toxicity of this preparation in rabbits.[117] In these studies one of two concentrations of Δ9-THC (0.1 or 1%) in 50-μl drops of mineral oil or vehicle control were applied to the eyes of rabbits six times daily for 30 days. Blood chemistry, hematology, and urinalysis was performed before and after the treatment period. All pre- and posttreatment values fell within normally accepted limits for rabbits, although some statistically significant changes occurred with greater frequency in the 1% THC-treated group than in either the 0.1% THC-treated group or the vehicle control. No changes were consistently found to occur in all groups. The ocular changes were restricted to lid or conjunctival reddening, which was unrelated to drug and was also unrelated to the increased level of pseudoeosinophils and lymphocytes on pathological examination. The ocular and systemic drug effects were minimal.[118] These studies were used to indicate the safety of the preparation, as required by the Food and Drug Administration prior to phase I clinical studies with a new drug preparation, and studies were subsequently initiated in human subjects.

Human Studies with Topical Drops

When used in humans, topical Δ9-THC was without effect on either ocular or systemic parameters (e.g., systolic or diastolic blood pressure, pulse, respiration rate, temperature) on either an acute (single drop)[119] or subchronic (4 drops per day for 7 days) regimen.[120] These findings stand in contradistinction to the small intraocular pressure fall ascribed to Δ9-THC when applied in a topical form in humans by others.[121] The regimen in the latter study was to use an application of 100 μl in a short time period with a certain degree of

ocular massage. This does not reflect normal drop use in ophthalmology and represents a rather unique circumstance. With this regimen it was reported that 0.05% of Δ9-THC decreased intraocular pressure by 4.8 ± 2.8 mm Hg in the treated eye and by 6.8 ± 2.5 mm Hg in the fellow eye at 3 hr after drug administration. A higher drug concentration (0.1%) evoked a maximum fall of 5.4 ± 2.6 mm Hg in the treated eye at 5 hr and a maximum fall of 5.2 ± 2.8 mm Hg at 1 hr in the fellow eye. No other adverse effects were noted except for a slight (12 mm Hg) fall in systemic blood pressure with 0.1% Δ9-THC. However, a maximum of only three volunteers was included in each group.

The normal ophthalmic drop varies between 25 and 35 μl, thus the quantity of drug given in this latter study[121] is at least four times greater than that achieved with a single drop[119] and may account for the slight change that was observed because of systemic drug absorption. The total amount of drug available from a single ophthalmic drop of 1% Δ9-THC would be about 0.3 mg at best, whereas in the studies of Merritt et al.[121] the amount of drug delivered in 0.1 ml of a 1% solution would be 0.1 mg, which is about equal to that noted in previous studies to induce a fall in intraocular pressure when given by intravenous infusion[73] and after oral administration.[80] How two experiments that basically deliver the same amount of topical drug show different results must be explained on the basis of the application technique and the fewer number of experiments in the work of Merritt et al.[121] Merritt and co-workers[122] later performed an expanded series of studies in six glaucoma patients in which topically applied drops of the same concentration as used previously[121] failed to induce a fall in intraocular pressure. The latter data confirm the findings from our studies.[119,120]

Studies of Marijuana Smoking as Treatment for Glaucoma

These results with topical drops are naturally quite disappointing because this represents a logical therapeutic mode of treatment if a drug is pharmacologically active. There is no question that smoking of marijuana and oral or intravenous administration of certain cannabinoids lead to a fall in intraocular pressure. Use of the material by these routes, however, is not ideal and a topical drug form remains a high-priority research area.[123]

Use of smoking as a treatment modality is not desirable for many reasons, despite the fact that drug absorption is not only maximal under these circumstances but it can also be optimized by the smoker who can titrate him/herself to a specific level of euphoria that is indicative of a pharmacological response. Marijuana smoking, however, leads to lung pathology resembling emphysema and the drug consumption necessary to achieve a dose level that controls glaucoma would be huge.

Consider that one marijuana cigarette reduces intraocular pressure for 4 to 5 hr yet glaucoma is a 24-hr-a-day disease and requires medication to reduce intraocular pressure to desirable levels (usually less than 21 mm Hg at a peak pressure is acceptable, although different ophthalmologists have slightly different criteria, i.e., 20 or 22 mm Hg, and the absolute value depends on the degree of retention of visual acuity and retinal function). The requirement for smoking, therefore, would be for at least four and possibly five or six marijuana cigarettes per day, leading to a use of at least 1460 "joints" and possibly as many as 2190 joints per year. By most criteria, this would be classified as "heavy" use and would make it difficult for that individual to actively participate in many normal activities (e.g., driving or other activities where the use of coordinative skills would be required) even though it would be anticipated that adaptation would occur regarding euphoric effects. Heavy smoking is usually defined as three joints a day 5 days a week, and moderate smoking as one joint a day 5 days a week.[124] Intravenous administration is impossible outside a clinical setting and the variability in intestinal absorption found after oral administration makes this approach less than optimal, at least for Δ9-THC.

Relative to the potential use of marijuana as an antiemitic agent in cancer chemotherapy recipients,[125] the use of the drug under these circumstances is much reduced because the latter patients are often on a much different treatment regimen. Cancer patients usually follow one of two chemotherapy treatment regimens: either a concentrated treatment schedule wherein chemotherapy is given several times per week for about 2 months, or a schedule calling for treatment each month for a whole year. Either regimen requires treatment with marijuana or Δ9-THC immediately before the chemotherapy in order to reduce the nausea that accompanies treatment of the cancer.[126,127] Use of the drug under these circumstances is limited to a maximum of approximately 25 to 50 times per year, far less use than would be necessary to control glaucoma. The utilization of marijuana or Δ9-THC in this instance is to control a specific problem associated with chemotherapy treatments, not the treatment of the disease per se, and thus represents an entirely different approach to its application in this branch of medicine.

That marijuana when smoked causes a fall in intraocular pressure is undisputed,[128] and several cannabinoids (of those thus far tested) also induce this same qualitative response. The fall in intraocular pressure is as good or better than currently marketed antiglaucoma drugs and not only occurs in normal volunteers but also in glaucoma patients.[80] The response also appears to be additive to normal medications, such as pilocarpine or epinephrine. Data also exists indicating that several Δ9-THC related compounds, such as benzopyrans, reduce intraocular pressure in humans after oral administration.[79,129-132]

It is therefore apparent that some years after the initial tentative probes into this area several derivatives of the cannabinoids have been identified or

synthesized that reduce intraocular pressure at systemic dose levels but do not cause systemic side effects. Thus, whereas marijuana cannot be considered a medication, compounds that are derived from the constituent parent compounds in marijuana are proving effective in reducing intraocular pressure.[133] The premise that reduction of intraocular pressure by these compounds will lead to preservation of remaining visual function has not been established at this point and must await considerable testing.[127,134] The possibility exists, therefore, that despite the negative results with topically applied Δ9-THC compounds can be developed where a full quantitative separation of effects can be made,[117] that is, the "desirable" effect of a fall in intraocular pressure can be dissociated from the "undesirable" side effects.

The acute and chronic effects of marijuana use have been outlined earlier[135]; these are of obvious concern in the development of any potential therapeutic agent. Although the reduction of intraocular pressure is undisputed as being caused by both marijuana and several derivatives, the long-term consequences of cannabinoid use in the treatment of disease processes is unknown. It would be unacceptable to regulate intraocular pressure while at the same time inducing complications through the use of the drug. Although it is realized that many problems or undesirable side effects take many years to become evident, as was the case with cataract induction caused by phospholine iodide, as much information as possible must be obtained before a therapeutic agent becomes generally available for public use. A topical drop may alleviate several of the problems seen in the smoker of marijuana, for example, lung pathology, because the absence of hydrocarbon intakes would negate potential hazards associated with smoking. Nevertheless, changes in hormonal status, behavior, reproductive capability, and other areas that have been identified as being modified in marijuana users, must be assessed. Compounds with as complete a separation of effects as possible must be sought to make use of these derivatives and their families viable as therapeutic agents.

Water-Soluble Compounds Extracted from Marijuana

A report of an extract (solvent unspecified) of marijuana that could cause a fall in intraocular pressure when given topically to human beings or dog[136] provided impetus to new studies. At one time it appeared that the cannabinoids offered the only means by which *Cannabis*-related drugs could be used to reduce intraocular pressure. New findings with water extracts of the raw plant material, which by their nature and separation from the raw material exclude cannabinoids,[137] have led to the possibility of a new class of compounds being identified that are, in fact, more active in reducing intraocular pressure than the cannabinoids on a per-milligram drug basis.[99] Indeed, the fall in intraocular pressure seen with these glycoproteins is as large as is possible in a normal

living eye. These changes occur in very low concentrations (as low as 1 μg per animal) at the present level of purification (which is almost total), thus providing another area worthy of intense study.

These newer compounds have reached a stage of purification where they have been identified as glycoproteins (or arabinogalactan-protein) based on molecular weight and sugar content.[137] Such pharmacologically related compounds appear to occur in extracts of at least one other plant, of the several which have been examined, although glycoproteins exist in almost all plants. The crude water extract is inactive when applied topically to rabbit eyes, yet is active when given intravenously. The fall in intraocular pressure is great, and purified compounds at 1 μg per animal cause a fall in intraocular pressure to a maximum of about 60%.

Given an eye at 20 mm Hg, the lowest intraocular pressure that can be achieved (except in retinal or choroidal detachment) is to the level of the episcleral venous pressure, which is between 7 and 9 mm Hg. The maximum fall in intraocular pressure, unless a drug also reduced episcleral venous pressure, is (20 - 7)/20 X 100% or 65%. Intraocular pressure decreases of this magnitude are regularly seen with several of the purified compounds. These compounds are probably closely related, as plants appear to have less genetic regulation of the detailed structure of these compounds than occurs with many other products. Apparently, as long as general chemical characteristics are fulfilled the plant exerts little regulation over the fine molecular structure of glycoproteins; thus, a family of highly related compounds is formed. Whether these characteristics are relatively unique to *Cannabis* remains to be determined, although at least one other plant extract, prepared in a manner similar to that used for the *Cannabis* extract, also reduces intraocular pressure.

The compounds, purified by column chromatography and other separation techniques, cannot be blocked by any conventional α- or β-adrenergic antagonists, nor by many other antagonists, such as those of prostaglandin (indomethacin), histamine (tripelennamine),[99] or acetylcholine (scopolamine or atropine), haloperidol (dopamine), chlorpromazine (adrenergic and dopamine), methysergide (serotonin), or aldosterone (spironolactone).[138] Whereas these new marijuana-derived drugs act in the rabbit following intravenous injection, they are inactive when given by any other route except intraocular injection. This may relate to their high molecular weight, which would prevent diffusion across either the corneal epithelium or the intestinal wall.

No response was found after either topical or intravenous administration in Rhesus monkeys. The lack of response after topical administration relates to the finding in the rabbit where absence of penetration, even across a deepithelialized cornea—and the epithelium is the major barrier of the cornea[139,140]—may be because of the large molecular size. Reconciliation of the lack of effect after intravenous administration in the monkey, compared to the finding in the

rabbit, may be related to the differences in the permeability of the blood-aqueous barrier of these two species. The rabbit has a very leaky blood-aqueous barrier that is susceptible to breakdown with minimal induced trauma. Indeed, one of the consequences of both Δ9-THC and the new water-soluble compound injections is an increase in rabbit aqueous humor protein concentration, which indicates an increase in blood-aqueous barrier permeability.

In addition, the fluid permeability of the rabbit blood-aqueous barrier[141] is much greater than that of the Rhesus monkey blood-aqueous barrier.[142] The greater leakiness of the rabbit ciliary epithelium would therefore allow the passage into the eye of the large-molecular-weight species from the systemic circulation, whereas this process could not occur in the monkey. It would appear that intraocular penetration of the material is necessary for activity to be expressed, indicating that an intraocular site of action (which implies a nonvascular component) is necessary for a response to be generated.

Surprisingly, direct intraocular injection of these compounds in the rabbit leads to a fall in intraocular pressure only after a delay of about 24 hr.[138] The fall in pressure is as great as that found after intravenous injection, although occurring at a much lower dose (0.01 μg by direct injection versus 1 μg per animal intravenously). The difference in response time is difficult to explain for at least four reasons. First, even if the entire quantity of intraocularly injected drug was to appear in the systemic circulation there would be an insufficient quantity to elicit such a large response. Second, the amount penetrating the eye must be small after intravenous injection, considering the volume of distribution in the body water (because the material is very water soluble), and the relative volume of the eye (unless a specific uptake system exists for these compounds in ocular tissues).[116] Third, if metabolism of the drug is necessary for activation, then the 2 hr needed after intravenous injection and subsequent intraocular penetration would seem to be all that is necessary yet intraocular injection requires a lag time of at least 24 hr. Fourth, the effect of intravitreal injection is only seen unilaterally, indicating a local intraocular phenomenon. One must conclude, therefore, that metabolism and/or penetration to a local site in the eye is important and that the enzymes that exist systemically to convert the compounds to their active forms also exist in the eye, albeit in a much lower concentration. The most probable explanation for the lag time is that intraocular diffusion is required for the intravitreal material to reach the ciliary processes. It is known that sucrose injected intravitreally reaches the anterior chamber with a half-time of 15 hr[143]; thus, a lag time of 24 hr is not unexpected with a molecule as large as 20,000 daltons. These data further indicate the specificity of the effect at the ciliary processes.

Direct intraocular injection of these new compounds at 0.01 μg and 0.001 μg per eye in the Rhesus monkey[138] leads to a unilateral increase

in intraocular pressure that is 50% greater than the baseline pressure in the normal eye, and is 24 hr in duration. This phase is followed by a fall in intraocular pressure to values approaching 10 mm Hg and a return to baseline by 48 to 56 hr. Evidently the material is active when administered intravitreally in the monkey eye; thus, the contention that it is the absence of intraocular penetration that prevents intravenous injections from affecting the monkey eye, as demonstrated here and elsewhere[99] appears correct. This finding also indicates that intraocular metabolism (or penetration to a local ocular site) at least in the primate, is important, because systemic concentrations as high as 20 mg per animal (about 3 kg in weight) did not cause any effect on intraocular pressure or any other ocular or systemic parameter that was measured or observed.[99] In the primate, therefore, the necessary metabolism of these compounds only occurs within the eye, or at least if occurring systemically, produces compounds that cannot penetrate into the intraocular fluids. However, the specific locus of action remains to be identified, but because total outflow facility is unchanged it is anticipated that aqueous humor formation is decreased.

The identification of a large intraocular pressure fall without concomitant systemic effects offers promise for the development of two areas of investigation. First, there is the potential for a therapeutic drug treatment to be developed that could aid in the treatment of open-angle glaucoma. For this to become a reality, the problem of drug penetration into the eye must be resolved, whether by topical or systemic (oral) route. The current high molecular weight of these compounds predisposes against these routes of administration with their large molecular size (about 20,000 daltons). If the active moeity is but a small component of the entire molecule, then penetration across corneal or intestinal membranes will become a less significant problem: This has assumed greater significance with the demonstration of intrinsic pharmacological activity in the primate.[138] Various methods exist for temporarily disrupting the corneal epithelium to allow the passage of nonionic molecules, such as with use of the surfactant and bactericidal agent, benzalkonium chloride,[144, 145] thus entry into the eye of a molecule on the order of 300 to 1000 daltons may be readily achieved.

Second, even if the materials prove not to be capable of development for clinical use they will provide a novel means of altering aqueous humor inflow, especially because the reduction is so dramatic. Such an effect will help in identifying the regulatory factors that influence the basic process of aqueous humor formation. The basic physiology and biochemistry of this process is becoming better understood, although large gaps still exist in our knowledge. The efficacy of these new compounds in reducing aqueous humor inflow and intraocular pressure in the absence of systemic blood pressure and overt behavioral changes offers a new approach to the comprehension of the basic physiology of aqueous humor formation. New modes of aqueous humor inflow

regulation may be uncovered and prove to be of therapeutic interest—if not with the present compounds, then with some offspring of them.

Future Areas of Investigation

Research should be directed toward the synthesis of a topical form of a water-soluble cannabinoid, perhaps with structural modification(s) to allow greater corneal penetration or to enhance pharmacological activity that is devoid of systemic and psychogenic side effects. Other studies should be aimed at the examination of other cannabinoid derivatives, the possibility of tolerance to continued drug use, the preservation of visual function, and the duration of drug effects. Topical drug delivery has several advantages (as discussed earlier) in addition to providing a replacement for the tear film if decreased lacrimation is a side effect of the cannabinoids that is hard to divorce from the pressure-lowering phenomenon. Furthermore, the total quantity of drug per marketed unit package would be reduced, thereby lowering the possibility of any potential abuse, although the lack of euphoria, and so on would act as its own deterrent to this type of activity.

Other areas where marijuana derivatives may play a role[125] are as an antiemitic in cancer chemotherapy patients, as an antiasthmatic agent (bronchodilator), and as an analgesic. The use of marijuana immediately preceding chemotherapy has proven effective in reducing emesis and subsequent weight loss, which is detrimental to patient survival. Considerable evidence now exists that this treatment modality compares favorably to currently used medication, indeed, performing better in some studies. The water-soluble compounds, described previously, also deserve further study to elucidate not only their mode of action but also to allow identification of the active component of the molecule and its possible chemical manipulation to prepare an active, therapeutically useful, compound.

The use of plant-derived materials in medicine is not unique to *Cannabis*; the effects of nutmeg, arrow poisons, and deadly nightshade have been known for centuries.[146] Many precedents exist for compounds of therapeutic benefit arising from plant material, including the whole antibiotic schema that arose from a mold; digitalis, and other glycosides, arising from plant material; opium and morphine from the poppy; and, as applied specifically to ophthalmology, the widely used antiglaucoma agent, pilocarpine, which is an alkaloid first obtained from the leaves of a South American plant, the jaborandi.[147]

Summary and Conclusions

The past 10 years have seen an evolution of the study of marijuana in ophthalmology, in which this laboratory has played an active role. From the initial observations of a fall in intraocular pressure in humans following

marijuana smoking,[70] our studies revealed that the rabbit model showed similar characteristics and they have identified the mode of action of the cannabinoids in this system. There appears to be a close relationship to findings in humans, at least with Δ9-THC, and an involvement of the adrenergic nervous system occurs in both human and animal models.

Structure-activity relationships have been identified, despite the lack of availability of substantial quantities of many of the cannabinoid derivatives. Modes of drug delivery for a drop form have been elucidated and efficacious forms have been examined for systemic and ocular toxicity. These steps have lead to the testing of at least one cannabinoid in a topical drop form in humans (the results of which have been disappointing in that no effect on intraocular pressure was noted) and the testing of several other compounds when given orally.

Despite this drawback, there is overwhelming evidence that either marijuana or cannabinoids reduce intraocular pressure when administered by a variety of routes. Further studies need to be directed toward a detailed structure-activity relationship in humans of compounds both effective in reducing intraocular pressure and with minimal or absent side effects.

Further detailed studies of the newly identified water-soluble compounds are necessary to determine whether or not these compounds can be decreased in molecular size while retaining pharmacological activity. The identification of an intraocular pressure-lowering effect in the primate provides greater impetus to this area because these compounds appear, at this time, to have potential for future therapeutic use with the caveats concerning maintenance of activity with size reduction and corneal penetration.

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