Marijuana and vision—after ten years' use in Costa Rica

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Several tests of visual function were applied to an abstaining user (10 years or more) group and a nonuser group carefully preselected to be free of clinical signs of eye disease. The groups were matched on several criteria. The results show that all findings from both groups are within established limits of normalcy. Small differences and trends were found between the groups. These would have been undetected without large samples. Relative to the non-user group, tests showed these user trends: increased basal lacrimation, increased intraocular pressure, increased photosensitivity, decreased dark adaptation, decreased color-match limits, and decreased Snellen acuity. These differences were associated with statistical probabilities, \( p = 0.07 \) to \( p = 0.001 \). There were no significant differences or clear trends between the user and nonuser groups in incidence of pathological fundus signs, conjunctival hyperemia, pterygia, or color-match midpoints.

Key words: marijuana, vision, acuity, intraocular pressure, pupil, hyperemia, dark adaptation.

There have been a number of excellent reports describing the visual and ophthalmic consequences of acute marijuana use. Alteration of color discrimination has been detected.\(^1\)\(^-\)\(^3\) Changes in resting pupillary diameters (PD) have been reported.\(^4\) Aqueous humor dynamics have been studied intensively and reductions of intraocular pressure (IOP) have been reported by several authors.\(^5\)\(^-\)\(^8\) Both vernier\(^2\) and Snellen acuity\(^9\) decrease following marijuana consumption. Thomas and Chester\(^11\) and Valk\(^10\) also described reductions in the total range of accommodation to between 2.50 and 5.00 diopters in a group of marijuana users. General changes have been reported in the conjunctival sac and the uveal tract with vascular symptoms similar to those found in iritis.\(^9\)\(^-\)\(^11\)

The majority of the studies which implicate eye function have considered the results of measurements made during or immediately following marijuana consumption. However, when chronic effects have been discussed in the literature they have usually been limited to days or weeks, whereas the "experienced" user has been accepted with levels of use as low as one marijuana cigarette a week.\(^13\) Consequently,
true long-term use, in the order of years and involving numerous cigarettes per day, is a virtually untouched area in the literature dealing with eye toxicity and function.

The visual experiments reported here were part of a broad group of socioanthropological and medical studies. The general design required that the measures should test a variety of eye functions as a means for generating or excluding future, more specific research into the consequences of long-term use. Test devices were limited to those that are well known in the ophthalmic community and whose results could be readily interpreted.

Methods

Costa Rica was chosen as the study site because of governmental cooperation, high literacy rate (90 percent), and high-quality medical personnel and facilities. Subjects were identified only after 2 years of interrelationship development and screening by teams of anthropologists and sociologists. The teams took up residence in and became part of the urban neighborhoods of San José. Data given by subjects were cross-validated with relatives and neighbors by the resident-team members. Life and nutritional histories were developed. After the research began, subjects and records were identified only by number. Personnel administering and scoring tests used these numbers and were not aware of user or nonuser group assignments.

Over-all subject selection assumed that the tests should be made to determine the limits of normal function in persons with 10 or more years’ experience with marijuana, whereas the users had consumed the drug for 10 or more years. At the time of the study the average user consumed nine marijuana cigarettes per day (range 1 to 40). had smoked 15.7 pack-years of tobacco cigarettes, had an incomplete primary school education, was a skilled worker, was a “moderate” alcohol user, was free of any disease which seemed remotely relevant to the project, was 29 years of age, and was a married man. Anthropologically the sample of matched pairs and the Costa Rican population, in general, are considered to be remarkably uniform by North American standards. Except where noted, results are given on the 39 matched pairs sample.

During testing corrective spectacles were worn. Subjects had agreed not to consume marijuana for a period of at least 3 hr. before going to the hospital for testing. Since they were taken by taxi to the hospital between 7:00 and 9:00 a.m., and usually waited 1 to 3 hr. at the hospital, it is likely that little or no smoking occurred in the user group for at least 10 hr. before testing. Marijuana is not consumed publicly in Costa Rica, where it is illegal and enforcement is vigorous.

Pupil measures. Pupil diameters of the right eye were measured in a Goldmann-Weekers dark adaptation apparatus at the end of a period of 30 minutes of total dark adaptation with fixation on a small red lamp in the adapting sphere. Pupil diameters were filmed immediately after the onset of the adapting lights (2.7 log footlamberts). A 20 sec. record of pupillary diameters was generated by measuring single motion picture frames (18 FPS) to the nearest 0.02 mm. across the largest diameter.

Intraocular pressure—water loading test. The subjects were seated in a quiet room late in the morning. After ingestion of 1 L. of water in about 3 min., IOP was immediately measured in each eye by anplanation and measured again at 20, 40, and 60 min. The utility of this pro-

*Thirteen samples of “street” origin marijuana cigarettes were obtained in a 3 year period. These were very uniform, weighing about 0.20 gm. each. Thin-layer and gas chromatography showed mean contents as percent by weight: Δ9 THC, 0.11 (range 0.09 to 0.35); cannabichromene, 0.16 (range 0.08 to 0.25); cannabidiol, 0.19 (range 0.02 to 0.44); cannabidiol (trace amounts, < 10^-6 gm.).
procedure in examining marginal changes in aqueous humor dynamics was described recently by Kronfeld.13

**Dark-adaptation threshold.** Thresholds were measured during dark adaptation of the right eye of each subject. The subject was seated in front of a Goldmann-Weekers adaptometer.14 The left eye was patched. Fixation lights were arranged with a chin support so that a 12° area was tested 14° temporal to the fovea of the right eye. Before dark adaptation there was adaptation to 2.7 log foot-lamberts for 4 min. Group data were scored for threshold and time at the inflection (alpha point) which signifies the end of the cone adaptation period and for threshold at 30 min.

**Decimal acuity with varied luminance.** A standard Bausch and Lomb Orthorater with Snellen acuity transparency was used in this test. The Orthorater was modified so that neutral tint filters could be placed in the viewing pathway. Seven rows of different Snellen letters could be seen by either the left or right eye. These letter lines ranged in size at threshold from 20/20 to 20/200. Each eye was tested separately. Then each eye was occluded in turn, and the appropriate column was read again as illumination was increased in log unit steps. The subject read the smallest visible line and if he made more than one error, read the next larger line. Final scores were converted to decimal acuity for each eye.

**Color matching—anomaloscope.** The Hecht/Schlaer anomaloscope uses a bipartite field. The left half field was a standard yellow. The right half field may be adjusted to match the color and brightness of the left field. Both eyes were measured. The subject was allowed to choose which eye was to be used first. The other eye was occluded. Initially, the right field was set so that it contained excess red or green. After the brightness had been adjusted to a match the subject indicated whether the field was too green or too red. Beginning with excess green, the adjustment was continued in steps with the variable mixture moving from the "too green" side until the subject reported that the two fields appeared equal in color. At that point the mixture was changed so that it was too red and the procedure was repeated. In this way the acceptable limits of the color match were defined. The technician also recorded the brightness settings as a means for identifying the brightness match. The sequence was repeated on the opposite eye. These color results were converted to the comparative units16 and contrasted with match midpoint data and match limit ranges previously found in the literature.

**The Schirmer test for lacrimal fluid secretion.** The test and its physiological basis have been described by Jones.17 In order to test the basic secretory system and exclude the reflex system, one drop of 0.5 percent proparacaine HCl was placed into each eye and this procedure was repeated after 5 min. Measurements were made for 5 min. on both eyes of each subject. Fluid migration was measured in millimeters. This procedure is occasionally rejected for use in clinics because of its lack of standardization18 and more objective, quantitative methods have been generated. The latter tests use fluorophotometric methods19 not available in Costa Rica.

**Fundus evaluation.** Color photographs of each fundus were taken. Photographs were made of each of the four quadrants of the fundus, with a fifth centered upon the optic disc. All exposed films were returned to the United States for commercial processing. This resulted in some losses, necessitating elimination of a "pair." Evaluations were made by a practiced staff member and were divided into categories: vessels, retina, disc, and macula. Regions were evaluated as "normal" or "abnormal," with comments on the extent of the apparent abnormality when present.

**Results**

**Pupil response.** Records of pupil size of the right eye were divided into 250 msec. periods. The first readable frame in each period for the first 11 periods was taken for measurement. From dark adaptation,
Pupil size was sampled at regular intervals during the first 2.75 sec. after the onset of the adapting light. Fig. 1 shows that the pupillary construction became asymptotic at about 2.2 sec. Mean pupil diameters are very similar for both user and nonuser groups; however, the user group means are uniformly smaller. Variability, as indicated by the standard deviation, was about twice as large for the user group early in constriction. After most active constriction was complete the variability of the two groups was about the same. Analysis of variance (ANOVA) disclosed no significant differences between the over-all group means.

We found that the number of individuals giving usable pupil data decreased rapidly after the onset of the light adaptation because many subjects had a strong tendency toward reflex withdrawal (blepharospasm or rolling the eyes upward) shortly after the onset of light adaptation. At the beginning (during response latency) and end of pupil measurements both user and nonuser groups contributed approximately the same number of measurements. However, during the period of greatest pupil activity reflex withdrawal from the illumination appeared more frequently in the user group (Fig. 2). Results were statistically significant ($p < 0.05$) if the analysis was confined to the period of active constriction.

**Intraocular pressure with water load.**

IOP was measured by applanation immediately after and at 20 min. intervals following the ingestion of 1 L. of water. The resulting IOP means for 78 eyes in both groups are shown in Fig. 3. The limit marks shown above mean values are ±1 S.E. ANOVA showed that there were no statistically valid differences between individual pairs of measurements, such as between users and nonusers, at any particular point on the time axis. Nor was there a difference between any two adjacent time periods. However, when taken as a whole, the analyses show that there was a difference ($p = 0.06$) where IOP was higher for the users. Fig. 3 suggests
Dark adaptation. Visual thresholds at times after the onset of dark adaptation are presented in Fig. 4. The smooth-drawn portion of the functions approximate the “average” subject whose final cone limb threshold and final threshold corresponded to the respective group means. The time between 0 and 4 min. was the light adaptation period. Statistical analyses were done at the “alpha” (A) point of inflection between cone- and rod-dominated portions of the function. The A point appeared at approximately 6 min. after the beginning of dark adaptation. Other mean points were generated at the asymptote for dark adaptation, which occurred at about 30 min. Limit marks are +(U, users), -(NU, nonusers) 1 S.E. By ANOVA the times to the A point were not statistically different for the user and nonuser groups. Thresholds taken separately for the cone and rod limbs were not different for the groups. However, the over-all ANOVA for both sets of thresholds indicated a marginal difference (p = 0.07). The users showed less complete adaptation than the nonusers.

Acuity at different luminances. Ability to read “Snellen” letters at different luminance levels was measured and the Snellen notation values were converted to decimal acuities (Fig. 5). Except at about -0.7 millilamberts, the nonusers mean monocular acuity was superior to that of the user group. ANOVA showed large, highly significant differences for acuity between light levels for both groups. Differences for left or right eyes taken separately or differences between groups at any par-
Fig. 5. Monocular decimal acuity means for 78 eyes viewing letters of the Snellen type at several luminances. Contrast ~ 95 percent.

![Graph](image)

**Table I. Results of evaluation of fundus photographs**

<table>
<thead>
<tr>
<th>Area</th>
<th>User</th>
<th>Nonuser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood vessels</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Retina (except macula)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Disc</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Macula</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

*Numbers represent individuals with areas judged abnormal. There are 78 eyes in each group.*

**Color match—anomaloscope test.** The widths of the brightness and color-match limits were measured by the Hecht/Schlaer anomaloscope. The upper portion of Fig. 6 shows the range of normative match midpoints produced by 49 observers studied by Willis and Farnsworth as described by Jameson and Hurvich. The midpoint lies in the center of the range of acceptable matches. The limits of the acceptable matches plus the midpoints for the normative group (“match limit range”) of 49 are displayed just below. Midpoints for the user and nonuser groups are filled circles. The related match limits are also shown to the left and right of each midpoint. ANOVA showed a statistical difference of $p = 0.01$ for the direction (green or red) from which the match was initiated. This result is expected. The analysis showed no difference between groups for the match midpoint. However, there was a statistically significant difference ($p = 0.01$) between the user and nonuser groups for the breadth of the match limits for color and for brightness. Brightness data are not pictured in Fig. 6. The widths of the match limits for color were 1.63 for the users and 3.42 for the nonusers. Limits for brightness of the users were 3.61 and those of nonusers were 5.21. For the color match, these values and the means have been converted to “comparative units” in Fig. 6 so that they may be compared with the normative data. The comparative unit scale was described by Jameson and Hurvich. All data presented in Fig. 6 are within the limits of normalcy. The primary difference between groups in this study is the extent of the match ranges which were judged acceptable. The smokers were less tolerant of deviations from the “midpoint.”

Although the preliminary screening with the Ishihara color plates was designed to eliminate persons with eye defects, the particular luminance level did not approach significance. However, ANOVA for overall differences between groups across all luminance levels was associated with a $p = 0.07$.
Table II. Summary of findings comparing user (U) and nonuser (NU) groups

<table>
<thead>
<tr>
<th>Test (condition)</th>
<th>Finding</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pupil response</td>
<td>U less than NU</td>
<td>NS*</td>
</tr>
<tr>
<td>Contributors to pupil data</td>
<td>U less than NU</td>
<td>(see text)</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>U greater than NU</td>
<td>p = 0.06</td>
</tr>
<tr>
<td>Dark adaptation</td>
<td>U less than NU</td>
<td>p = 0.07</td>
</tr>
<tr>
<td>Acuity vs luminance</td>
<td>U less than NU</td>
<td>p = 0.07</td>
</tr>
<tr>
<td>Color match midpoint</td>
<td>U requires more red</td>
<td>NS</td>
</tr>
<tr>
<td>Color match range</td>
<td>U less than NU</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Brightness midpoint</td>
<td>U more than NU</td>
<td>NS</td>
</tr>
<tr>
<td>Brightness range</td>
<td>U less than NU</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Schirmer</td>
<td>U more than NU</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Fundus abnormality</td>
<td>U more than NU</td>
<td>NS</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>U more than NU</td>
<td>NS</td>
</tr>
<tr>
<td>Pterygia</td>
<td>U more than NU</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS indicates large deviation from accepted significance levels.

Farnsworth Dichotomous Test, Panel D-15, 20 was administered later. None of the subjects who had previously passed the Ishihara test failed to pass the Farnsworth test.

**Lacrimal fluid production.** Basal (in distinction to reflex) lacrimal fluid production was measured by the Schirmer test. Results of tests performed on both eyes simultaneously indicate that the mean distance of fluid migration for the users' eyes was 2.8 mm. and for the nonusers' eyes, 2.6 mm. ANOVA for differences between groups indicate that the u group showed more fluid migration (p = 0.001).

**Other observations.** Results of the evaluation of the fundus photographs are presented in Table I. Photographs of five fundus regions of eyes in each group were examined. Areas judged abnormal are listed. Nine users had at least one fundus area judged abnormal and seven nonusers showed at least one abnormal fundus area. Although these are probably high for a randomly drawn sample, there is no basis for assuming a difference in incidence of abnormality between the two groups.

The data from the dynamic acuity test have not been presented. These results showed evidence of such great variability that no conclusion can be justified. An analysis of clinical examination data showed the presence of conjunctival hyperemia in 16 of the user group and 13 of the nonuser group. Similarly, two users were found to have pterygia whereas none of the controls had them. Numbers such as these are difficult to submit to statistical analysis. However, there may be a trend in the user group toward signs of more frequent irritation of the conjunctiva. Results are summarized in Table II.

**Discussion**

It is important to consider carefully the finally matched subject samples, the methodology, and the philosophy which produced them. Before development of the matched groups, an extensive clinical evaluation had been done to select out of the basic samples (N = 240) all "abnormal" subjects. Four users and four nonusers were excluded because of uncorrectable visual acuity; 3 users and 13 nonusers for color vision defect; 20 users and 17 nonusers for positive serological test for syphilis; eight users and 17 nonusers for pulmonary lesions; and three users and nine nonusers for other serious diseases. Then the user and nonuser groups were carefully matched on an array of medical, educational, social, and anthropological criteria. If a bias was instituted by these procedures, it would serve to reduce differences between the user and nonuser groups.

The participants in each sample were unfamiliar with the types of judgments which were required from them in the various eye tests. Consequently, the variability associated with the results from
Table III. Some symptoms of nonspecific irritation of the anterior segment of the eye and observations in users and as reported in the literature

<table>
<thead>
<tr>
<th>Symptom</th>
<th>In eye disease</th>
<th>Trends in chronic users</th>
<th>Acute users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hyperemia</td>
<td>Increased</td>
<td>Slightly increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Light sensitivity</td>
<td>Increased</td>
<td>Increased</td>
<td>Not measured</td>
</tr>
<tr>
<td>Acuity</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Conflicting reports</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>Increased</td>
<td>Slightly increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Pupil diameter</td>
<td>Decreased</td>
<td>Slightly decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>Increased</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

*As described by Duke-Elder.21 24

1 No consumption for 4 to 10 hours.

these extensive samples would be expected to be greater than that found in intensive testing on a few highly practiced subjects. It may be argued that one should accept as real only those group results where differences are associated with probability coefficients of 0.05 or less. This traditional but arbitrary cutoff level could be dangerous if applied without attention to sampling techniques. For these reasons, we have elected to consider values of $p = 0.07$ or less as indicative of real trends.

An elaborate discussion of the results of this project can yield little more than is presented in Table II. There is little experimental literature on chronic use to provide a background for discussion. With this caution, it is emphasized that the following discussion is an integration with the literature on acute marijuana use and with classical and recent concepts in ophthalmology of both statistically significant findings and trends from our experiments. The relevant clinical signs are presented as "typical" but will vary widely between individual cases.21

**Anterior segment irritability.** There are threads common to the majority of the findings of differences between the user and nonuser groups and these relate also to the acute-use literature. Among these are symptoms which are typical of many irritative states of the anterior segment of the eye.22 23 Excellent general descriptions of the symptoms have been presented by Duke-Elder23 and by Duke-Elder and Perkins.24 Table III compares these common symptoms of eye disease with findings associated with the user group of this project and with reports from the literature on acute use.

Conjunctival hyperemia is typical of many irritative states and also has been documented repeatedly as a result of acute marijuana use.4 10 11 In this study the user group had abstained from marijuana consumption for at least 4 and more likely 10 to 12 hr. prior to testing. Clinically determined conjunctival hyperemia was only slightly more frequent in the users than in their matched counterparts. This may be because of an adaptation to chronic use, dissipation of the condition, or masking of the effect by the high incidence of hyperemia in the nonusers.

Light sensitivity or "photophobia" is common21 in irritations of the anterior segment due to disease but its pathophysiology is poorly understood.25 There was no quantitative measure of "light sensitivity" in our tests but the high frequency of reflex withdrawal of user eyes from the light which was used to excite pupillary constriction tends to suggest heightened sensitivity of the user group. In addition, there was a statistically significant difference in brightness limits and color-match limits for the anomaloscope tests. If subjective brightness sensitivity is increased in the user group, it is possible that this accounts for their unusual performance on the anomaloscope-based color measures.

Acuity is often decreased in anterior segment disease. This may be due to many causes, not the least of which are slight changes in the refraction or transmission.
characteristics of the various optical layers of the anterior segment, usually caused by edema. This type of acuity loss would be uncorrectable by optical methods. An apparently optically uncorrectable acuity deficit was found in the chronic users, although subjects were carefully refracted and corrective lenses provided. In acute users reduced Snellen and vernier acuity has been reported, but Hepler et al. found no change.

Intraocular pressure elevation and elevation of protein content of the aqueous humor is also a corollary of diseases of the anterior segment of the eye. Green and Pederson have shown that protein elevation in the anterior chamber is seen in the rabbit anterior segment which was treated with Δ⁹-THC. The findings we have presented on chronic user IOP conflict with several reports of decreased intraocular pressure in nonchronic users. There are great differences in the established degrees of "experience" of the subjects. Flom et al. replicated previous findings of reduced IOP in acute smokers with little use-experience but found little or no IOP change in subjects with extensive use history. This important findings emphasizes the experience variable, which has been considered rarely in prior publications.

Mean pupil diameter was slightly but very consistently decreased during the acute phase of constriction in our users. The characteristics of the pupillary active light response in conditions of anterior segment irritation are not known, but the affected resting pupil is often smaller than normal in clinical cases of eye irritation. Duke-Elder accounted for this as a mechanical effect of iris vascular engorgement due to irritation. Bhattarchjee considered the constricted pupil a typical component of the syndrome of eye irritation which he associated with the liberation of prostaglandins from eye tissues. Hepler et al. reported mild pupillary constriction during marijuana smoking.

Prostaglandins have been associated recently with the entire syndrome of anterior segment irritation. This literature has been reviewed by Eakins et al. and more recently Neufeld and Sears. Prostaglandin production in the eye appears to be closely connected with the consequences of disease or trauma of the anterior segment. If prostaglandins and their release are specifically inhibited, the irritative response of the eye (as seen in Table III) does not occur. Green and Bowman reported that Δ⁹-THC (tetrahydrocannabinol) inhibits the formation of prostaglandins. If this is correct in the eye, for all products of THC, it is unlikely that prostaglandin production can be directly responsible for the signs of irritation which may be seen in the acute phase of marijuana consumption. However, in the absence of other information, it is possible that in the long-term chronic user there is a prostaglandin rebound or hyperproduction during periods of abstention. The moderations of prostaglandin effects or physiology which could occur during adaptation to 10 years of use are difficult to guess. As in cigarette smoking, a more important question is, "What trends are set whose results are felt clearly in 15 to 20 years?"

The visual and ocular signs that have been described in chronic users but not found in our results may also originate directly or indirectly from neurophysiological effects. There are no direct data on chronic THC-neural interaction in the eye; however, changes in pupil dimensions, vasomotor activity, accommodation, and lacrimation are discussed classically in association with the balance between sympathetic and parasympathetic divisions of the autonomic nervous system. These were reviewed by Walsh and Hoyt. More recent findings have also implicated neural control of intraocular pressure. Even the indications of heightened brightness sensitivity may have specific neural origins. Bieger and Hockman have recorded large changes in lateral geniculate nucleus function in the presence of circulating Δ⁹-THC. Also the modulation of visual function in both retina and optic nerve has a well-estab-
lished link to the sympathetic nervous system.\textsuperscript{11, 13} Ng et al.\textsuperscript{14} seem to have presented a clear case for modulation of general peripheral sympathetic activity by $\Delta^2$-THC. Recently a direct link has been established by Green and Kim\textsuperscript{15} for the control of several IOP factors by sympathomimetic actions of THC in rabbits. There is no reason to assume independence between the conjunctival or uveal irritative signs and the neural implications of chronic use as indicated by brightness sensitivity or "photophobia." This link has been established for some time as the "trigeminal syndrome,"\textsuperscript{16} a common clinical entity. The primary factors in this hypothetical link are yet to be identified.

The results presented here are available because of the extensive cooperation given by the parent project and its professional staff in the United States of America and Costa Rica. Of particular value were efforts by Drs. William Carter, Wilmer Coggins, and Paul Doughty from the University of Florida and Dr. Frederico Faerron from the Social Security System, Republic of Costa Rica. The Vision Committee, NAS-NRC working group 36, assisted in experimental design.

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