the multifocal ERG (4), and standards for the pattern ERG (5), electro-oculogram (6) and visual evoked potential (7). Recommendations for extended protocols are in preparation. We recommend that commercial recording equipment have the capability of recording ERGs under conditions that are outside the present standard but that are nevertheless either widely used or likely to be needed in the future. This document is not a safety standard, and does not mandate particular procedures for individual patients.

The organization of this report is as follows:

Introduction

Basic technology

- Electrodes
- Stimulation
- Electronic recording equipment

Clinical protocol

- Preparation of the patient
- ISCEV Standard ERG
- Recommended additional ERG response
- ERG analysis and reporting
- Pediatric ERG recording

Table 1. **Examples of specialized types of ERG (not covered by this ISCEV standard)**

Macular or focal ERG

Multifocal ERG (see published guidelines (5))

Pattern ERG (see published standard (6))

Early receptor potential (ERP)

Scotopic threshold response (STR)

Direct-current ERG

Long-duration photopic ERG (on-off responses)

Double-flash ERG

Chromatic stimulus ERG (including S-cone ERG)

Dark and light adaptation of the ERG

Scotopic and photopic luminance-response analyses

Saturated a-wave slope analysis

Specialized early and premature infant procedures

Basic technology

ELECTRODES

Recording electrodes: Electrodes that contact the cornea or nearby bulbar conjunctiva should be used for Standard full-field recording. These include contact lens electrodes, conductive fibers and foils, conjunctival loop electrodes and corneal wicks. For most users, contact lens electrodes will provide the highest amplitude and most stable recordings; such electrodes should be centrally transparent with an optical opening as large as possible, and incorporate a device to hold the lids apart. The corneal surface should be protected during use with a non-irritating and non-allergenic ionic conductive solution that is relatively non-viscous (e.g., no more viscous than 0.5% methyl cellulose). More viscous solutions can attenuate signal amplitude. Users should be aware that signal amplitude may be reduced with other types of corneal and conjunctival electrodes as the point of ocular contact moves away from the cornea apex. Topical anesthesia is necessary for contact lens electrodes but may not be required for other types of corneal and conjunctival electrodes. It is necessary that all electrophysiologists master the technical requirements of their chosen electrode, to ensure good ocular contact, to ensure proper electrode impedance, to ensure that waveforms are comparable to standard ERGs, and to define both normal values and variability (which may be different with different electrodes) for their own laboratory. ERGs recorded with the active electrode on the skin have low amplitudes and higher noise levels. These do not meet the ISCEV standard and such recordings should be reported as a deviation from the Standard

Reference electrodes: Reference electrodes may be incorporated into the contact lens-

speculum assembly to make contact with the conjunctiva ("bipolar electrodes"). This is the most stable configuration electrically. Alternatively, electrodes can be placed near each orbital rim, temporal to the eye as a reference for the corresponding eye. The forehead is also an acceptable reference site, although there is a risk of signal contamination by ocular cross-over or from cortical evoked potentials. Use of other reference positions deviate from this Standard.

Ground electrodes: A separate skin electrode should be attached to an indifferent point and connected to ground. Typical locations are on the forehead or ear.

Skin reference electrode characteristics: The skin should be prepared by cleaning, and a suitable conductive paste or gel used to ensure good electrical connection. Skin electrodes used for reference or ground should have 5 kΩ or less impedance measured between 10 and 100 Hz (4). If more than one skin electrode is used (e.g., for reference and ground) they should all have similar impedance.

Electrode stability: The baseline voltage in the absence of light stimulation should be stable. Some reference electrode systems may need to be made of non-polarized material to achieve this stability.

Electrode cleaning: Recording the ERG involves the exposure of corneal electrodes to tears and potential exposure of the skin electrodes to blood if there is any abrasion of the skin surface. Electrodes (if not disposable) must be suitably cleaned and sterilized after each use to prevent transmission of infectious agents. The cleaning protocol should follow manufacturers' recommendations and current national standards for devices that contact skin and tears.

STIMULATION

Light diffusion: Full-field (Ganzfeld) stimulation should be used. With focal flashes, the area of retinal illumination is not uniform, and its extent is unknown. Full-field dome stimulators are generally preferable to ocular diffusers (such as 100-diopter or opalescent contact lenses) since it is difficult with the latter to measure the luminance, extent and uniformity of the stimulus. It is incumbent on manufacturers and users of

diffusers to verify that full-field stimulation meets the requirements of this standard.

Stimulus duration: The standard is based on flash stimuli with durations that are considerably shorter than the integration time of any photoreceptor. Thus, stimuli should consist of flashes having a maximum duration of 5 ms.

Stimulus wavelength: Flash stimuli should have a color temperature near 7000°K, and they should be used with domes or diffusers that are visibly white. Colored filters can be used to enhance the separation of rod and cone ERGs, but this is not part of the standard (Note 1).

Stimulus strength: Flash stimuli are defined in terms of time integrated luminance or 'flash luminance' at the surface of the Ganzfeld bowl. In physical terms, this represents luminous energy per unit solid angle (steradian) per unit area, which should be measured in photopic candela-seconds per meter squared ($cd \cdot s \cdot m^{-2}$) (Note 2).

Each ISCEV Standard ERG should be elicited by flashes of the designated flash luminance, to minimize response variation. However, to account for minor variability in equipment and calibration, all values may vary within ±10% (0.05 log unit). For an ISCEV Standard ERG, the stimulus and background strengths are as follows:

(1) For rod stimulation: 0.01 $cd \cdot s \cdot m^{-2}$

(2) For all other standard responses: 3.0 $cd \cdot s \cdot m^{-2}$ (This flash was formerly designated as the "Standard Flash.")

(3) Photopic adaptation and background luminance: 30 $cd \cdot m^{-2}$

For the recommended additional response: use either 10.0 or 30.0 $cd \cdot s \cdot m^{-2}$. (Laboratories should indicate the chosen value, and name the response accordingly).

Nomenclature: Stimulus (and response) names are described by the state of light adaptation, and the flash luminance in $cd \cdot s \cdot m^{-2}$. (E.g. The dark-adapted response to 3.0 $cd \cdot s \cdot m^{-2}$ is called the "Scotopic 3.0 ERG" *in addition* descriptive terms (such as "rod response," "mixed rod-cone response," etc) may be used.) This scheme of naming should also apply to non-standard stimuli, which might be used for special protocols or

because of equipment limitations. (E.g. if flashes of 15.0 cd•s•m^{-2} are used under scotopic conditions they should be specified as a "Scotopic 15.0 ERG.")

Background illumination: In addition to producing flashes, the stimulator must be capable of producing a steady and even background luminance across the full field, for photopic adaptation. A white background of 30 cd•m^{-2} should be used (±10% allowance for variations in calibration) for this standard. A chromatic background may also be used for special purposes in non-standard ERGs.

Adjustment of stimulus and background luminance: A methods for modifying both the stimulus and background strength is required. Stimulation systems should be capable of producing flashes over a range of at least 3 log units in strength, either continuously or in steps of not more than 0.3 log unit. The method of attenuation should not change the wavelength composition of either the flash or background luminance. We recognize that the stimulus and background requirements for a full range of other ERG tests will be more extensive, and we recommend that equipment manufacturers exceed this minimum standard (Note 3).

Stimulus and background calibration: The flash luminance produced by each flash within the full-field stimulus dome must be documented by the user or manufacturer, with an integrating photometer placed at the location of the eye. The photometer must meet international standards for photometric measurements based on the photopic luminous efficiency function (photopic luminosity curve), and must be capable of recording the total output of very brief flashes. For most stroboscopic stimulators, light output per flash varies with the flash repetition rate; therefore, separate calibrations will need to be made for single and repetitive stimuli. The background luminance of the dome's surface is calibrated in a non-integrating mode. Users should consult the ISCEV guidelines for calibration of electrophysiologic equipment (4) for a more detailed treatment of calibration procedures. We recommend that manufactures of stimulations supply a suitable photometer with their equipment.

Recalibration: See the ISCEV guidelines for calibration (4). Light output from a dome varies with time from changes in the flash tubes, power sources, line voltage, the background lights (particularly if they are incandescent), attenuation systems, or

reflectance of the dome. Responsibility for electronic stability and warnings about sources of instability should rest with the manufacturers of the equipment. The frequency with which recalibration of flashes and backgrounds is required will vary from system to system and could be as high as weekly for some units. Self-calibrating units are encouraged.

ELECTRONIC RECORDING EQUIPMENT

Amplification: The bandpass of the amplifier and preamplifiers should include at least the range of 0.3 to 300 Hz and be adjustable for oscillatory potential recordings and special requirements. The input impedance of the preamplifiers should be at least 10 MΩ. Amplifiers should generally be AC (alternating current) coupled (i.e., capacitatively coupled) and capable of handling offset potentials that may be produced by the electrodes (Note 4).

Patient isolation: The patient should be electrically isolated according to current standards for safety of clinical biologic recording systems in the user's country.

Display of data and averaging: The final record should represent, without attenuation, the full amplifier bandpass. Good resolution can be achieved with oscilloscopes or computer-aided (digitizing) systems but not with direct pen recorders. To avoid a loss of information, digitizers should sample ERGs at a rate of 1 kHz or higher in each channel. With computer-aided systems, it is important that ERG waveforms be displayed promptly so that the operator can continuously monitor stability and make adjustments during the test procedure. Recording units that digitize ERG signals can usually average them as well. All single flash responses should be presented with at least 20 ms of baseline preceding the flash, to allow judgment of baseline stability.

Clinical protocol

PREPARATION OF THE PATIENT

Pupillary dilatation: The pupils should be maximally dilated and the pupil size noted for all ERG recordings in this standard.

Pre-adaptation to light or dark: The recording conditions outlined below specify 20 min of dark adaptation before recording rod ERGs, and 10 min of light adaptation before recording cone ERGs. The choice of whether to begin with scotopic or photopic conditions is up to the user, provided these adaptation requirements are met. If contact lens electrodes are used, the wearing time can be minimized by dark adapting first, and inserting the electrodes under dim red light at the end of the adaptation period. Care should be used to avoid too bright a red light, and an additional 5 min of dark adaptation may be needed for recovery after lens insertion.

Pre-exposure to light: We advise that fluorescein angiography or fundus photography be avoided before ERG testing, but if these examinations have been performed, a period of dark adaptation of at least one hour is needed. It is usually preferable to record scotopic ERGs to weak flashes before the ERGs to stronger flashes, to minimize light adaptation during the scotopic testing, and to reduce the time that the patient wears an electrode.

Fixation: A fixation point should be incorporated into stimulus domes. A stable eye is important so that eye movements do not alter the corneal electrode position, produce electrical artifacts, or allow blockage of light by the electrode or eyelid. Patients who cannot see a fixation target may be instructed to look straight ahead and keep their eyes steady. Patients should be monitored to assess compliance, and account for difficulties in eye opening or fixation.

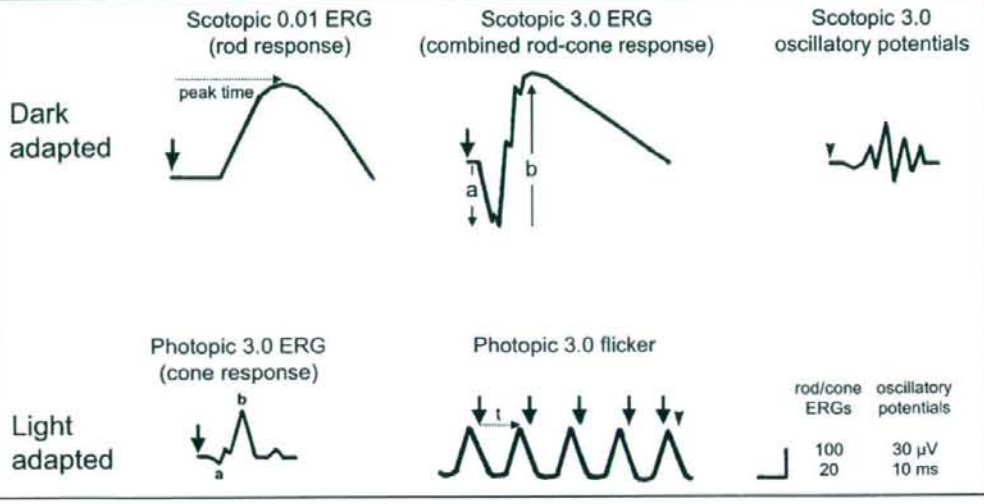

Fig. 1—Diagram of the six basic ERG responses defined by the Standard. These waveforms are exemplary only, and are not intended to indicate minimum, maximum or even average values. Large arrowheads indicate the stimulus flash. Dotted arrows exemplify how to measure time-to-peak (*t*, implicit time), *a*-wave amplitude and *b*-wave amplitude.

ISCEV STANDARD ERG (see Figure 1)

Scotopic 0.01 ERG (rod response): Dark-adapt the patient for a minimum of 20 min before recording the scotopic ERG (and longer if the patient had been exposed to unusually bright light). The scotopic 0.01 ERG is normally the first signal measured after dark adaptation, since it is the most sensitive to light adaptation. The stimulus is a dim white flash of 0.01 cd•s•m^{-2}; with a minimum interval of 2s between flashes.

Scotopic 3.0 ERG (combined rod-cone response): This is produced by a white 3.0 cd•s•m^{-2} flash in the dark-adapted eye. There should be an interval of at least 10s between stimuli.

Scotopic 3.0 oscillatory potentials: Oscillatory potentials should be obtained from the dark-adapted eye, using the 3.0 cd•s•m^{-2} flash stimulus. Oscillatory potentials may also be recorded from the light-adapted eye (photopic 3.0 oscillatory potentials). The high-pass filter must be set at 75-100 Hz, so that an overall bandpass of 75-100 Hz on the low end and 300 Hz or above at the high end is achieved. Users should be aware that there are several types of electronic and digital filters, which may have different effects

upon physiologic signals (e.g., phase shifts or ringing). More information about filter selection and use is presented in the ISCEV guidelines for calibration (4).

The oscillatory potentials vary with stimulus repetition rate and change after the first stimulus. To standardize the oscillatory potentials, repetition of the flickering stimulus should be given 15 s apart to the dark-adapted eyes (1.5 s apart to light-adapted eyes), and only the second or subsequent waveforms be retained or averaged.

Photopic 3.0 ERG (single-flash cone response): Use the 3.0 cd•s•m^{-2} stimulus. To achieve stable and reproducible cone ERGs, a minimum of 10 minutes light adaptation is required with a background of 30 cd•m^{-2} measured at the surface of the full-field stimulus bowl.

Photopic 3.0 flicker: Flicker ERGs also reflect activity of the cone system, and should be obtained with 3.0 cd•s•m^{-2} stimuli, under the same conditions of light-adaptation as the photopic 3.0 ERG. Recording the flicker ERG in the light-adapted state reduces discomfort and allows the photopic adaptation to be standardized. Flashes should be presented at a rate of approximately 30 stimuli per second (30 Hz), and the rate that is chosen should be constant for the laboratory. The first ERG to the flickering stimulus will be a single-flash waveform; thus, the first few waveforms should be discarded so that stable conditions are reached. Some flash tubes do not produce full output while flickering, and separate calibration or a change in light attenuation may be needed to conform to the standard.

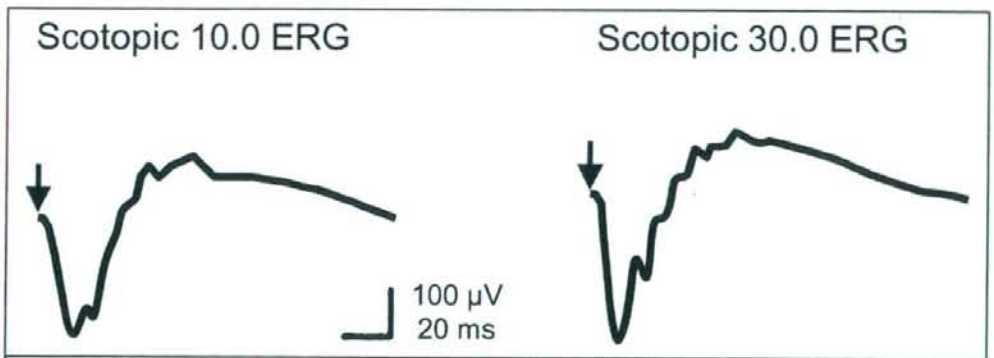

Fig. 2—Diagram of the recommended additional bright flash response, either at 10.0 (left) or 30.0 cd•s•m^{-2} (right). Arrows indicate the time of the stimulus flash.

RECOMMENDED ADDITIONAL ERG (See Figure 2)

Scotopic 10.0 or 30.0 ERG: An additional dark-adapted ERG to a stronger flash is recommended for routine testing. This response shows better a-wave definition (no double peak), larger oscillatory potentials that are easier to characterize, and more distinction of negative ERG waveforms (for critical recognition of diseases with relative b-wave reduction). Also this stronger flash may give better signals in patients with opaque media or immature retinae. We suggest a flash luminance of either 10.0 or 30.0 $cd \cdot s \cdot m^{-2}$. Both of these values are in wide usage, but there is insufficient evidence as yet to choose between them. This flash should ordinarily be presented after scotopic 3.0 ERG, to the dark-adapted eye, with an interval of at least 20 s between stimuli. This response should be described according to the exact stimulus value used, e.g. "scotopic 10.0 ERG", or "scotopic 30.0 ERG". Note that these stronger flashes are not recommended as an addition to the photopic ERG, because the higher flash luminance may reduce the b-wave amplitude due to the photopic hill phenomenon.

ERG ANALYSIS AND REPORTING

Single flash ERGs: In general, b-wave amplitude and time-to-peak (implicit time) is measured for all ERGs (except oscillatory potentials), and the a-wave should also be measured when recognizable as a distinct component. According to current convention, the a-wave amplitude is measured from baseline to a-wave trough, the b-wave amplitude is measured from a-wave trough to b-wave peak; the a-wave and b-wave implicit times are measured from the time of the flash to the peak of the wave (see figure).

Oscillatory potentials: There is considerable debate in the literature about how to measure and describe oscillatory potentials (Note 5). Their appearance is highly dependent upon adaptation state and filter characteristics of the amplifier, but most authors describe three major peaks often followed by a fourth smaller one. Simply observing the presence of three peaks, and their normality relative to the standards of the laboratory, may be adequate for many clinical purposes at our present state of knowledge.

Flicker ERG: The amplitude of flicker ERG is measured from the trough to the peak

(averaging several typical responses. The implicit time is measured from each stimulus onset to the corresponding peak.

Averaging: Averaging is not required ordinarily to record quantifiable ERGs with the recommended types of electrodes. Averaging a limited number of ERGs may decrease variability and help to reduce background noise, if present. Averaging may also be used to identify and measure very weak pathologic ERGs. Artifact rejection must be a part of any averaging system. Signal repetition rates should not exceed the recommendation in the standard for each type of ERG.

Normal values: We recommend that each laboratory establish or confirm normal values for its own equipment and patient populations giving attention to an appropriate sample size. All ERG reporting (whether for local records, publication, or even for non-standard ERGs) should include normal values that are adjusted for age, and should show the *limits of normal.* Some manufactures distribute norms for their standard protocols, and several large series have been published recently that give normative data. However, ERG norms for amplitude may have to be scaled up or down depending on where the user's electrode rests on cornea or conjunctiva. Note that ERG parameters increase rapidly during infancy and decrease modestly with age thereafter. At elderly ages, the fall in amplitude can be substantial. Because some ERG parameters (such as *b*-wave amplitude) are not necessarily normally distributed, calculations of standard deviation may be misleading. To describe the limits of normal, the median value (not the mean) should be used, and the actual values on either side of the median that bracket 95% of the normal range of ERGs (in other words, the 95% percentile determined by direct tabulation of ERGs). Although circadian variations of the ERG are small under ordinary recording conditions, we recommend that the time of ERG recording be noted on all records since it could become relevant for certain diseases or for repeat measurements.

Reporting the ERG: Standardization of ERG reporting is critical to the goal of having comparable data worldwide. ERG reports should include representative waveforms of each of the standard ERGs displayed with amplitude and time calibrations and labeled with stimulus variables and the state of light or dark adaptation. These should include at least 20 ms of baseline prior to the stimulus, for single-flash responses, and where feasible should indicate the stimulus time for each flash with a marker or line (for flicker as well as single-flash). We suggest that when single flash stimuli are used

without averaging, two waveforms of each ERG be displayed to demonstrate the degree of consistency or variability. The flash luminance ($cd \cdot s \cdot m^{-2}$) and the background luminance ($cd \cdot m^{-2}$) should be given in absolute values. *Reports should indicate whether the techniques of recording meet the international standard, and any deviation should be described explicitly.* All reports should give patient results listed along with normal values and ranges. Finally, reports should note the time of testing, pupil diameters, and any conditions that are not specified by the standard, including type and position of electrode, sedation or anesthesia, and the level of compliance.

PEDIATRIC ERG RECORDING

The ERG can be recorded from infants and young children. The younger the infant, the more chance that adult norms will not apply. Somewhat lower amplitudes and longer implicit times generally apply below 6-12 months of age under dark-adapted conditions, and below 2-3 months of age under photopic conditions. Below 6 months of age, the scotopic 3.0 ERG may be poorly defined in healthy infants; the scotopic 10.0 or 30.0 is usually well defined in all infants. In general, very young or premature infants pose special problems and require special techniques and norms outside of this Standard.

Most pediatric patients can be studied without sedation or general anesthesia (topical anesthesia is necessary for contact lens electrodes). Small infants can be restrained if necessary. Noncompliant children (especially ages 2-6 for whom containment can be difficult) may become compliant with oral sedation. Medical guidelines should be followed with respect to indications, risks, medical monitoring requirements and the choice of a sedative/relaxant versus general anesthesia. Considering the variability of pediatric records, there will generally be little effect on ERG amplitude or waveform with sedation or light anesthesia, although full anesthesia may modify the ERG.

Contact lens electrodes are applicable to infants and young children, but pediatric sizes will be required with eyelid specula. Non-contact lens and skin electrodes vary in their applicability to children; greater comfort is often offset by greater movement or smaller. Special care is required with children to monitor electrode position and compliance to minimize artifacts.

The ERG matures during infancy, and newborn and infant signals must be interpreted

with great caution. Later in infancy and childhood, ERGs approach adult waveform and amplitude. Pediatric ERGs should ideally be compared to those from normal subjects of the same age, although there may be little normative data available. Because movement and poor fixation can make pediatric records variable, several repetitions of each ERG should be recorded in order to recognize reproducible waveforms and choose the best examples. Standard protocols may occasionally need to be abbreviated in order to obtain the ERGs most critical to the diagnostic question under investigation. Stronger flashes may help to reveal poorly developed ERGs. Reports should note the degree of cooperation and any medications used.

Notes

1. Chromatic stimuli offer certain advantages in the separation of cone and rod ERGs, but the calibration of colored stimuli and the relation of the ERGs produced by them to the standard ERG require special procedures. White flashes should be used for the standard ERGs, whether or not other stimuli are used in addition.

2. White stimuli produced by a combination of narrow band sources, such as red, green and blue light-emitting diodes (LEDs), may not be equivalent to broad-band white light as a stimulus for both rods and cones. Manufacturers must ensure that appropriate photopic and scotopic filters are incorporated into their stimulation and calibration systems so that stimulus output is equivalent to the standard for all conditions. Separate scotopic calibration may be necessary for LED systems, and if so the proper stimulus for eliciting rod ERGs will be 2.5 log units below a scotopically-calibrated standard flash. The word 'intensity' is widely used to describe the luminance of surfaces. However, in photometry, 'intensity' quantifies the strength of point sources of light. Luminance is the appropriate term for extended sources such as those used for ERG stimuli and backgrounds.

3. We recommend that the flash source of commercial instruments be capable of generating strengths at least 2 log units above the basic 3.0 $cd \cdot s \cdot m^{-2}$ flash and be attenuable through 6 log units below that same flash. Regardless of whether attenuation is achieved by filters or electronic means, we also strongly recommend that commercial units incorporate a means of inserting additional colored and neutral density filters. These capabilities will allow electrophysiologists to perform a variety of useful protocols beyond the Standard, and will meet possible future changes in the Standard. We also suggest that

background luminance be adjustable to perform electro-oculography with the same equipment. Commercial units should also allow the insertion of colored and neutral density filters into the background illumination system to meet a variety of needs.

4. DC (direct-current) amplification can produce signals identical to those from AC amplification, but it is extremely difficult to use because of drift in baseline and offset potentials; we strongly advise AC recording except for laboratories with special requirements and expertise.

5. An overall index of oscillatory potential amplitude can be obtained by adding up measurements of the three major peaks, preferably from lines spanning the bases of the adjacent troughs, but alternatively from adjacent troughs directly (to allow use of measuring cursors with digitized systems). Some authors advise measurement of individual peaks.

AKNOWLEDGEMENT

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総説

小口病の100年

三宅養三

〔要　約〕

小口病は先天停在夜盲の一角を担う重要な疾患であり，1907年に小口忠太により報告された。小口，水尾，中村，川上らによる初期の研究の後，1960年代から現在にいたるまで機能生理，分子遺伝，光学的手法を用いた多くの研究がなされてきたが小口病の謎は依然として解けていない部分が多い。発見の経緯，初期の研究，最近の研究，先天停在夜盲の分類の発展をまとめてみた。

はじめに

小口病は1907年（明治40年）に小口忠太（図1）により報告された先天停在夜盲の分類に属する疾患である[1]。小口病が発見されてから100年が経過し，この謎に満ちた疾患の病態生理がどの程度解明されたかを振り返ってみたい。

Ⅰ．発見の経緯

日本眼科学会百周年記念誌，日本の眼科の歴史・明治編より一部引用する。小口は東京大学眼科で河本重次郎教授に師事後，陸軍軍医として東京衛戍病院に在勤中に本症を発見した。因みに小口の年齢は31歳であった。22歳の男性患者は夜盲を訴え来院したが，他医では徴兵逃れのための詐病が疑われていた。小口はその特異な眼底を次のように記載している[1]。「視神経乳頭，網膜動静脈に異常はない。周辺部まで検索しても，色素斑や白点は認めない。ただ周辺部に到るにつれて網膜反射が強くなり霜降り様に見える。光線の加減によってはこの部に細白点が散在しているようにも見えるが，アトロピン散瞳下で精査したところは白点ではなかった。周辺部の網膜血管が黒ずんで浮き出して見え，血管の一側に沿った反射が見られる。」小口の最初の報告には，この眼底の詳細なカラー描写（図2）[1]のみならず，各種視機能検

図1　小口忠太（明治8－昭和20）
この写真は愛知医科大学（現名古屋大学医学部）学長の頃のもの

三宅　養三：愛知淑徳大学医療福祉学部視科学専攻

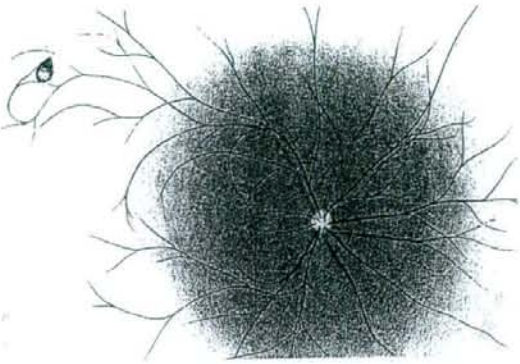

図2　小口が発表した「夜盲症ノ一種ニ就イテ」に掲載された小口病患者の眼底図譜

査や当時認知されていた各種夜盲症との鑑別診断が細かく記されており，この疾患が過去に報告のない新しい夜盲症であることを確認させるのに十分の記載である[1]。

また患者の供述で，日が暮れると見難くなり暁の頃になると多少見難さが改善するとする本症に独特の暗順応特性を最初の報告で記載している事実は，驚愕に値する。この患者の両親がいとこ婚であることや兄弟姉妹7人中6人に夜盲があったことより，常染色体劣性遺伝が強く疑われた。小口病の遺伝形式が常染色体劣性であることは，その後川上[2]により実証された。

1910年に小口は日眼会誌に本症の第2例を報告し，さらに1例を加え，3例の本症を1912年にGraefe's Archiv Ophthalmologieに発表し，本症が国際的に認知されるに到った。その後，河本重次郎はこの疾患を「小口病」と命名した。

Ⅱ．水尾・中村現象の発見

小口病の特異な現象として，1914年に水尾源太郎と中村文平により報告された水尾・中村現象がある[3]。これは患者を長時間暗所におくと眼底の特異な色調はしだいに失われ，やがて正常所見になるという現象である（図3）。眼底が正常化するのに要する時間は多くは2〜5時間であるがさらに長時間を要する症例もある。逆にこの正常化した眼底を明所におくと，60分程度でもとの特異な眼底に戻る。この発見のいきさつは日本眼科学会誌100年史に福島義一により詳細に記されている。

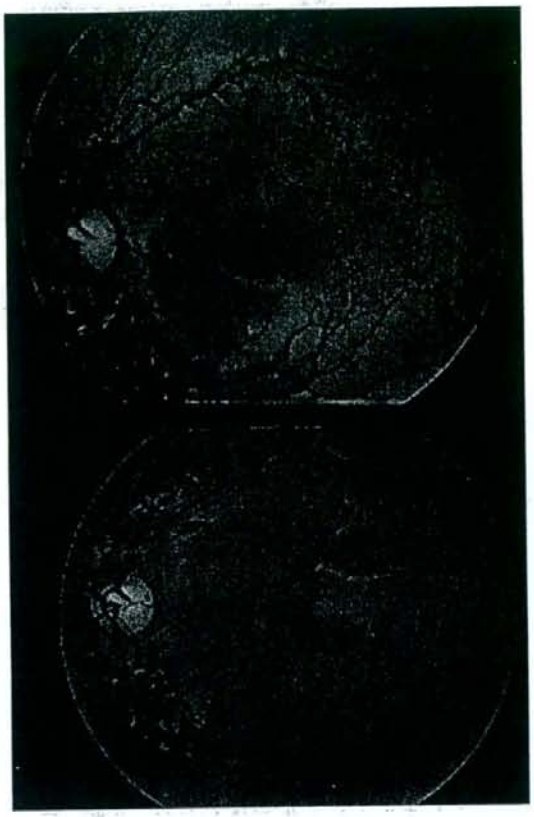

図3　水尾・中村現象
小口病特有の眼底反射（上）が長時間暗順応により正常化する（下）

Ⅲ．暗　順　応

上述したように本症の暗順応の基本的特性は，すでに小口の最初の論文[1]で示唆されていたが，その後中村文平による詳細な報告[4]があり，暗順応機能は全ての症例で異常であった。多くの症例が極度に遅延した杆体暗順応を示し，錐体暗順応（暗順応曲線第1相）が長時間続き，その後緩やかな杆体暗順応（第2相）が出現する。眼底所見の暗所での正常化，および明所での再現の時間因子と明暗順応機能との間には一義的な関係はみられない[4]。

Ⅳ．その後の研究

上述した初期の研究は1920年代で終了し，その後1960年代から現在にいたるまで小口病に関

する新しい研究がなされた。これらの研究は互いに関連性があり，その結果の解釈には包括的な理解が必要であるため，ここにまとめて述べてみる。

(1) 他覚的視覚生理学的研究

1960年代に入り，網膜電図（ERG）や眼球電位図（EOG）が臨床の場で使用されるようになり，永田誠（日眼会誌，1963），窪田靖夫（日眼会誌，1965），Carrら[5]による本症の結果が報告された。この中で小口病の病態生理に関する固定概念を作ったのはCarrらの電気生理所見とレチナルデンシトメーターによるロドプシンの量的，質的測定による結果であった[5]。Carrらの得た所見では，暗順応下で記録した強い刺激光による杆体・錐体混合反応は正常のa波と強く減弱したb波を示し，視細胞層の障害では異常を示すはずのEOGは正常であった。さらにレチナルデンシトメーターで測定したロドプシンは量的，質的に正常であり，これらを総合して考えるに，小口病の夜盲の機序は杆体視細胞の外節には存在せず，それより中枢であることが予想される。ERGのa波が正常でb波に強い減弱が見られたことやEOGが正常であったことより，視細胞の内節も否定でき，Carrらは杆体双極細胞あるいはそのシナプスに夜盲の責任病巣があるとの説を打ち立てた。この仮説はその後長年にわたって，国際的に信じられてきた。

図4に我々の自験例のERG（強い白色刺激による杆体・錐体混合反応）を30分暗順応後とより長時間の暗順応後に記録したものを示している[6]。30分暗順応では症例の反応が一様であることが分かる。すなわち正常に比べb波の強い減弱がみられるが，Carrらの報告と異なりa波も減弱している。律動様小波はよく残存している。自覚的暗順応で示されたように，ERGも長時間の暗順応によりその振幅が回復することが水口勇臣ら（日眼会誌，1963），窪田靖夫（日眼会誌，1965）らにより示された。ただ極めて興味深い所見は，暗順応を延長することによりa波の振幅は正常大にまで回復するのにb波はそれほど回復しない症例が多いことである（図4）。その結果，十分に長い暗順応後でもa波がb波より大きい，いわゆるnegative ERGを示している。

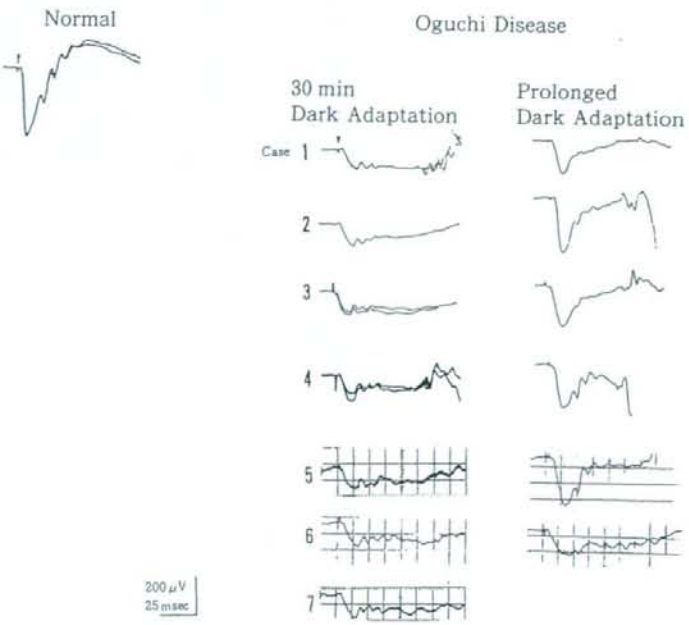

図4 正常者（左），7例の小口病患者の30分暗順応後（中）と長期暗順応（右）のERG
30分の暗順応（中）ではa波に著しい減弱がみられ，b波はさらに減弱している。律動様小波は残存している。長時間の暗順応（右）ではa波はよく回復しているが，b波の回復は悪い。

この回復したERGも一度強い光刺激を与えると瞬時に長時間の暗順応前の反応に戻ってしまい，このような変化は他の疾患では見られない現象である。

筆者は上述のCarrらの結論[5]に疑問を持っていた。その理由は，自験例を含めた過去に報告された本邦の小口病のERGやEOG所見がCarrらのものと異なったからである。図4に示したようにERGのa波の振幅が明らかに正常より小さく，この所見は小口病の杆体視細胞自体に異常があることを示している。さらにEOGも日本の報告の多くが異常を示していた[6]。Carrらの述べたロドプシンが量的，質的に正常でありERGのa波やEOGが異常であるとすると，筆者は夜盲の責任病巣は杆体のphototransductionに存在する可能性が強いことを報告した[6]。

(2) 遺伝子学的研究

筆者の想像通り，1995年に日本人の小口病患者において杆体視細胞のphototransductionであるアレスチン遺伝子に変異が同定された[7]。ついで1997年にはYamamotoらが米国の白人患者でやはり杆体のphototransductionであるロドプシンキナーゼ遺伝子を同定した[8]。この両変異の違いは臨床所見の差として現時点では捉えられていない。いずれもよく似た臨床症状を示すのである。

以上のいきさつから，小口病の夜盲の責任病巣はCarrらのいう杆体双極細胞あるいはそのシナップスであるとの説は誤っており杆体のphototransductionに存在するとした筆者らの説が正しかったように見える。しかしそれでもまだ謎は残るのである。上述したように強い刺激光による杆体・錐体混合反応のERGでは，30分の暗順応の記録ではa波も非常に小さく杆体自体の異常を示唆しているが，それ以上の長時間の暗順応で経過を追うとa波は正常大の振幅に回復してもb波の回復は悪く，ERGはnegative typeを示すことが多く，この時点では双極細胞の機能不全を暗示している。この結果は小口病の夜盲の責任病巣は杆体のphototransductionであるが，それに加えて双極細胞の何らかの機能異常も示唆されるのである。

(3) 眼底の特異な色調の研究

“霜降り状”あるいは“はげかかりたる金箔状”の眼底は本症の特徴であるが，水尾・中村現象を含め，その機序は謎である。組織学的所見も山中（1924），小口（1925），桑原ら（1963）の報告があり，この中には視細胞層と網膜色素上皮層の間にリポフスチンなどに富む“特殊な層”の存在を示唆したものもあった。この特殊な層の存在が仮に特異な眼底の色調と関連する場合，水尾・中村現象のように順応とともに刻々と変化する状態を説明するのが難しいように筆者には思える。

小口病眼底における最近の研究を紹介する。小口病眼底と色調が極めて類似する所見が若年網膜分離症の周辺部眼底にしばしば見られるが，これも長時間の暗順応により正常化し，水尾・中村現

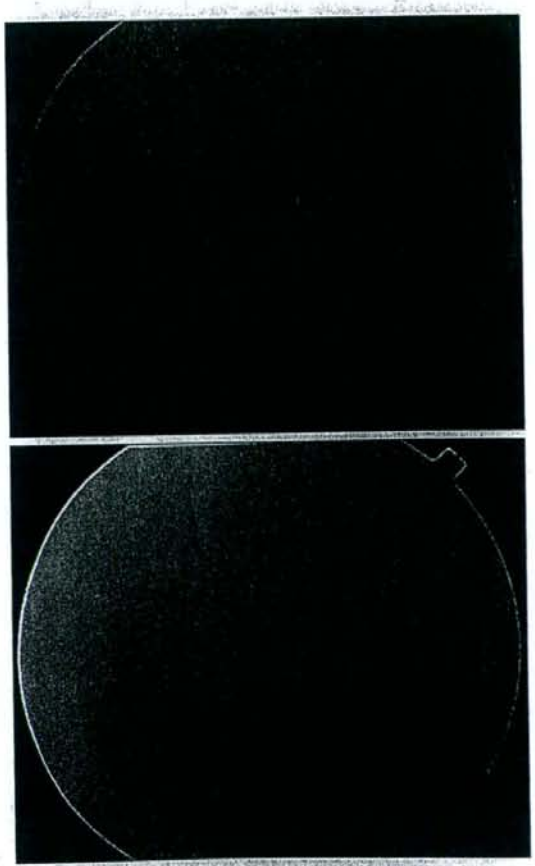

図5　黄斑円孔により vitrectomy が施行された小口病患者の術眼（上）と非術眼（下）における同じ眼底部位での比較。明らかな色調差がみられる

象を示すことが報告された[9]。彼らはこの眼底変化はミュラー細胞機能不全によるカリウムイオンの網膜内異常蓄積によると考えた。

若年網膜分離症では硝子体出血を合併することがあるが，筆者は若年網膜分離症のこの眼底異常反射がvitrectomyで網膜と硝子体の強固な癒着をとり完全な硝子体剝離をおこすことで変化することを見出した[10]。さらに未発表のデータであるが，その後黄斑円孔のためvitrectomyを受けた小口病患者を検査する機会を得た。図5に示すように，手術眼と非手術眼の眼底の色調は明らかに異なっていた。なぜvitrectomyで硝子体剝離を人工的に作成すると若年性網膜分離症や小口病に見られる特異な眼底色調が正常に近い色に変わるのであろうか。上述したDe Jongらの仮説が正しいと仮定すると，強固に癒着した硝子体を網膜から人工的に剝離させると，網膜内境界膜にも何らかの変化が起こる可能性がある。例えば一部（あるいは広範囲）の内境界膜も一緒に剝がされるかもしれない。それに伴いミューラー細胞の機能に変化が生じ，カリウムイオンの硝子体内の放出が増加し，この異常反射を寛解させるのかもしれない。

V．先天停在夜盲の分類の発展

小口病の発見により先天停在夜盲の分類は，白点状眼底，眼底正常の夜盲症（狭義先天停在夜盲），小口病の3つとなった。その後筆者らは狭義先天停在夜盲がERGの分析から異なった2つの疾患から成ることを見出し，完全型（CSNB 1），不全型（CSNB 2）と命名した[11]。これらが別の責任遺伝子変異を持つことが証明され，不全型は小口病に次ぐ新しい先天停在夜盲として認知された。その結果先天停在夜盲の分類は白点状眼底，小口病，完全型，不全型となった。さらに筆者らの研究により，白点状眼底のかなりの症例が錐体dystrophyを合併し進行性疾患であることが判明し，本症を停在性夜盲に含めるかどうかの議論が国際的になされている。

小口は大正8年に愛知県立医学専門学校に赴任され，大正11年にこれが愛知医科大学（現名古屋大学医学部）に昇格とともに教授となられ，その後同大学学長，名古屋医科大学教授，名古屋帝国大学教授を歴任され，昭和14年に退官された。昭和8年には数々の業績，特に小口病の発見に対し，学士院賞が授けられた。先天停在夜盲の日本人の貢献は小口病にはじまり，その後も名古屋大学で大きな発展をとげた。天の小口忠太教授もお喜びのことと思う。

おわりに

小口病の発見経緯，初期研究とその後の研究発展につき述べた。この謎に満ちた夜盲症はその病態生理に幾多の未知の部分が残されている。

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