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Title: CLASSIFICATION OF SUPERFICIAL LESIONS OF THE EYE WITH AN OPTICAL BIOPSY SYSTEM: FIRST TRIALS WITH THE LOS ALAMOS INSTRUMENT

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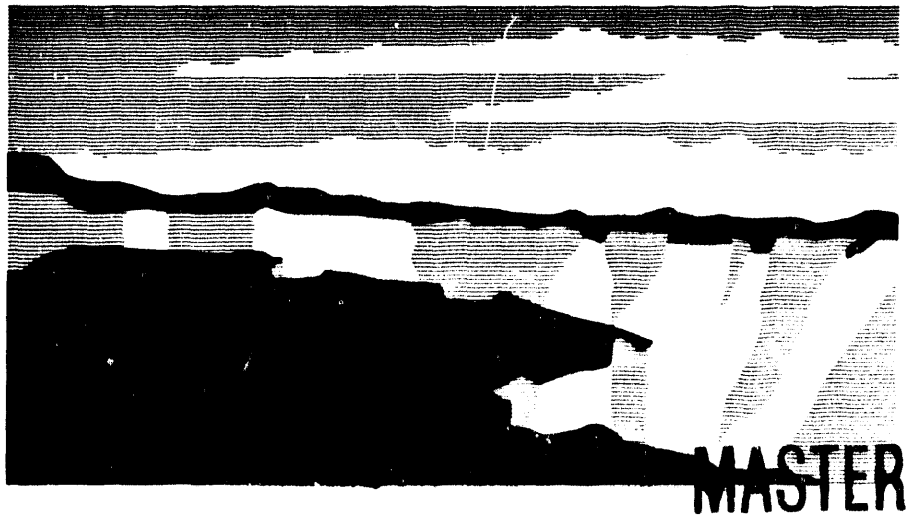

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Classification of Superficial Lesions of the Eye with an Optical Biopsy System: First Trials with the Los Alamos Instrument

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ABSTRACT

By measuring the optical backscatter and absorption properties of biological tissue, an optical biopsy system may provide a noninvasive alternative to conventional histopathological analysis.

Classification of Superficial Lesions of the Eye with an Optical Biopsy System: First Trials with the Los Alamos Instrument

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*Dedicated to the memory of Thomas R. Loree (1 February 1936 - 27 February 1993).

INTRODUCTION

The clinical diagnosis of a lesion often requires that a histological analysis be made of a physical specimen of the suspect tissue. The procurement of the tissue sample may itself involve risk, stress, and expense to the patient, so that a risk/benefit analysis must be made to justify the decision to take a biopsy. Therefore, an effective, noninvasive method for distinguishing malignant from benign growths on the conjunctiva of the eye, for example, would have considerable clinical utility. Many variations of superficial growths, as well as pigmented and non-pigmented conjunctival lesions, are frequently encountered in ophthalmological practice. The definitive way currently of classifying ocular surface lesions, in particular distinguishing malignant tissue from benign, is excision of the lesion with histopathologic diagnosis (4,6). Nevertheless, because these lesions involve the conjunctiva and sometimes the sclera, they are accessible to a light probe and thus are candidates for diagnosis based on their optical characteristics, or "signature". Potential optical measures have been developed previously for detecting and classifying cataractous changes in the ocular lens (1,6-9). While some of these approaches might be suitable for a routine, noninvasive clinical technique, most either require some subjective interpretation of the obtained optical data, or, do not yield a complete enough data set to provide definitive discriminations of pathological conditions. In the present work, we have utilized an optical biopsy system (OBS) developed at Los Alamos National Laboratory which is safe for patient use and provides a large amount of optical data from the sampled tissue. An earlier version of this system has been used to study age-related changes in the ocular lens (10). The purpose of the present study is to establish the potential clinical utility of the OBS by determining if characteristic features in the optical signatures, obtained from a variety of ophthalmic lesions, are correlated with the histological features of tissue biopsies obtained from these patients.

METHODS

The Optical Biopsy System

The OBS probes the absorption, scattering, and fluorescence properties of tissue. The instrument used in this study differed from that described earlier (10). White light is directed into the target tissue through one or more optical fibers, and collected from the tissue by a different set of optical fibers. Both sets of fibers are contained in a single probe of about 1 mm in diameter that is placed in contact with the tissue. Because the delivery and collection fibers are non-coincident, light directly reflected from the tissue is not collected. Photons entering the target tissue may

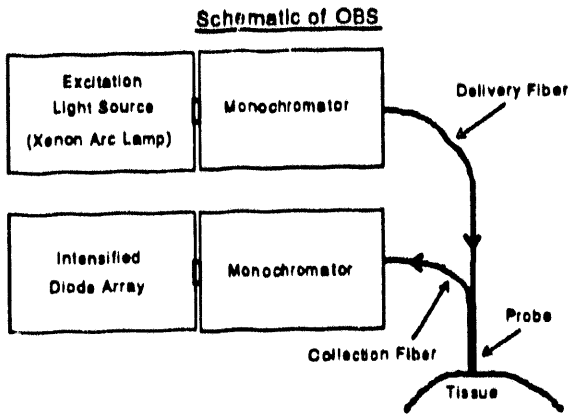

Figure 1. The Optical Biopsy System.

experience three possible fates other than reflection: (1) elastic (Mie) scattering (with some photons directed back into the collection fiber), (2) absorption, or (3) absorption by a suitable chromophore with re-emission of a photon at a longer wavelength (fluorescence). Fluorescence in the conjunctiva and sclera, however, is weak and the detected signal is primarily a function of the scattering and absorption properties of the tissue. No attempt will be made here to separate the effects of scattering and absorption.

Figure 1 is a schematic of the OBS system. The light source was a pulsed, xenon arc lamp (EG&G FX-249Q), focused onto the input of a monochromator. The output of this monochromator was collected by two, 400 μm optical fibers and delivered through a hand-held probe to the tissue. For the measurements described here, the zeroth order of the monochromator was used. Therefore, white light was incident on the tissue. The light returned by the tissue was collected by a single, 200 μm optical fiber (contained in the same hand-held probe as the delivery fibers), dispersed by a spectrograph (Thermo Jarrell Ash, Monospec 18) and detected by an intensified diode array (Princeton Instruments IRY-700 S/RB). The output of this multichannel analyzer was digitized, displayed, and stored on an IBM-compatible PC, which also controlled the operation of the entire system.

To make an accurate measure of the absorption and scattering properties of the tissue, the system response was first determined by taking the ratio of each tissue spectrum to a spectrum obtained from a sample of Spectralon (Labsphere, Inc.). Spectralon is a thermoplastic material with a >99% diffuse reflective characteristic in the wavelength range 400 - 900 nm, and a >95% diffuse reflective characteristic from 250 to 400 nm. A background spectrum was subtracted from both the tissue and Spectralon spectra. The OBS was used to obtain the optical signature of conjunctiva and sclera over the wavelength range of 200 to 900 nm (useful range = 250 to 800 nm). Each recorded spectrum consisted of an average of the tissue returns from 10 flashes of the lamp, and took approximately 1 sec to collect. Averaging individual readings in this fashion reduced the noise in the measurements as well as the effect of flash-to-flash variations in lamp output.

Safety Considerations

The white light power conducted through the fiber array delivered less than 1 μJ per flash to the conjunctival tissue in a flash duration of 5 μsec FWHM. Based on safety standards for laser and broadband sources (2,3), no ocular hazard existed for the exposure regime used to obtain the optical signatures.

Subjects

Eleven subjects with superficial eye lesions were recruited from the patient populations of the University of Texas Heath Science Center Eye Consultants Clinic, the Brady-Green Clinic, and VA Hospital of San Antonio. Four normal subjects were recruited from among the University staff and the investigators. The study was approved by the Institutional Review Boards of the UTHSCSA and VA Hospital, and consent was obtained from all subjects prior to the study.

RESULTS

The patients in this study had lesions falling into the following groups: pinguecula or pterygia (n=2), nevi or other pigmented lesions (n=4), and primary acquired melanosis (PAM) (n=5). All but one of these patients had the diagnosis confirmed by histopathological analysis from biopsy material. All these lesion types produced backscatter spectra that differed substantially from the signature of normal conjunctiva. The backscatter spectra from normal conjunctiva and from a pinguecula are shown in Fig 2. In normal conjunctiva, the amplitude of the scattered signal is high in the UV and short-wavelength visible, and then declines throughout the visible and IR. The spectra are noisy in the IR because of detector and system characteristics.

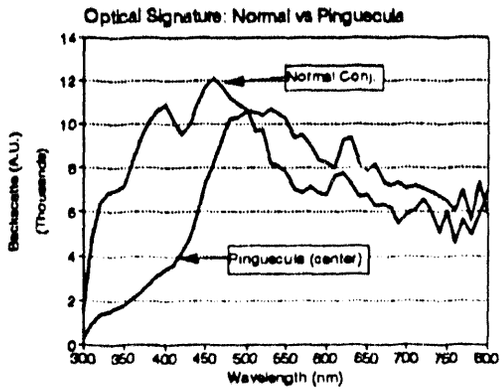

Figure 2. Optical signature of normal conjunctiva compared to that of a pinguecula. Backscatter amplitude in arbitrary units (A.U.).

In the case of the pinguecula, the backscatter amplitude from 300 to 400 nm was markedly reduced, compared to the normal conjunctiva. The scattering of the longer wavelengths was relatively unaffected by the pinguecula. The spectral difference in the normal tissue compared to the pinguecula was quite large and was obvious on the computer display during data acquisition. It may be possible to use the optical signature, obtained in this way, to determine the lesion margins.

There was remarkably lit le variation in the backscatter spectra of conjunctiva between normals. Figure 3 shows the backscatter spectra from three normal subjects, taken at the same location on their eyes, three times each by three different operators. There is close agreement between all of the spectra.

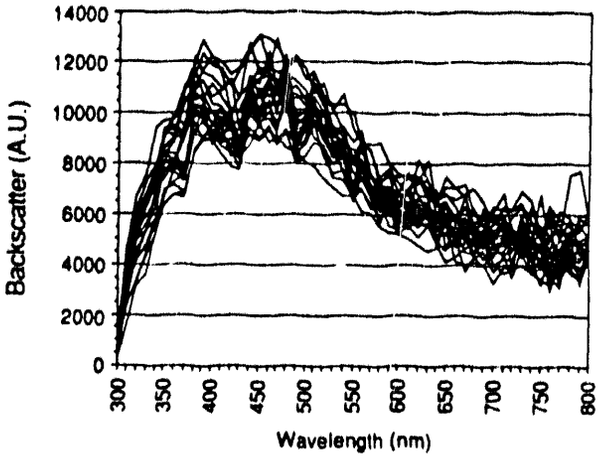

Figure 3. Reproducibility of OBS measurements. These spectra were obtained in triplicate by 3 operators from a similar site on the conjunctiva of 3 normal subjects and overlaid on the same set of axes.

The cases of PAM were studied with considerable interest, particularly to see if the OBS could distinguish a case with atypia from one without atypia. The presence of atypical cells in the tissue biopsy is an indicator of increased malignant potential of an acquired, pigmented lesion. Although, in our cases of PAM, the backscatter spectra were usually reduced across the spectrum compared to normal, a consistent difference associated with atypia was not found in the data set.

Pigmented lesions produced characteristic changes in the scattering signature: Figure 4 shows that the return in the short-wavelength region (300 - 400 nm) is very attenuated, and the overall backscatter is reduced throughout the visible and IR. Although suppression of the short wavelength backscatter is to be expected with a darkly-pigmented lesion, an interesting finding was

that the backscatter signature was altered from the normal for perhaps a millimeter beyond the visible limits of the lesion. Whether this optically-detectable change can be correlated with histologically-detectable changes is an important issue. Unfortunately, insufficient tissue was obtained with the clinical biopsies to demonstrate such a correlation.

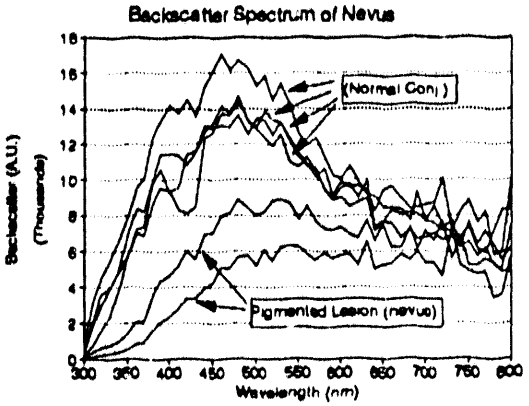

Figure 4. Backscatter spectra from a nevus and from normal conjunctiva.

DISCUSSION

The OBS system is safe for human use with no ocular hazard due to light intensity or exposure duration. Patients tolerated the OBS well; no medical complications were encountered resulting from its use. The practical application of the instrument was readily mastered and was accommodated reasonably well into the clinical setting.

Normal conjunctiva has a remarkably consistent optical backscatter signature that shows only slight differences due to location, subject, and instrument operator, at least as obtained with the Los Alamos OBS. Although the superficial lesions examined with the OBS in this study all had backscatter signatures differing from those of normal conjunctiva, there were insufficient clinical data in the present group of subjects to determine if the system was able to discriminate specific types of lesions, e.g. malignant from normal tissue. Given the distinct cytoarchitectural characteristics of malignant tissue, however, it is worth pursuing this question with the OBS. Another, important application, suggested by our first experience with this instrument, is that the OBS may be an effective method for determining lesion margins without extensive, invasive biopsies.

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