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Paper Session II-C - Optical (Non-Invasive) Diagnostics for Use on Space Missions

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Optical (Non-invasive) Diagnostics for Use on Space Missions

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ABSTRACT

Optical diagnostics, though still in the developmental stages, identify and quantitate the spectra of metabolizes and drugs without puncturing the skin (non-invasive) and without using chemical reagents. Once they are clinically validated, optical devices will begin to replace many clinical tests that use chemical reagents for diagnostics, particularly those tests that require regular monitoring and possess properties that are amenable to spectral analysis. Optical devices have a potentially important role aboard spacecraft because of the limited space available for maintaining an inventory of medicines and diagnostic devices. Despite the constraints, the spacecraft must provide the immediate and constant capabilities for diagnosing and treating a wide range of diseases of the crew. Maintaining the crews' health and safety remain the highest priorities.

INTRODUCTION

Although crews are thoroughly examined and treated for illnesses prior to missions, they are subjected to various stresses during flights that can increase their susceptibilities. They can also be the unwitting carriers of organisms, many of which are difficult to detect and which might remain dormant for long periods. Thus, ensuring the health of crews remains a critical element for the successful completion of the various missions. For extended missions, the spacecraft must stock an inventory of different diagnostic kits (each containing its own specific reagents) and medications in order to test for and treat a broad range of diseases accurately and quickly. The diagnostic kits and devices must conform to the constraints imposed by size, weight, and power consumption. After their use, the spacecraft must safely store or degrade the chemical reagents, blood and other body fluids, and the non-reusable devices. In contrast, optical devices perform diagnoses non-invasively, do not require samples of blood or body fluids, can operate almost continuously without using reagents or supplies. Thus, optical devices offer potential advantages for diagnostics on extended missions that are not readily provided by test kits that use chemical reagents.

Tables 1 and 2 show several routine tests now performed exclusively using chemical reagents, though some of the tests are non-invasive. Once they are clinically validateed optical technologies will begin to replace many clinical tests that use chemical reagents for diagnostics (Fischbach, 1988), particularly tests that are amenable to spectral analysis, such as blood chemistry and drug monitoring.

Table 1. Body Fluids Commonly Used for Diagnostics

Body Fluid	Non-invasive Collection	Invasive Collection
Blood	none	all samples: fingerstick, venipuncture, arterial stick
Urine	most samples	infrequent: catheterizations
Saliva	most samples	

Source: D.S. Sobel and T. Ferguson. 1985. *The People's Book of Medical Tests*. Summit Books, NY.

Table 2. Major Categories of Substances in Blood that are Commonly Analyzed

Analyses	Examples	Reason Performed
Blood chemistry	blood urea nitrogen, calcium, glucose, potassium, sodium	Determines whether the concentrations lie within the normal physiological ranges
Complete blood count	platelet count, red blood cell count, white blood cell count and differential	Provides information about numbers of red and white blood cells and platelets
Drug monitoring	antibiotics, barbiturates, digoxin, theophylline	Effectiveness depends upon staying within the therapeutic range while avoiding toxic levels
Hormones	aldosterone, cortisol, estrogens, renin	Determines whether concentrations lie within normal ranges;
Immunological	immunoglobulins	Diagnoses diseases associated with abnormal immunoglobulin levels

Source: D.S. Sobel and T. Ferguson. 1985. ***The People's Book of Medical Tests.*** Summit Books, NY. Pgs. 13-14.

STATUS OF NON-INVASIVE DIAGNOSTICS IN DIABETES

The advent of self-monitoring of blood glucose represents the most significant advance in the treatment of diabetes since the discovery of insulin (ADA 1993). Over the years, self-monitoring has allowed millions of people with diabetes to manage their disease and improve the quality of their lives. People with diabetes significantly improve their health when they maintain blood glucose concentrations within the normal range. Their health improves as a result of reducing the severity of complications that are associated with diabetes and by delaying the onset of the complications. Although current invasive devices, when used on a regular schedule, reliably and accurately monitor blood glucose, they do not meet the special needs of many people. For example, people who are trying to achieve "tight glycemic control" increase both the frequency of insulin administration and glucose monitoring. However, they have collectively experienced almost triple the incidence of hypoglycemia because tight control therapy offers no margin for error. Though highly motivated to succeed, these people find it difficult to juggle the conflicting demands of strict schedules that frequent monitoring imposes with hectic and unpredictable activities at home and work. On the other hand, many people with diabetes are often not sufficiently motivated to adhere to the regular schedules of self-monitoring and thereby fail to manage the disease properly. They find excuses for not using current invasive (finger pricking) techniques, such as the cost, pain, inconvenience, social awkwardness, and burdensome record-keeping. Thus current invasive devices for the self-monitoring of blood glucose, while undeniably essential, have left many problems unsettled.

In recent years, extensive research efforts have been focused on the development of a non-invasive means of monitoring blood glucose concentrations that people with diabetes can use as readily at work as at home (Arnold and Small, 1990; Bodenner et al., 1991; Ham et al., 1991, 1994; Robinson et al., 1992; Small et al., 1993). In order to achieve wide-spread acceptance and improve motivation, a non-invasive, self-monitoring glucose meter has to be highly reliable, safe, socially

acceptable, convenient, painless, and affordable. In short the availability of a non-invasive device that eliminates the shortcomings of the current invasive blood glucose monitoring meters offers a powerful incentive for improving adherence and attaining tight glycemic control.

Most non-invasive technologies are not new. They developed along with the emergence of modern medicine and have been thoroughly incorporated into it. Table 3 illustrates a few well known non-invasive and minimally invasive techniques.

Table 3. Representative Non-invasive and Minimally Invasive Diagnostic Procedures

Instrument	Principal Application	Discomfort/Dangers
Audiometry	testing of hearing	time consuming
Breath test	detection of alcohol	none
Electrocardiograph	recording of electrical activity of heart	often involves shaving patches of hair for electrodes
Magnetic resonance imaging	examination of brain and internal organs	patient lies inside cylinder without moving; aggravates claustrophobia
Ophthalmoscope	observations of eye structures	bright light is uncomfortable
Otoscope	examination of middle ear	minor
Oximetry	measurement of blood oxygen	minor
Sphygmomanometer	blood pressure measurement	cuff pressure
Stethoscope	listening to heart sounds	none
Thermometer (mercury)	measurement of body temperature	inconvenient
Ultrasound	examination of internal organs and of embryos and fetuses	minor
X-rays (conventional and CAT scans)	examination of internal organs	poses radiation hazard; some dyes causes adverse reactions in patients

Our research addresses the pressing need of people with diabetes for an improved and simplified method of monitoring blood glucose. We are developing an optical device that uses near-infrared spectroscopy for monitoring blood chemistry (glucose) non-invasively (without drawing blood) . This technology, sometimes called “reagentless chemistry”, involves identification and quantitation of the spectra of different chemicals in the blood. When fully developed, the patient will use a device that detects spectral signals that are generated as a result of illuminating a finger (Fig. 1), ear lobe, lips, underside of the tongue, or other optically translucent area (Ham et al., 1993). Signal processing techniques are used to remove background noise and quantitate spectral signals (Ham, 1994; Ham et al., 1993, 1994; Ham et al., 1995).

We believe that the non-invasive device for detecting blood glucose must meet at a minimum of five requirements: (1) identifies and quantitates blood substances by their spectral “fingerprints” (absorption peaks); (2) measures the substance in the blood directly using a safe, low-intensity, near infrared source; (3) determines concentrations of blood substances using signal processing techniques; and (4) measures the substance in the blood independently of both skin pigmentation and site (finger, web, lips, sublingual, earlobe, etc.) where the light impinges, (5) monitors as frequently as needed ranging from occasionally to continuously. Table 4 summarizes the blood concentrations of several substances some of which are readily amenable to spectroscopic analysis.

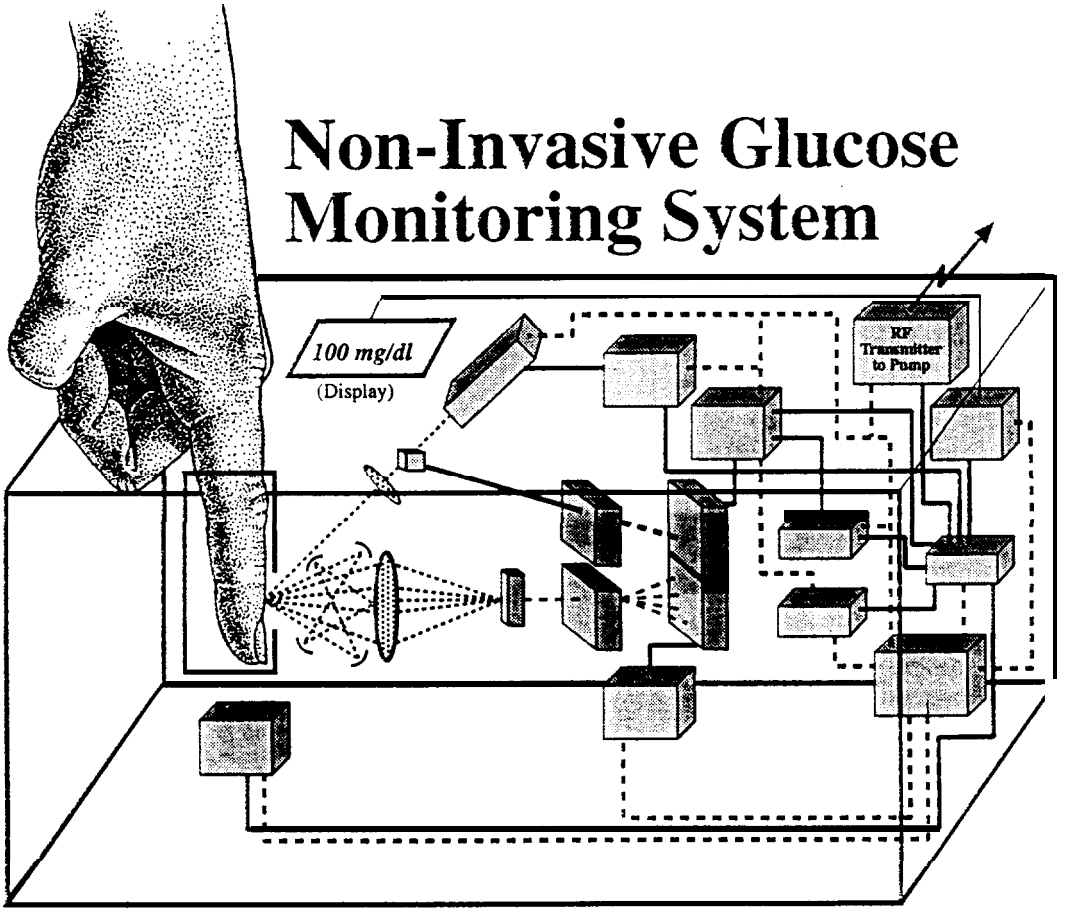

Figure 1. Non-invasive glucose monitoring system. This finger represents only one of several different sites for analyzing concentrations of blood glucose and other constituents.

Table 4. Blood Concentrations of Representative Substances

Substance	Normal Concentrations (mg/dl)	Classification
Calcium	9.2-11	essential mineral
Digoxin	.8-2	heart drug increases contractile strength
Gentamicin	4-10	antibiotic
Glucose	70-110	primary energy source
Phenobarbital	15-39	tranquilizer ("sleeping pill")
Sodium	300-330	essential salt
Urea nitrogen	8-23	end product of protein metabolism

Sources H. Lullmann et al. 1993. ***Pocket Atlas of Pharmacology.*** Thieme Medical Publishers, NY.
D.S. Sobel and T. Ferguson. 1985. ***The People's Book of Medical Tests.*** Summit Books, NY.

A robust discrimination strategy which can detect and predict glucose concentrations with an acceptable level of accuracy using spectrophotometric methods serves as a pivotal element in a highly reliable non-invasive monitoring system for measuring blood glucose (and other substances). Oximetry, a non-invasive technique, is widely used for monitoring oxygen levels in blood. Optical sensors detect the spectral properties of oxygenated and deoxygenated hemoglobin and quantitate the spectra (Buerk, 1993; pgs. 137-139). The oxygen signal is strong because of the high concentration of hemoglobin in the blood. By comparison, most other chemicals in the blood are difficult to monitor because of their extremely low concentrations and overlapping spectra with other chemicals (Amato, 1992). Thus, the detection and prediction of the spectral signals of most blood chemicals requires far more elaborate signal processing than for monitoring oxygen levels. We must overcome six major technical obstacles in developing an optical system, such as: (1) removal of baseline variations that instrumentation drift and ambient conditions introduce into the spectroscopic data (Hazen et al., 1994; Small et al., 1993), (2) removal of intrinsic high background absorption due to water, (3) removal of high frequency noise due to the detector and removing the background absorption due to water, (4) removal of large numbers of overlapping absorption spectra and molecular interactions of other blood constituents with glucose, and (5) reduction of degradation of signal of interest due to interference of other blood substances, i.e., red blood cells (45% of blood volume), and (6) resolving the major optical properties of skin, which is an anistropic and inhomogeneous medium (Anderson and Parrish, 1982). During the past two years we have successfully solved the first three technical obstacles and partially solved the fourth.

To date, we have quantitated levels of blood glucose ranging in concentration from O to 600 mg/dl (100 mg/dl is the normal value) (Ham, 1994; Ham et al., 1994, 1995). The development of the technique of optical monitoring of blood chemistry represents a high priority for people with diabetes who presently must prick their fingers several times each day to monitor blood glucose using chemical reagents (Robinson et al., 1992). Buerk (1993) listed 13 behaviors of an ideal biosensor. Although these generic behaviors are shared among biosensor types, such as electrochemical, enzyme-based, and optical, only optical sensors can monitor blood chemistry non-invasively (Tables 2 and 4) and without using chemical reagents. The optical technologies that we and others are developing for monitoring blood glucose are transferable to many other clinical applications. An optical device, which can function over wide spectral ranges, can replace a single diagnostic test kit that is frequently used or replace many different types of test kits. In short, optical sensors offer an advantage for routine tests that are frequently performed, such as glucose monitoring, and for extended space missions.

ACKNOWLEDGMENT

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