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SOLICITATION NO./CLOSING DATE/If not in response to a program announcement/solicitation enter GPG, NSF 95-27
99) January 2, 1997

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TO WHICH AWARD SHOULD BE MADE
Utah

CODE (IF KNOWN)

ADDRESS OF AWARDEE ORGANIZATION, INCLUDING ZIP CODE
Office of Sponsored Projects
1471 Federal Way
Salt Lake City, UT 84102

GANIZATION, IF DIFFERENT FROM ABOVE

ON CODE (IF KNOWN)

ADDRESS OF PERFORMING ORGANIZATION, IF DIFFERENT, INCLUDING ZIP CODE
Department of Bioengineering
2480 MEB
University of Utah
Salt Lake City, UT 84112

N (Check All That Apply)
a) ☐ FOR-PROFIT ORGANIZATION ☐ SMALL BUSINESS ☐ MINORITY BUSINESS ☐ WOMAN-OWNED BUSINESS

ECT Personal Sensors for the Diagnosis and Management of Metabolic Disorders

ROPOSED DURATION (1-60 MONTHS)
36 months

REQUESTED STARTING DATE
July 1, 1997

ES) IF THIS PROPOSAL INCLUDES ANY OF THE ITEMS LISTED BELOW

OR (GPG I.A.3)
NG ACTIVITIES (GPG II.D.1)
GED INFORMATION (GPG II.D.10)
TAL POLICY ACT (GPG II.D.10)
II.D.10)
OR. RESEARCH (SGER) (GPG II.D.12)
II.D.12)

☐ VERTEBRATE ANIMALS (GPG II.D.12) IACUC App. Date _____
☐ HUMAN SUBJECTS (GPG II.D.12)
Exemption Subsection____or IRB App. Date _____
☐ INTERNATIONAL COOPERATIVE ACTIVITIES: COUNTRY/COUNTRIES _____
☐ FACILITATION FOR SCIENTISTS/ENGINEERS WITH DISABILITIES (GPG V.G.)
☐ RESEARCH OPPORTUNITY AWARD (GPG V.H)

PI/PD POSTAL ADDRESS
University of Utah
2480 MEB
Salt Lake City, UT 84112

PROJECT SUMMARY

We propose to develop a widely applicable, generic technology for the clinical analysis of the major low molecular weight biochemicals important in the diagnosis and management of metabolic disorders. This technology portion of the project focuses on the development of inexpensive, direct reading, quantitative, dip stick type, chemical sensors for those analytes most important to the diagnosis and management of metabolic disorders, including carbohydrates, amino acids, and vitamins. With the exception of glucose monitors for diabetics and the blood spot test for PKU (phenylketonuria), inexpensive, widely applicable tests for other carbohydrates and amino acids are not available. Such tests must now be performed in an appropriate clinical chemistry laboratory and are not available for point of care testing or in the primary care or home environments.

We further propose to develop an efficient decision tree-based economic model applicable to two major clinical areas:

1. The screening and diagnosis of large populations for inborn errors of metabolism-Population Screening.
2. The empowerment of patients and providers in the management of chronic metabolic disease-Disease Management.

The goal is to utilize appropriate clinical input and readily available data bases to estimate the cost reduction potential of new and different technologies and approaches to screening and disease management.

We further propose to develop a group of education and information dissemination activities for the bioengineering, medical, and industrial communities, enabling these communities to apply our economic model to their biomedical technology research and development activities and assessment.

Information on the model, together with information on the unique chemical analysis technologies, will also permit the assessment and possible applicability of these technologies to other health related areas.

We will utilize the economic analysis tools to focus our own biochemical technology development on those inborn errors of metabolism with the greatest cost reduction potential. This will begin with the very well defined, well known, and clinically significant problem of galactosemia, which we will use as our initial case study. We will further utilize the modelto focus our technology development on the management of chronic metabolic disease. Again, we will use the management of galactosemia as the initial case study. A second more complex case problem, is diabetes, which will also be studied.

Finally, using the economic model applied to the wide spectrum of inborn errors of metabolism and their associated diseases, we will develop a preliminary priority "ranking" for technology focus and sensor development, based on the overall cost reduction potential associated with the screening and management of those diseases.

Our technology, economic analysis, and education activities will all be made known to the bioengineering, clinical, and industrial communities in the hope and expectation that our experiences can help enhance the development and application of cost reducing medical technologies in a much wider sphere.

The project includes three principal investigators with specific expertise in the technology area, the economic analysis area, and the education area. It includes a Clinical Advisory Team consisting of clinicians, researchers, and health care providers in the local area as well as a National Advisory Board. The project also includes close collaboration with industries who have the interest and potential to make the technology widely and inexpensively available.

CERTIFICATION PAGE

Certification for Principal Investigators and Co-Principal Investigators

I certify to the best of my knowledge that:

(1) the statements herein (excluding scientific hypotheses and scientific opinions) are true and complete, and
(2) the text and graphics herein as well as any accompanying publications or other documents, unless otherwise indicated, are the original work of the signatories or individuals working under their supervision. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if an award is made as a result of this application.

I understand that the willful provision of false information or concealing a material fact in this proposal or any other communication submitted to NSF is a criminal offense (U.S.Code, Title 18, Section 1001).

Name (Typed)	Signature	Date
PI/PD J.D. Andrade		12/26/96
Co-PI/PD R.P. Huefner		12/26/96
Co-PI/PD S.E. Kern		12/26/96
Co-PI/PD		
Co-PI/PD		

Certification for Authorized Organizational Representative or Individual Applicant

By signing and submitting this proposal, the individual applicant or the authorized official of the applicant institution is: (1) certifying that statements made herein are true and complete to the best of his/her knowledge; and (2) agreeing to accept the obligation to comply with NSF award terms and conditions if an award is made as a result of this application. Further, the applicant is hereby providing certifications regarding Federal debt status, debarment and suspension, drugfree workplace, and lobbying activities (see below), as set forth in the *Grant Proposal Guide (GPG)*, NSF 95-27. Willful provision of false information in this application and its supporting documents or in reports required under an ensuing award is a criminal offense (U.S. Code, Title 18, Section 1001).

In addition, if the applicant institution employs more than fifty persons, the authorized official of the applicant institution is certifying that the institution has implemented a written and enforced conflict of interest policy that is consistent with the provisions of *Grant Policy Manual* Section 510; that to the best of his/her knowledge, all financial disclosures required by that conflict of interest policy have been made; and that all identified conflicts of interest will have been satisfactorily managed, reduced or eliminated prior to the institution's expenditure of any funds under the award, in accordance with the institution's conflict of interest policy. Conflicts which cannot be satisfactorily managed, reduced or eliminated must be disclosed to NSF.

Debt and Debarment Certifications (If answer "yes" to either, please provide explanation.)

Is the organization delinquent on any Federal debt? Yes ☐ No ☒

Is the organization or its principals presently debarred, suspended, proposed for debarment, declared ineligible, or voluntarily excluded from covered transactions by any Federal Department or agency? Yes ☐ No ☒

Certification Regarding Lobbying

This certification is required for an award of a Federal contract, grant or cooperative agreement exceeding $100,000 and for an award of a Federal loan or a commitment providing for the United States to insure or guarantee a loan exceeding $150,000.

Certification for Contracts, Grants, Loans and Cooperative Agreements

The undersigned certifies, to the best of his or her knowledge and belief, that:

(1) No Federal appropriated funds have been paid or will be paid, by or on behalf of the undersigned, to any person for influencing or attempting to influence an officer or employee of any agency, a Member of Congress, an officer or employee of Congress, or an employee of a Member of Congress in connection with the awarding of any federal contract, the making of any Federal grant, the making of any Federal loan, the entering into of any cooperative agreement, and the extension, continuation, renewal, amendment, or modification of any Federal contract, grant, loan, or cooperative agreement.

(2) If any funds other than Federal appropriated funds have been paid or will be paid to any person for influencing or attempting to influence an officer or employee of any agency, a Member of Congress, and officer or employee of Congress, or an employee of a Member of Congress in connection with this Federal contract, grant, loan, or cooperative agreement, the undersigned shall complete and submit Standard Form-LLL, "Disclosure of Lobbying Activities," in accordance with its instructions.

(3) The undersigned shall require that the language of this certification be included in the award documents for all subawards at all tiers including subcontracts, subgrants, and contracts under grants, loans, and cooperative agreements and that all subrecipients shall certify and disclose accordingly.

This certification is a material representation of fact upon which reliance was placed when this transaction was made or entered into. Submission of this certification is a prerequisite for making or entering into this transaction imposed by section 1352, title 31, U.S. Code. Any person who fails to file the required certification shall be subject to a civil penalty of not less than $10,000 and not more than $100,000 for each such failure.

AUTHORIZED ORGANIZATIONAL REPRESENTATIVE	SIGNATURE	DATE
NAME/TITLE (TYPED)		

TELEPHONE NUMBER	ELECTRONIC MAIL ADDRESS	FAX NUMBER

C. Project Description

1. Specific Aims and Objectives

- To develop a widely applicable, inexpensive technology for clinical analyses of the key biochemicals important in the diagnosis and management of metabolic disorders (Technology)
- To develop an efficient, understandable, decision-tree-based economic model suitable for making succesively refined estimates of economic impacts of technology for:
  1. the screening and diagnosis of metabolic diseases, and
  2. the empowerment of patients and providers in the management of chronic metabolic diseases.

  (Economics)
- To develop education activities for the bioengineering, medical, and industrial communities to enable them to apply the model to their biomedical technology R and D activities (Education).
- To utilize the economic model to focus our biochemical technology development on those inborn errors of metabolism with the greatest cost reduction potential, using galactosemia for the initial case study.
- Using the economic model, to prioritize future technology developments based on their cost reduction potential.

The overall objectives are illustrated in Figure 1 (below). Our novel technology for the direct, sensitive, inexpensive measurement of specific bio-chemicals important to metabolism and metabolic diseases (1, 2, 3) can lead to more effective therapy and management of those diseases. The economic analysis component will determine the cost reduction potential of both screening and chronic disease management, thereby permitting the technologists to focus their activities on those chemicals and diseases with the greatest cost reduction potential (4, 5). The education component works closely with technology and economics to make the technologist, economist, health care provider, and patient populations aware of the technology, of the economic model, and of the cost reduction prioritization analysis.

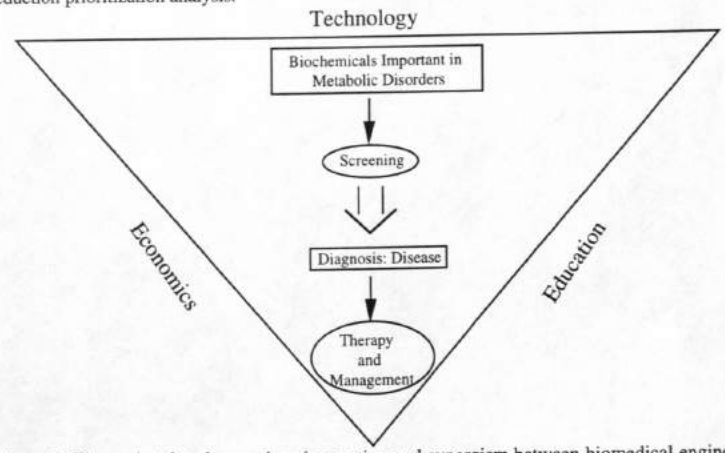

Figure 1. The project involves a close interaction and synergism between biomedical engineers (technology), economists (economic analysis), and educators (education); see the text for details.

2. Significance and Impact

Health care cost concerns in many nations are driving a growing interest in point of care-based technologies for screening, diagnosis, and even treatment (5-7) Innovations and enhanced technologies in meter-less chemical analysis devices, employing immobilized and dry reagents, make it possible for individual patients to monitor their own glucose, cholesterol, pregnancy hormone, and other parameters.

There is growing need for devices which can use non-invasively derived samples, particularly urine, saliva, and sweat (1, 8, 9). There is an evolving trend in encouraging and empowering consumers and potential patients with greater education, awareness, and responsibility for their own health care. This has lead to a recent proliferation in home medical, "self diagnosis," computer packages (6, 10-12). These products attest to the growing interest in the public becoming more involved in assuming more responsibility for their own education and health care.

We are embarked on projects to research and develop consumer and patient friendly, dipstick-type devices applicable to non-invasively derived fluids for education, analytical, and potential diagnostic usage (1-3).

Such sensors will make it possible to enhance research and diagnosis in a wide range of problems and pathologies related to metabolism and bioenergetics, obviating the requirement for generally more expensive and time consuming standard analytical methods, often based on gas and liquid chromatography (13, 14).

A good example is the screening of new borns and infants for inborn errors of metabolism, particularly inborn errors of carbohydrate and amino acid metabolism (15, 16). Such screening is done today in most of the United States for high incidence metabolic diseases. It is not routinely done for those inborn errors of lesser incidence, in large part because of the high costs associated with such screening. Such an inborn error of metabolism is indeed a chronic disease which must in general be monitored and managed for the lifetime of the patient. Many of these metabolic errors can be corrected and managed by suitable diet. However, such chronic management requires the ability to make periodic and regular chemical determinations. The availability of truly inexpensive means of reliably performing such analyses will greatly reduce the chronic and severe problems associated with undiagnosed inborn errors of metabolism and will greatly facilitate the chronic management of such diseases.

Although progress is being made in the development and provision of tools and devices to enable self-monitoring of blood pressure, pulse, and temperature (6, 10-12), the very major constraint is the limited number of suitable inexpensive home based means for appropriate clinical chemistry measurement s. The public has responded positively to the availability of home based chemical measurement technologies for the management of diabetes, the diagnosis of pregnancy, cholesterol levels, and now AIDS. Specific, sensitive, quantitative, inexpensive dip-stick type devices are needed for a much wider range of analytes particularly for carbohydrates and amino acids to enable and empower the growth and expansion of patient self-care.

Diabetes is perhaps the best example of a wide spread metabolic disease (17). More than seven million Americans suffer from diabetes and its complications. Over ten percent of U.S. annual health care dollars are devoted to managing diabetes. This is of the order of one hundred billion dollars per year. Recent studies have shown that a more intensive therapeutic approach to the management of diabetes would greatly benefit those afflicted by delaying complication times, delaying blindness by about eight years, delaying end stage renal disease by about six years, delaying lower extremity amputation by about six years, and an overall five year prolongation of life. Such a disease management program requires tight glucose control together with more enhanced diabetes education and patient/physician interaction. It also requires effective, inexpensive, chemical analysis methods which can be applied by the individual patient, including glycohemoglobin, microalbumin, cholesterol, and related perameters. Diabetes has a very high incidence and a very high societal impact.

Newborns in the United States are regularly screened for some inborn errors of metabolism during their first days of life (21-25). If the incidence of the disease in the newborn population is high enough that one missed case will result in state expenditures larger than the cost of screening all newborns, then it is cost beneficial to screen all newborns (20). Typical screenings cover phenylketonuria (PKU), galactosemia, maple syrup urine disease (MSUD) and homocystinuria (20). All states screen for PKU and hypothyroidism, 26 states screen for galactosemia, 20 screen for MSUD, 19 screen for homocystinuria, and three screen for histidinemia (21). These screenings require that a blood sample be drawn and sent to a clinical chemistry laboratory, with results taking 2-3 days. This is generally too long. Infant metabolic screening costs range from $30-$50 per test. Current newborn screening programs for inborn metabolic errors include screening of umbilical cord blood, newborn blood, and urine (22).

Galactosemia has an incidence of roughly one in one hundred thousand and is therefore often considered inappropriate for screening. The result is severe growth retardation and mental retardation if undiagnosed and untreated even in the first few days of life. Undiagnosed cases of galactosemia are a major cost to society.

More common inborn errors of metabolism such as phenylketonuria (PKU), with an incidence of roughly one in ten thousand, are routinely screened today. All newborns are screened for PKU, but that is not the case for galactosemia, for three reasons:

1. PKU testing is relatively inexpensive, straight forward, and easily implemented.
2. PKU has a relatively high incidence and can be easily treated if detected.
3. The detection of galactosemia requires chemical analysis which are considered to be somewhat expensive and cumbersome, and given the relatively low incidence, often considered to be not cost effective in some states and in many nations.

What determines cost effectiveness (18, 19)for a screening application is the incidence, the availability of treatment if detected, the cost to society of that treatment, the cost to society if untreated, and of course the cost of the screening procedure. The availability of simple, direct reading, quantitative, inexpensive, multi-channel sensors for the key inborn errors of metabolism would permit all such screening to be essentially "piggy backed" on the existing PKU screening activity. Thus, for only the cost of the sensor alone such screening could be widely implemented, thereby totally changing the cost-benefit calculation.

The great significance of the technology proposed here is that it would allow the direct measurement of critical biochemicals, particularly carbohydrates and amino acids,by straight forward, inexpensive means. Analysis of such chemicals today generally requires gas or liquid chromatography techniques (13-16), not amenable to a quantitative direct reading, dip stick modality.

Recently, a shift toward point-of-care testing–testing done at or near the patient's bedside-has taken place. This type of testing can reduce cost while decreasing delays in treatment. It reduces pre-analytic errors due to collection, storage, transportation, and reporting. Results are ready in minutes, leading to faster diagnosis and faster treatment implementation. The net results are decreased hospitalization, lower costs and improved quality of care (13). Dipsticks will reduce medical costs due to labor savings, time savings, and decreased misdiagnosis (18).

3. Relation to PI's Goals

J. Andrade, the senior PI, has been involved for the past five years in trying to encourage the nation's biomedical engineers to focus on technologies and processes which could significantly decrease the costs of health care. He, together with Dr. Jaron and Dr. Katona, organized and chaired the NSF workshop on Cost Reducing Health Care Technologies (26) which lead to the 1993 meeting of the American Institute for Medical and Biological Engineering and its proceedings, Medical and Biological Engineering in the Future of Health Care (5), which had a major focus on cost reducing technologies. He has taught courses related to those subjects in the Department of Bioengineering at the University of Utah, together with Steve Kern and Robert

COVER SHEET FOR PROPOSAL TO THE NATIONAL SCIENCE FOUNDATION

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NAME OF PERFORMING ORGANIZATION, IF DIFFERENT FROM ABOVE	ADDRESS OF PERFORMING ORGANIZATION, IF DIFFERENT, INCLUDING ZIP CODE Department of Bioengineering 2480 MEB University of Utah Salt Lake City, UT 84112
PERFORMING ORGANIZATION CODE (IF KNOWN)	

IS AWARDEE ORGANIZATION (Check All That Apply) (See GPG II.D.1 For Definitions) ☐ FOR-PROFIT ORGANIZATION ☐ SMALL BUSINESS ☐ MINORITY BUSINESS ☐ WOMAN-OWNED BUSINESS

TITLE OF PROPOSED PROJECT: Personal Sensors for the Diagnosis and Management of Metabolic Disorders

REQUESTED AMOUNT	PROPOSED DURATION (1-60 MONTHS)	REQUESTED STARTING DATE
$ 769,327	36 months	July 1, 1997

CHECK APPROPRIATE BOX(ES) IF THIS PROPOSAL INCLUDES ANY OF THE ITEMS LISTED BELOW

- ☒ BEGINNING INVESTIGATOR (GPG I.A.3)
- ☐ DISCLOSURE OF LOBBYING ACTIVITIES (GPG II.D.1)
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- ☐ HISTORIC PLACES (GPG II.D.10)
- ☐ SMALL GRANT FOR EXPLOR. RESEARCH (SGER) (GPG II.D.12)
- ☒ GROUP PROPOSAL (GPG II.D.12)
- ☐ VERTEBRATE ANIMALS (GPG II.D.12) IACUC App. Date _____
- ☐ HUMAN SUBJECTS (GPG II.D.12) Exemption Subsection ___ or IRB App. Date _____
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- ☐ FACILITATION FOR SCIENTISTS/ENGINEERS WITH DISABILITIES (GPG V.G.)
- ☐ RESEARCH OPPORTUNITY AWARD (GPG V.H)

PI/PD DEPARTMENT	PI/PD POSTAL ADDRESS
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PI/PD FAX NUMBER: 801-585-5361	

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CO-PI/PD				
CO-PI/PD				

NOTE: THE FULLY SIGNED CERTIFICATION PAGE MUST BE SUBMITTED IMMEDIATELY FOLLOWING THIS COVER SHEET

*SUBMISSION OF SOCIAL SECURITY NUMBERS IS VOLUNTARY AND WILL NOT AFFECT THE ORGANIZATION'S ELIGIBILITY FOR AN AWARD. HOWEVER, THEY ARE AN INTEGRAL PART OF THE NSF INFORMATION SYSTEM AND ASSIST IN PROCESSING THE PROPOSAL. SSN SOLICITED UNDER NSF ACT OF 1950, AS AMENDED.

PROJECT SUMMARY

The Project Summary should include a statement of objectives, methods to be employed, and the significance of the proposed activity to the advancement of knowledge or education. Avoid use of first person to complete this summary. **DO NOT EXCEED ONE PAGE.** (Some Programs may impose more stringent limits.)

We propose to develop a widely applicable, generic technology for the clinical analysis of the major low molecular weight biochemicals important in the diagnosis and management of metabolic disorders. This technology portion of the project focuses on the development of inexpensive, direct reading, quantitative, dip stick type, chemical sensors for those analytes most important to the diagnosis and management of metabolic disorders, including carbohydrates, amino acids, and vitamins. With the exception of glucose monitors for diabetics and the blood spot test for PKU (phenylketonuria), inexpensive, widely applicable tests for other carbohydrates and amino acids are not available. Such tests must now be performed in an appropriate clinical chemistry laboratory and are not available for point of care testing or in the primary care or home environments.

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Hueffner, the Co-PI's. For about the past five years, Joe has redirected his academic research activities to developing technologies to facilitate patient empowerment, primarily direct reading, dipstick type devices for the measurement of important biochemicals in non-invasively derived body fluids (1, 2). He is deeply committed to expanding the education and awareness of patients and to involving patients in their own health care decisions. The activities described in this grant relate directly to both his short term and long term continuing career goals.

Dr. Robert Hueffner's career is also in the mainstream of improving the quality of health care through improved health policies and improved interaction between patients, providers, and the technology/engineering community.

Dr. Steven Kern has been interested in and involved in cost reducing technologies since his graduate student days at the University of Utah. He is applying that interest and experience to his rapidly developing academic career in anesthesiology and bioengineering.

Please refer to the biosketches of the three Co-PI's for further information.

4. Background and Work in Progress

There are two very special molecules that play unique and central roles in biology: adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NADH) and its phosphate form (NADPH), a ubiquitous electron donor. ATP is generally recognized as the energy currency in biology. The two molecules are closely coupled in many biochemical processes and can be regenerated or recharged. They are the basic coupling agents of cellular metabolism. A very large number of biochemical enzyme processes involve one of these two molecules.

It is very fortuitous that biology has evolved two bioluminescent processes dependent on these two molecules: the firefly luciferase reaction, which acts on firefly luciferin in the presence of ATP to produce an oxidized product which chemiluminesces (27). The bacterial luciferase reaction, which in the presence of alkyl aldehydes, produced by an NAD(P)H reaction, and $FMNH_2$, also produces an excited chemiluminescent product which chemiluminesces. Both reactions produce photons with high efficiencies in the presence of oxygen. However, both the luciferases and luciferins involved are chemically different.

There is a large body of literature on the development of biosensors for ATP and ATP-dependent processes and for NADPH and NADPH-dependent processes, using the firefly and bacterial luciferase enzymes, respectively (1, 2, 28-30). Such biosensors generally employ fiberoptic or other wave guided means of delivering the luminescence to a device which can accurately measure light intensities (28-30). Although one of the most portable and most sensitive photon detectors available to the scientist, physician, or patient is his or her own eye, it is notoriously difficult to calibrate for accurate measurements of even relative light intensity. The human two dimensional photon detection system, however, can reliably and accurately measure changes in spatial position.

We are using the human eye's spatial detection capabilities as a readout system for the analysis of carbohydrates and other key molecules using ATP-dependent kinase-based, phosphorylation reactions (1, 2).

It is perhaps surprising that there has not been more interest in using the exquisite imaging photon detector, which practically all of us have, the human eye. The eye is so beautifully accommodating, adapting, and auto-ranging, that it is a notoriously bad detector of photon intensity, the basic signal in practically all fluorescence and luminescence-based analytical devices. But the human eye is ideally suited for the detection of images or patterns.

We have developed a set of technologies which allows ATP concentration to be measured by the spatial position of the bioluminescence, permitting a quantitative detector designed and optimized for human visual detection (1-3).

For the past fifteen years, Andrade and co-workers have worked on fluorescence based immuno sensors using total internal reflection evanescent wave optics (31). That work was highly

successful, led to several patents, and in modified form is being commercially developed. About six years ago the group became quite interested in bioluminescence and the possibility of using luciferases as labels and tags for immunoassay. The more they got into this area, the more it just seemed reasonable to use bio- or chemiluminescence as the readout rather than fluorescence, thereby eliminating the need for an excitation light source. As they got into the literature even more, they were surprised to learn of the exquisite sensitivity and specificity of the two most well characterized bioluminescent reactions. As they learned more about biochemistry and bioenergetics, they finally realized that ATP and NADH are the two most critical molecules in all of biology and that having a system with high specificity and sensitivity for these molecules and the ability to generate its own signal led to an enormous range of possibilities. The problem was that the simplicity of the system was limited by the need for sophisticated light detectors. As noted above, most bioluminescence sensing systems utilize photo-multiplier tube or related detectors.

With the group's growing interest with patient empowerment and cost reducing health care technologies some four years ago, they began to struggle with means by which a sensor could be produced which could be read without the need for an instrument, i.e. by the patient's own eyes. The problem, of course, was the human eye's astonishing ability to accommodate to changes in intensity thereby making it a very non-objective intensity detector. The trick was to display the signal in space. The general concept is presented in Figure 2 (1-3).

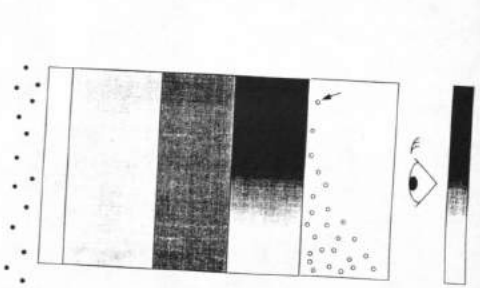

Figure 2. The "Business Card" geometry dipstick sensor, read by looking at the far right edge. Liquid sample is applied to the far left edge (See the text for details).

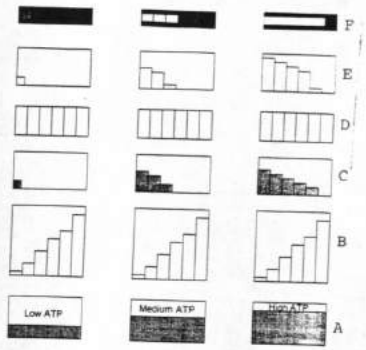

Figure 3. The mechanism of action of the sensor. The bottom blocks (A) refer to concentration of ATP on the sample. The next block up (B) is the apyrase distribution; the center blocks (C) are the resultant ATP concentrations. D refers to the luciferase/luciferin zone. E is the light output, and F is what you see looking at the upper edge of the sensor. Also see Figure 2.

Imagine the sensor with the shape of a thick business card. One dips one end of the business card in the solution to be analyzed. In our case, initially, this is urine. The urine wets and is wicked into the card. Let us assume for now, for simplicity, that we are only interested in analyzing the ATP content of that sample. Actually, we would be analyzing a specific biochemical

analyte, but we are now trying to describe for you the generic ATP detection sensor. The analyte will come a bit later. Assume that the solution has a uniform ATP concentration. It moves into a region where reagent has been deposited mainly for pH and buffer control. The dry reagent is solubilized and the now buffered pH controlled ATP containing solution moves into a zone which we call the consumase gradient. Here we have an enzyme which actually consumes ATP. You will see why in just a moment. It consumes it in a position sensitive manner. It is a high consumase concentration at the top of the figure, and a zero consumase concentration at the bottom. The spatially modulated ATP now makes its way into the final zone of the sensor which contains luciferase and luciferin; the two reagents which together with oxygen and ATP produce the bioluminescence. At the top of the device, where the consumase was highest, there is very little ATP. At the bottom of the device where it was lowest, there is a maximal amount of ATP. Now imagine that you are observing light generated by the bioluminescent process by looking at the edge of the business card. What you see is a very thin band, very dark on your right and relatively bright on your left. It is clear that the position of the light in that band has some relationship to ATP concentration. Now let's go to Figure 3.

Here we have it in a more schematic version. At the far left imagine we have a sample containing low ATP. That sample enters a zone in which there are six discrete consumase concentrations. You can think of this as six independent channels if you like, each accepting an identical volume of solution with identical but low ATP concentration. In this particular example, the consumase is of high concentration and the ATP concentration is low so that essentially all the ATP is consumed except in the left most channel. A small amount of ATP thus enters the next zone, the luciferase zone, and results in light but of relatively low intensity. At the far right of the figure we have a high ATP concentration. Now the ATP concentration is high enough that even though much of it is consumed by the consumase, a sufficient amount gets through into the luciferase zone, producing light. There is more ATP on the left side of that high ATP example and so the light is of course brighter. Think of the output of these sensors, i.e. the top of Figure , as analogous to a glowing thermometer. The length of the glow is thus proportional to ATP concentration. The intensity of the glow is also related to ATP concentration (it is the intensity that is normally measured but requires a relatively expensive intensity detector). In our case, as long as the glow is above the detection threshold for the human eye, and the non-glowing region is black enough that the human eye can detect significant contrast between the glowing and non-glowing region, then that particular position is indicative of ATP concentration.

This works remarkably well, as shown in Figure 4. This is a laboratory example in which the consumase (potato apyrase) has been deposited in one dimension of an eight by eight multi-well plate and ATP solutions ranging from 10^{-7} to 10^{-4} molar have been placed in the other dimension. The wells already contain luciferase and luciferin of constant concentration. Examining this plate after one minute of equilibration and reaction time, one sees that indeed the position of the glow is proportional to ATP concentration. Note that in the case of very high ATP concentration, the glow/no-glow region is at position A, whereas at 10^{-5} it is approximately at position C, and at 10^{-6} it is position E. Visual detection is quite straight forward. This particular image was taken with a CCD camera. Photographic recording is also very rapid and sensitive. This particular example was designed to have a wide dynamic range, three orders of magnitude in ATP. One can design the gradient for a much smaller range such as one order of magnitude with about ten percent accuracy within that range. So, depending on the design of the apyrase steps, one can produce a sensor with any requisite sensitivity and range.

This is what we refer to as the generic ATP sensor, or the ATP detection platform. This generic sensor is being developed by Protein Solutions, Inc. in Salt Lake City. They are developing an analogous sensor for the NADH dependent bioluminescence reaction. This sensor is slightly more complicated because two enzymes are involved in the bioluminescence reaction:

$$NADH + FMN + H^+ \xrightarrow{\text{oxidoreductase}} NAD^+ + FMNH_2$$

$$FMNH_2 + RCHO + O_2 \xrightarrow{\text{luciferase}} FMN + RCOOH + H_2O + \text{light}$$

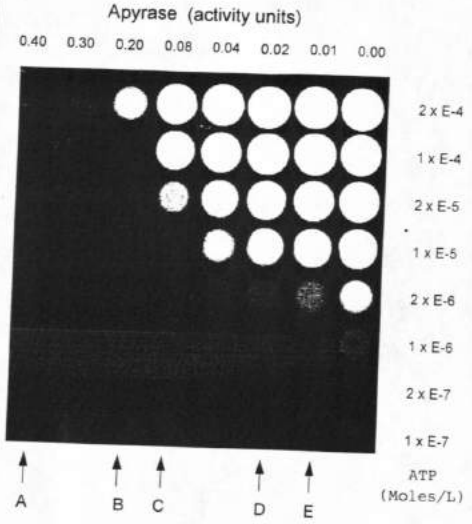

Figure 4. Eight ATP sensors (horizontal) each with identical apyrase step gradient various ATP concentrations (right, vertical axis) have been applied to each of the sensors (see text for details).

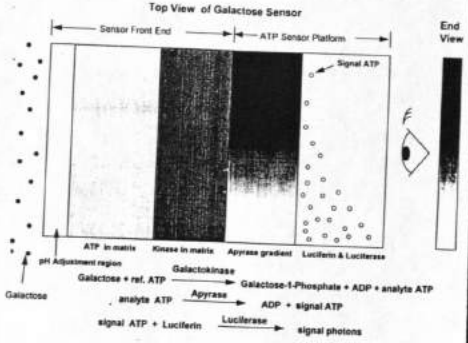

Figure 5. Schematic of galactose sensor.

The consumase in this case is an NADH oxidase and thus the NADH concentration is appropriately modulated and spatially detected.

Development of ATP specific and NADH specific detection platforms is well underway with Joe Andrade's group at the University of Utah in collaboration with Protein Solutions, Inc (37). The bioluminescence biosensor project involves Dr. Russell Stewart, Assistant Professor of Bioengineering, who has expressed the various luciferases by recombinant means in E. coli. These proteins have been engineered to facilitate their purification and immobilization as well as their stability in the dry state (3). Dr. C.-Y. Wang, a post doctoral fellow in Russell Stewart's group and also employed part time for Protein Solutions, recently completed his Ph.D. work under Joe Andrade's supervision, and his thesis forms the technological basis of the ATP specific sensor (3). Mr. Dong Min, a Ph.D. student in Joe Andrade's group is working on the NADH specific sensing platform (37).

Protein Solutions is an industrial partner in this grant and has agreed to make the two sensing platforms to the project at no cost. Please refer to letter on the last page of the proposal.

The major technological objective of this program is to use these ATP and NADH specific sensors, together with kinases and phosphatases in the case ATP, and oxido-reductases in the case of NADH, to produce an array of sensors specific to and sensitive for the critical low molecular weight biochemicals involved in metabolism, particularly the carbohydrates and amino acids.

Most analytes can be measured or monitored by a variety of methods. A good example is glucose. There are at least 6 different ways to analyze glucose using biosensors (32). One glucose analysis pathway is to react it with ATP in the presence of hexokinase, or even more specific enzymes, to produce glucose phosphate. The consumption of ATP due to the phosphorylation of glucose is a direct measure of glucose concentration, hence, a glucose sensor based on ATP-specific bioluminescence.

Admittedly, this is not new, but its implementation in a biosensor which is direct reading, disposable, inexpensive, ultra sensitive, quantitative, has a wide dynamic range, rapid, and stable coupled with direct visual detection, serves as a demonstration for the more widespread application of enzyme and substrate specific analysis based on ATP consumption or production. This method lends itself to the development of sensors for practically all mono-, di-, and poly-saccharides.

Such sensors will make it possible to enhance research and diagnosis in a wide range of problems and pathologies related to metabolism and bioenergetics, obviating the requirement for generally more expensive and time consuming standard analytical methods, often based on gas and liquid chromatography (13, 14).

5. Structure and Organization of the Project (Please refer to Figure 1, pg 5)

Joe Andrade, the senior PI; Robert Huefner, co-PI; and Steven Kern, co-PI, will serve as the project executive committee. Joe, Bob, and Steve have worked together on a variety of projects for the past five plus years including courses dealing with bioengineering applied to reducing the cost of health care, conference organization and proceedings (5), analysis of the Oregon list with respect to the focus of biomedical engineering research and development (38).

The three will meet formally at least twice a month and generally weekly. They will each be responsible for the planning, supervision, and conduct of the three key parts of the project, Figure 1. About fifty percent of the budget funds are allocated to the technology portion, directed by J.D. Andrade. About thirty percent of the funds are directed to the economic analysis, directed by R. Huefner with the assistance with N. Waitzman. The remaining twenty percent are directed by S. Kern, with the assistance of J. Andrade. The effort for the economic analysis is a little higher in the first year, and the effort for the educational component is higher in the third year. The group will meet with the Clinical Advisory Team and others at least quarterly to obtain the clinical and health care cost inputs required for the economic analysis and for the selection and prioritization of the technologies. The National Advisory Board will meet once each year as part of a one to two day symposium in Salt Lake City related to this project. The project's web site and e-mail communication mechanism will be instituted almost immediately and will serve as a means to gather input from and provide information to the larger community. Please refer to Education Section for details.

The National Advisory Board will meet early in the project period within the first three to six months, to provide appropriate input on project plans and developments. It will meet early in year two to provide a thorough analysis and critique of the first year of operation and of the plans for the remaining two years of the project. It will then meet about half way through year three to provide a comprehensive review and critique of the project to date and to provide suggestions, guidance, and related input regarding dissemination and expansion of the project to other areas and other communities. It is likely that that final meeting will be as part of a national symposium which might well involve other groups funded under this competition.

The boards are described in Section E--Biosketches.

6. Experimental Plan-Technology

The experimental plan is divided into two basic sections:

sensors dependent on the detection of ATP concentrations involving firefly luciferase and generally kinases for each of the specific metabolites and

sensors specific for NADH or NADPH involving NADH specific sensor and specific oxido-reductase enzyme for each metabolite of interest.

There are literally hundreds of specific sensors which can be developed for each category. Some of these are important in inborn errors of metabolism, others are important for the diagnosis for liver disease, others are important for the analysis of anaerobic and aerobic glycolysis, others

are important for the analysis and diagnosis of nutritional deficiencies, and many other applications. We have chosen to focus on carbohydrate specific sensors which represent the ATP based class, and amino acid specific sensors which represent the NADH based class. This is because of the importance of carbohydrates and amino acids in inborn errors of metabolism, and because there are today no simple, inexpensive means of monitoring a range of carbohydrates and a range of amino acids.

The specific carbohydrate and specific amino acid sensors which we choose to develop will of course depend on the clinical input and the economic analysis. Although we have chosen galactose and galactosemia as the initial example, the experience and knowledge we generate will be applicable to any other carbohydrate sensor.

The technology is novel yet generic and of such a wide potential applicability that it can be directed an focused to those problems of major clinical and cost reduction utility.

ATP-Based Systems: Carbohydrates

Figure 5 depicted a prototype galactose sensor discussed in terms of its various functional zones: at the far left, the sampling region, containing galactose analyte. The sample is wicked into the sensor by capillarity forces. The sample enters a pH adjustment region, then enters a zone which provides the ATP needed for the galactose specific reaction. The galactokinase zone, in the presence of ATP and galactose, phosphorylates galactose, consuming ATP. The apyrase region spatially modulates the ATP signal for direct visual detection. The final detection zone contains luciferin and luciferase, transducing the ATP gradient to an easily viewed photon gradient.

Conceptually, the galactose sensor can be split into a sensor front portion comprising the galactose-sensitive region, and an ATP sensor comprising the apyrase and luciferin/luciferase containing regions. The sensor is based on the partial consumption of ATP which in turn is spatially modulated by the apyrase gradient and converted to light in the transduction region by luciferase and luciferin. The resultant signal photons are spatially distributed to yield an indication of the original galactose concentration. Operation of the sensor begins when the sensor contacts a solution containing galactose.

ATP concentration is thus an indicator of the concentration of galactose. The phosphorylation of the sugar and the dephosphorylation of the ATP occur before the ATP reaches the apyrase/luciferase gel layer where light emission is initiated. Thus, the kinase serves as a specific mediator of ATP concentration by catalyzing its reaction with galactose. One ATP molecule is consumed for every one molecule of galactose reacted.

The depleted ATP reaches the luciferin/luciferase transducer zone resulting in a light signal, which is inversely proportional to the concentration of galactose in the test sample. The luminescence is imaged or waveguided onto photographic film for detection, or detected by the unaided eye. Comparison with standards will allow for a rapid estimation of the concentration of galactose in the sample. The final sensor will include a scale along the light output zone which will permit the operator to read out the galactose concentration by correlating the scale with a sharp inflection region between light and no light.

The specific tasks for the ATP-based part of the project include:

1. Characterize the available galactokinases with respect to cost, specificity, pH and temperature stability, and sensitivity.

Several enzyme types and sources will be reviewed. The process will include electrophoresis studies to determine maximum purity, cross-reactivity studies with other sugars to determine maximum specificity for galactose, intrinsic fluorescence studies over a range of operating temperatures to determine maximum temperature stability of the kinases, measurement of kinase activity over a range of operating pH values to determine maximum pH stability, and monitoring of ATP consumption over time to determine maximum activity.

2. Study galactose in water solution using the luciferase based ATP detection system.

We will perform a series of experiments to determine the optimum concentrations of galactokinase (GK) and ATP for detecting galactose in the concentration range of 0 to 100mg/dl. The corresponding molar concentration range is from 0 to 5.5mM. Because each mole of galactose will theoretically consume one mole of ATP, the corresponding ATP detection range is 0 to 5.5mM. Our ATP detection system is sensitive to 10^{-7}M ATP so there should be little difficulty in detecting these amounts of galactose.

For these studies, the amount of ATP in solution should be nearly equal to the largest amount of galactose we wish to detect. Less ATP would adversely affect sensitivity at high levels of galactose, more ATP would adversely affect sensitivity at low levels of galactose. The amount of galactokinase will affect the required incubation time. More galactokinase will decrease the incubation time, less will increase the time in the specificity zone. Optimum values of both ATP and galactokinase will be determined. Figure 6 presents the luminescent pattern of a preliminary experiment after the galactose, galactokinase and ATP have been incubated for the required period of time (time is dependent on amount of analyte and galactokinase) and the firefly luciferase system has been added and had time to react. No consumase (apyrase) gradient is present here. The left hand side is fully luminescent because all the ATP in solution reacts with the luciferase and luciferin to create light. The right hand side is completely dark because all of the ATP was used to phosphorylate the galactose and none is left to react with luciferin to produce light.

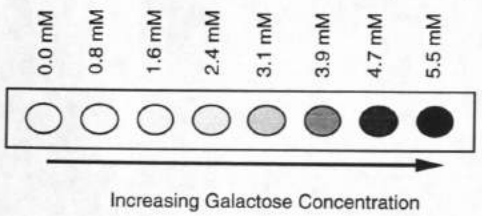

Figure 6. For a single concentration of galactokinase and 5.5 mM ATP, a one dimensional gradient of galactose is presented

The optimum concentration of ATP and GK will be determined and will serve as the baseline for future work.

3. Study the singular effect of individual urine components on the luciferase-based ATP detection system, including: glucose, lactose, fructose, maltose, pentose, chlorine, sodium, urea, creatinine, uric acid, ketone bodies, and pH.

These screenings will be performed with the ATP/galactokinase solution optimized in objective 2 using the same concentrations of galactose previously tested. A two dimensional microtiter arrangement will be used to individually screen the carbohydrates, pH and the salts found in urine. One axis will be a galactose gradient, the other will be the urine component gradient. A series of dilutions ranging from zero to maximum expected concentration will be used.

In addition to these chemicals, we will arrange an array of pH values common to urine (4.8-8.5). Additional buffer solution will likely have to be added to restore a pH of 7.8 (optimal for the light producing luciferase-luciferin reaction.) Different enzymes perform optimally at different pH values, ultimately, the sensor will incorporate the appropriate buffering system to ensure optimum pH values for each enzymatic reaction (pH adjustment region on figure 2.)

4. Quantitate galactose in commercial urine standards using the luciferase based ATP detection system.

We will incubate commercial urine standards containing known amounts of galactose in our optimized specificity solution (ATP/galactokinase). The result of this incubation will be applied to the signal transduction solution (luciferase/luciferin) and compared to the baseline values obtained in objectives 2. and 3. Once different amounts of galactose are detectable, we will apply the incubated samples to the spatial modulation solution (apyrase gradient) prior to detection by the signal transduction solution. This last step will allow quantification of galactose in liquid urine samples.

We will quantify clinically relevant amounts of galactose in commercial urine standards using our luciferase-based ATP detector system.

5. Study device stability and reliability with emphasis on the preservation of galactokinase and ATP.

Preservation studies of galactokinase and ATP will be conducted, focusing on incorporating the enzyme and substrate into a trehalose/agarose sol, which will be gelled and dehydrated under low particulate and partially sterile conditions to minimize contamination. The sols will be of varying agarose and trehalose concentrations to determine optimum conditions. Several drying condition will also be studied including vacuum drying, air drying, cold drying and inert gas drying. Various storage conditions will also be studied. The dehydrated gels will be stored in vacuum sealed foil packs at room temperature, 4°C, and -20°C for periods ranging from one day to 20 weeks (or until the end of the grant period). This work is similar to what we have already done for the dehydration and preservation of firefly luciferase (3).

These five objectives will be repeated in years two through three using other carbohydrates and kinases, with the goal of producing a multi-channel carbohydrate sensor which meets the optimum cost reduction needs. A possible example is given in Figure 7.

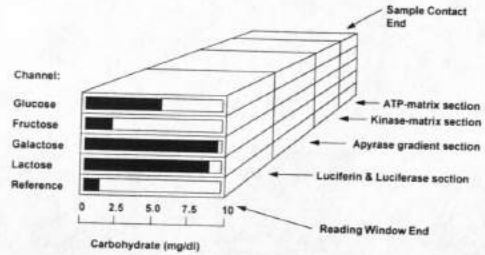

Figure 7. A schematic example of a multi-analyte carbohydrate sensor.

NADH-Based Systems: Amino Acids

The NADH based sensors are more complicated as both a luciferase (bacterial) and an oxidoreductase (FMN/NADH) are required. $FMNH_2$ is unstable and must be generated locally so that it can be acted upon by luciferase. The kinetics of the enzyme and other reactions suggest that the two enzymes must be in intimate contact with a high oxidoreductase/luciferase ratio (37, 39).

This is accomplished by having a bacterial luciferase/oxidoreductase transduction region, similar to the far right zone in the ATP sensor (Figure 2).

The apyrase analog here is an NADH oxidase, not involving FMN. Several such enzymes are available and will be evaluated (40). This will result in an NADH sensor analogous to the ATP sensor described above. Much of this work will be in year two of the grant.

The amino acid specific ends of the sensors will utilize the 1.4.1 class of enzymes, with special attention to the branched chain amino acids (33, 35) which are important in inborn errors of metabolism. We will also consider other important organic acids (30, 33, 36, 37). This work will be done in the latter part of year two and in year three. Some amino acids can also be analyzed via the ATP route (see EC. 2.5.1.6 for example). Those will also be considered.

Also in year three we will work on sensors incorporating both ATP and NADH specific detection. It is important to note that <u>each</u> enzyme used must be evaluated and tested using the steps discussed above for the galactokinases.

7. Economic Impact Analysis

<u>Purposes of the Economic Impact Analysis</u>

The purposes of the economic analysis are to assist in selecting disease conditions and chemical measures (considering their promise for cost reductions) which are made the focus of the proposed study, and then to more fully assess the likely economic results of the disease/technology combinations studied. The analysis will contribute directly to this study as well as providing a protocol for similar studies, using this study as a prototype. The analysis will illustrate:

- That economic analysis may be performed at various levels of precision and cost, and hence should be designed to fit the circumstances of the situation.
- How preliminary assessments may be made with limited information, time, and resources.
- Procedures by which greater precision may be efficiently achieved.
- Reasons and methods for the integration of economic and technical analysis.

The analysis of economic impact will move through four elements, each integrated into the overall study and yet each making an individually identifiable contribution to the study.

- The first element makes initial assessments of the potential economics of applying the technology to various conditions. It uses information and understanding which is easily available from experts and the literature, to select disease conditions suitable for the full study.
- The second element makes more certain estimates of economic impact for the conditions being addressed by the study. It more thoroughly reviews the understanding of these disease conditions and makes more detailed analysis of the available data regarding the outcomes of alternative treatment protocols influenced by the information readable from dipsticks. It identifies standard costs, from the cost of illness literature: resources used (direct cost) and resources lost (indirect cost). It considers both the human capital and willingness-to-pay (WTP) measures of cost-of-illness. Human capital theory emphasizes the investment character of health from a societal standpoint, where productivity is lost due to morbidity and mortality(a "depreciation" of human capital), whereas WTP is closely aligned with individual valuation in terms of utility as embodied in welfare economics literature. While WTP may be more true to the foundations of microeconomic theory, there are great practical difficulties is assessing the value individuals place on life and limb (4, 41, 42). But cost identification from either approach lays the foundation for cost-benefit and cost effectiveness analysis (43).
- The third element outlines further economic analyses for prototype clinical tests of the dipsticks, which might follow upon this proposed study. It again identifies standard costs, for current protocols for disease conditions studied and then for the potential reductions in these costs through proposed changes in protocols. This element also may describe additional economic studies, of substantial expense but to be done before the prototype tests, involving the assemblage and analysis of additional information. This will only be done if the analysis of more readily available information leaves uncertainties so great that expensive, but practicable, development of new data is prudent before the prototype studies.
- The fourth element uses the experience of the other three elements to reflect upon and anticipate the administrative and policy issues which this dipstick technology raises or addresses. An example is the criticality of patient, nurse, and physician education and the extent to which benefits are externalities not captured by the health care provider or payer.

In a sense these elements are stages, but they are highly interrelated and will, to a large extent, be simultaneously pursued throughout the project.

<u>Approach to the Economic Analyses</u>

Decision trees, with outcomes estimates, will be the primary tool of the analyses. Clinicians and practice guidelines will be the basis for outlining the chains of events and choices involved in the development and treatment of disease conditions. The probability of events, as well as the costs and benefits of possible outcomes, will first be estimated using easily available information. Sensitivity analysis will test the impact of the uncertainties of these estimates (e.g. of the cost saving from earlier diagnosis) upon the decisions and conclusion of this study (e.g. whether to include a specific disease condition among those for which dipsticks will be designed). This will guide the search for additional information to refine the estimates and will provide the basis for assessing the range of uncertainties remaining to be tested by prototype studies. This approach gives more emphasis to an iterative process of interaction between economists, physicians, and engineers, but still builds upon the consensus regarding central technical aspects of economic analysis provided by recent studies (44, 45). The emphasis will be upon the use of decision trees and sensitivity analyses as a way of thinking about economic outcomes and guiding engineering analyses, although the approach will provide the basis for engineers to link with the more elaborate and refined models now becoming available (46).

<u>Information Sources</u>

The economic analyses will depend upon existing information:

- The medical literature regarding prevalence of disease conditions, protocols, and medical outcomes and associated literature on cost.
- National data bases, such as the National Ambulatory Medical survey, regarding prevalence of treatments with related information regarding diagnoses, procedures, and prescriptions which can be combined with price information to estimate overall and component expenditures.
- State data bases, such as the Hospital Discharge Data of the Utah Health Data Authority, regarding prevalence of treatments and charges which can be adjusted to costs (e.g. using the Medicare cost-to-charge index) to estimate actual costs and resource use in impatient settings.
- Health plan data bases, such as the of the Utah Public Employees Health Plan, regarding the prevalence and costs of treatments to provide a comprehensive longitudinal data base to enhance the analysis of resource utilization with respect to the subject disease conditions and to provide the basis for a local prototype analysis.

<u>Outcomes and Products of the Economic Analyses.</u>

The economic analysis will produce three primary outcomes. The first is guidance to the study as a whole, in the selection of disease conditions and chemical measures for which dipsticks are to be developed. The economic analyses are only a part of the basis for these decisions, so this analysis will be closely integrated with the rest of the study, with Huefner and Waitzman regularly collaborating with Andrade and Kern in the prosecution of the study. Huefner has collaborated

with Andrade in past efforts, as well as with Waitzman. The outcome will be a project in which economic analysis has been an integral and integrated element, with a specific product of estimates of the economic outcomes of the use of dipsticks.

The economic analyses also will describe a methodology to incorporate economic analysis in studies of medical technology, to assist other biomedical engineers in using and understanding manageable approaches to economic analyses. The dipstick technology will provide a case study, to point out significant differences in investigations involved in broad population screening (e.g. of infants for galactosemia) vs. managing identified conditions (e.g. diabetes) and in the analysis of technology to manage identified, and sometimes rare, disease conditions vs. managing less costly and widely prevalent conditions. It also will raise policy and administrative concerns such as the distribution of benefits and costs and the resulting incentives or disincentives for cost-saving technology.

Finally, the economic analyses will provide a review of administrative and policy issues which it has addressed or identified. This will be a preliminary analysis, and prototype studies are likely to produce new surprises. But the preparation of the decision trees, the sensitivity analyses of these trees, and the estimates of outcomes -- all involving interactions of those addressing the technology, the clinical, and the economic aspects of this technology -- offers opportunities to gain insight to policy issues and to narrow the risks of future surprises.

8. Education Activities

Educational activities include:

- Teaching of health care cost issues in a new bioengineering design course at the University of Utah, starting January 1998.
- Organizing a special session at the 1998 Fall BMES Meeting to present the key materials from the course along with student presentations of course research projects.
- Establishing a collaborative effort with other institutions who receive grants from this offering to develop a cohesive curriculum approach to teach health care cost issues.
- Creating an incentive for students and faculty in bioengineering programs to consider cost issues in their research by establishing a Cost Reducing Technology Student Award at the annual BMES Meeting.

1. Design Course at University of Utah Winter 1998

To raise awareness and stimulate interest in cost reduction as a key criteria for pursuing research into new biomedical endeavors, we will develop a course which will integrate principles of health care economic analysis into a bioengineering design course focused on cost reducing technologies. The course would initially be offered at the University of Utah during the first year of funding. Issues of cost analysis are not typically part of the training and background of bioengineering students. As such, it is important to present this material in a context which is meaningful and relevant to their experiences. We feel the issues of cost analysis should be incorporated in an engineering design course. This presents a model for students to apply the information in their current and future projects as researchers or product developers in industry.

The course "Bioengineering Research & Development for Health Care Cost Reduction." will begin in 1998. The focus would be to initially teach fundamentals of cost analysis in health care with an emphasis on understanding the cost impact of early diagnosis and treatment of disease. This would include understanding the components that have contributed to health care costs, determining to whom cost reduction is important both historically and currently in the changing dynamic of health care reimbursement, and different methods for analyzing health care services to identify potential areas where technology can impact cost reduction as undertaken in the economic analysis of this proposal.

Since this grant proposes to investigate a new technology for diagnosis and screening for patient disease conditions and condition management, we will place emphasis on the role of applying technology strategies at different levels of care. Specifically, we will examine the role of treating a disease through patient self care, primary care, secondary, and tertiary care to understand

the different impacts that can be made at each level of the disease process before it progresses to the next level of care and technology sophistication. The students will choose a clinical problem and undertake a research project to research and propose a cost reducing technology specific to that condition. The project will likely focus in a medical area pertinent to their specific dissertation research but is not limited to this.

The class will also address issues that impact cost of commercial technology development to give a full context for the issues surrounding technology's role in the cost of health care. We will review the regulatory policies and issues of the Food and Drug Administration for different classes of medical devices, therapeutics, and procedures to understand the impact that regulatory intervention has in driving the cost of medical technology. This will lead to issues of clinical testing and evaluation to prospectively assess clinical effectiveness and whether projected impacts in cost reduction are achieved. Finally, issues related to physician education on cost issues and patient understanding of the potential role of technology to reduce health care costs will be discussed. These issues raise awareness of the importance of professional advocacy by the biomedical engineering community to assure that its voice is represented in the on going cost of healt care debate.

2. Fall BMES Meeting, 1998

The course instructor (Dr. Kern) will organize a session at the Fall BMES Meeting to focus on cost reducing technologies and means for assessment and analysis of the cost impact of new technologies. The session would combine information about the course with presentations of research projects on cost reducing health care technologies by students who participated in the course. A course syllabus and certain key reference materials for developing similar courses at other universities would be provided and maintained on a World Wide Web Site. This would serve as an initiation point for forming a collaborative effort with other institutions who receive awards from this grant offering to develop a cohesive approach to promoting the role of technology as a means to reduce health care costs.

3. Dissemination of course syllabus and materials

To facilitate collaboration with faculty at other universities, a syllabus and workbook from our class experience would be provided for review, comment and comparison with related activities at other institutions. The goal would be to refine the course material through feedback and experience from multiple institutions. A World Wide Web site for dissemination of the curriculum, research, and outcome results from collaborating institutions would be maintained for the bioengineering community. At the following BMES Meeting in 1999, a Cost Reducing Technology session would be organized with presentations by all collaborators and their students on activities developed to teach cost reduction and cost effectiveness.

4. Cost Reduction Research Award at the BMES Meeting, starting Fall 2000.

To incentivize collaborative participation, the BMES conference session would serve as a competition in the final year of the grant for a Cost Reducing Design Award to be chosen from student submissions to the special session. The award would be chosen by an independent panel of reviewers which would include Principal Investigators from other grantee institutions, members of industry, and physicians and would be of significant size ($5,000-$10,000) to continue to stimulate student interest in understanding health care cost issues. It is hoped that over time this would evolve a core of researchers, teachers, and product developers for whom cost reduction is a primary focus of their work. The year three budget includes $5,000 for this award. We will seek funding from corporations and foundations interested in bioengineering to keep the award competition running annually after the grant has ended.

Summary

Our education goals begin on a local level in order to establish a format for effective presentation and incorporation of cost analysis into our bioengineering curriculum. Based on that experience and the experience at other grantee institutions, a collaborative effort will be promoted

to create a cohesive approach to understanding and assessing the role of bioengineering in reducing the cost of medicine. Finally, students will be challenged to consider cost reduction issues in the research they conduct for their dissertations through the mechanism of a Cost Reduction Research Award to be presented annually at the BMES Fall meeting. The goal is to create a generation of researchers and bioengineers who consider cost reduction benefits resulting from their research.

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E. Biographical Sketches

The one to two page biosketches for each of the key professional participants (Andrade, Huefner, Kern, and Waitzman) and the chair of our National Advisory Board (Clark) are attached. Andrade was briefly described in Section C-3.

Huefner works with health care costs in terms of policy and administrative matters, as in having chaired the Governors Task Force on Health Care Costs and in relating the concerns of health care cost, quality, and access. He and the Center he directs deal with reforms and market transition as policy issues (technical consultants to the Utah Health Policy commission; publisher of Utah's Health, An Annual Review), as ethical issues (co-edited Changing to National Health Care, Ethical and Policy Issues; sponsored the establishment of the American Association of Bioethics and then staffed it until staff support was moved to the University of Minnesota at the end of 1996), and as administrative issues (consultant to the John Macy/New York University study: Implementation Issues and National Health Care Reform; co-director of University of Utah program for physician executives jointly sponsored with the Business School and the School of Medicine).

Waitzman continues to extend his economic analyses of birth defects (4). Related to this work is a major study he completed with colleagues on the benefits of folate supplementation of foods to prevent of neural tube defects, published in the American Journal of Public Health (May 1995). He has recently been on advisory panels of a major study of the cost of epilepsy sponsored by the Epilepsy Foundation of America, and of a National Institutes of Health grant proposal to analyze the costs of neonatal intensive care units. He is presenting a paper in June, 1997 on the cost-benefit relationship of ultrasound to detect birth defects at the New York Academy of Sciences.

National Advisory Board (NAB)

The National Advisory Board is designed to provide a national and international perspective to our activities. They are aware of major regional, national, and other initiatives; the improvement of access to health care; quality of health care; and cost of health care.

The board will be chaired by Dr. Edward B. Clark, Chairman of the Department of Pediatrics at the University of Utah and Medical Director of Primary Children's Medical Center. Dr. Clark joined the University of Utah earlier this year (1996).after a distinguished career at the University of Rochester and John Hopkins. His major research focus is Pediatric heart related ailments. His broad experience across the entire spectrum of pediatrics makes him ideally suited to chair this National Advisory Board.

Barry Zallen, M.D. is Health Center Director for Harvard/Pilgrim Healthcare in Burlington, MA. He has been involved in the development and implementation of Harvard Community Healthplan's Triage and Education in Burlington, MA. He has been involved in the development and implementation of Harvard Community Healthplan's Triage and Education System. The goal of this system was to provide patients with readily available health information in their homes which would reduce the demand for physician services and bring the patient into a more equal decision making role in their own health management (see Ref. 6). He will help to guide new application for the sensor platforms under development.

John E. Wennberg, M.D., M.P.H. is the Director of the Center for the Evaluative Clinical Sciences and Professor of Epidemiology at Dartmouth Medical School. He is a nationally recognized leader in efforts to reform the doctor-patient relationship and improve the delivery of quality health care to all Americans. His wide-ranging public presentations to medical gatherings, public interest groups, and congressional hearings, as well as his commentaries on editorial pages and in the electronic media, have gained attention around the nation. Dr. Wennberg has served on the Institute of Medicine's Health Sciences Policy Board and on the Committee on Technological Innovation in Medicine. As a founder and continuing board member of the Foundation for Medical Decision Making, he was instrumental in the design of interactive videodiscs for use by patients to help them share with their physicians in the decision-making process about treatment.

Dr. Wennberg began his academic research with work regarding why similar geographical areas may present dramatically different rates for certain surgical procedures. Building on this

research, his professional writings now explore outcomes research, patient preferences, the changing role of primary-care physicians, and the effect of the supply of resources on the patterns of utilization (5,47, 48).

Philip Lee, M.D. is presently Assistant Secretary for Health, U. S. Department of Health and Human Services. He will retire in early 1997. Formerly on the faculty of the University of California at San Francisco when he held such positions as Director of the Institute for Health Policy Studies and Chancellor of the University, is academic and governmental leadership provide particularly broad perspectives of public health and health care delivery, and position him to be especially valuable in understanding health economics and public policy and their intersection with bioengineering and technology. He also would bring to the discussions a special understanding of disease prevention and health promotion through primary health care.

Paul Feldstein is the FHP Foundation Distinguished chair in Health Care Management, Graduate School of Management, University of California at Irvine. As the author of many books and articles on health care economics, including his very popular text on health care economics, he would give the National Advisory Board a particularly well developed understanding of the economics of health care. In addition, his work in Washington, D.C. with of Office of Management and Budget and the Social Security Administration, as well as his work in Geneva with the world Health Organization, would add to the Board's strength in health policy.

Dorothy Rice is professor, University of California at San Francisco's School of Nursing, in its Institute for Aging. She is the former director of the National Center for Health Statistics. As one of the initiators and most important contributors to the cost of illness literature, she would bring invaluable perspective as well as technical expertise to the discussions of the cost saving potentials of technology.

Paige Sipes-Metzler has served as Executive Director of the Oregon Health Services Commission and has been involved with the development and implementation of the Oregon Health Care Plan since its inception by now Governor John Kitzhaber. Sr. Sipes-Metzler has worked closely with Kern and Andrade in using the Oregon health prioritization data base to help focus bioengineering research and development on those areas with the greatest cost reduction potential (38).

Not all members of the NAB are confirmed as of the date of submission of this proposal. We expect to add several additional members to the Board prior to the initiation of the project.

Clinical Advisory Team (CAT)

A local Clinical Advisory Team will meet at least quarterly during the first year of the project and at least twice a year during years two and three to provide clinical input and direction. The team will be chaired by Dr. Brent James, Executive Director of the Intermountain Health Care (IHC) Institute for Health Care Delivery Research. IHC is a provider network based in Salt Lake City. Dr. James is internationally known for his work on outcomes, measurements, and assessments and total quality management applied to health and medical care (see Ref. 5, pp. 53-56).

Dr. Edward B. Clark, Chairman of the Department of Pediatrics, will serve on the CAT as well as chair our National Advisory Board. His back ground was briefly described earlier and his two page biosketch is included.

Dr. Owen Ash, Chief Executive Officer of ARUP Inc., (Associated Regional University Pathologists) is an expert in all areas of clinical chemistry and clinical diagnostics. ARUP Inc. is one of the major clinical chemistry laboratories in the western United States, performing

approximately one hundred thousand tests per month with 700 employees and an annual income of nearly one hundred million dollars.

Howard G. McQuarrie, M.D. has been the Medical Director of the Utah Public Employees Health Program (PEHP) since 1982. As a consultant, he has been actively involved in developmental programs including Prevention Programs (*Healthy Utah, Prevention Plus*), global fee structuring for episodes of care (*Designated Service Plan*) and is currently involved actively with the University of Utah Medical School Faculty Practice Organization in development of *Centers of Disease Management*, which is modeled to provide a continuum and seamless care for high cost chronic illnesses such as Cystic Fibrosis, Hemophilia, Low Back Pain, adult and Pediatric Asthma. The Centers will be reimbursed globally for an interval of care, i.e., 1 year. Dr. McQuarrie has special interest in Continuing Medical Education, Clinical Research and the development of innovative systems to adapt to the changing medical environment as it relates to managed health care. He is currently lead author and facilitator for a "*Health Guide*" for members of PEHP with the objective for the reader, to use the information to more prudently select health care options.

Dennis Nielson, M.D., Ph.D. is Associate Professor of Pediatrics, University of Utah. He is a leader in the Health Sciences faculty in efforts to reduce the costs of high quality health care. He is engaged in efforts to improve health and reduce health care costs through public health, lifestyle, and patient responsibility, and most particularly through better management of chronic disease. In the latter effort he has initiated programs for more specialized capitated care for chronic disease and now is the team leader of the University's Center for Disease Management which contracts to provide such care.

Several additional members of the Clinical Advisory Team will be added prior to the initiation of grant activities.

Protein Solutions, Inc.

Suite 320 391 G Chipeta Way Salt Lake City, UT 84108 Phone/Fax: 801-583-9301

December 23, 1996

Joe Andrade, Bob Huefner, Steve Kern
Department of Bioengineering
College of Engineering
University of Utah
Salt Lake City, Utah 84112

Dear Joe, Bob and Steve:

This letter confirms that Protein Solutions, Inc. is willing to participate in your NSF - Whitaker Project "Personal Sensors for the Diagnosis and Management of Metabolic Disorders".

We look forward to working with you in the development of sensors for specific carbohydrates and amino acids which your program identifies as having both clinical significance and cost reduction potential.

Concerning our recent discussions, I would like to confirm that our generic ATP and NADH biosensors will be made available to you for this work on a no cost basis.

Best of luck in successfully qualifying for this funding program.

Sincerely,

Richard A. Van Wagenen, Ph.D.
Vice President for Research and Development

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