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Quarterly Progress Report Number 4

Transcutaneous Analyte Measuring Methods
(TAMM Phase II)

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Biotronics Technologies, Inc.

June, July, August, September, 1992

Naval Medical Research and Development Command

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(TAMM Phase II)

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October 12, 1992

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June, July, August, September, 1992
Contract Number N00014-91-C-0190

Prepared for
Naval Medical Research and Development Command
Bethesda, Maryland

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Abstract

The major objective of this extended quarter was to complete the analysis of pre-clinical data collected at the National Naval Medical Center (NNMC) in Bethesda, Maryland for the purposes of accuracy evaluation and algorithm development so as to allow for the initiation of field instrument development.

Data on the first 250 patients were collected at the Bethesda NNMC beginning on June 23, 1992 during two separate time periods. Testing was completed on August 4th. All patients were military personnel undergoing physical examinations. This patient group was selected to be representative of combat age military personnel.

Meanwhile, testing of the second group of 250 patients began at Froedtert Lutheran Memorial Hospital in Milwaukee on September 9, 1992 in conjunction with the Department of Endocrinology and the "Shared Clinic" of the Medical College of Wisconsin. Patients tested are people with various medical problems that were being treated on an out-patient basis. Testing will be completed on or about November 30th.

Data analysis began on July 6, 1992 and continued through the months of July, August and September. The objective of the analysis was to develop mathematical algorithms for all 9 blood analytes of interest:

1. Sodium
2. Potassium
3. Chloride
4. Calcium
5. Bicarbonate
6. Urea
7. Glucose
8. Hematocrit
9. Hemoglobin

The Bethesda test data have been processed through a variety of pattern recognition algorithms including the following:

1. Regression analysis;
2. Discriminant analysis;
3. Neural network analysis; and
4. Genetic neural network analysis (NETGEN).

Algorithms have been developed for all 9 analytes, but algorithm development will continue in an effort to provide the best tracking algorithms for each analyte as data with extended analyte ranges becomes available.

Accuracy evaluation and algorithm development has proceeded to the point of confidence needed to initiate field instrument development.

Biotronics is also prepared to return a TAMM NIR-800 Array Spectrometer to Bethesda NNMC programmed for on-site chemical analysis after software revisions have been completed. Delivery of this instrument is expected by December 15, 1992 pending Navy approval of additional costs.

Pre-Clinical Data Collection

The NIR-800 Array Spectrometer was set up at the clinic of the Department of Military Medicine at the Bethesda NNMC on June 22, 1992. Testing began on June 23 using computer procedures detailed in the report for the previous quarter. Lieutenant Commander Lisa Hilderbrand was of tremendous assistance in arranging facilities and personnel for this testing. During a 7-day period ending July 2, 125 patients were processed. Each patient contributed a blood sample that was analyzed in the laboratory for the following blood analytes:

1. Sodium (Na^+)
2. Potassium (K^+)
3. Chloride (Cl^-)
4. Bicarbonate (CO_2)
5. Urea (BUN)
6. Glucose (GLU)
7. Creatinine (CREA)
8. Total protein (TP)
9. Albumin (ALB)
10. Calcium (Ca)
11. Phosphorous (PHOS)
12. Uric acid (URIC)
13. Enzymes: AST, ALT, ALKP, TBIL, LDH
14. Hematocrit
15. Hemoglobin

During the second NNMC period, which began on July 20 and ended August 4, an additional 125 patients were processed.

Testing at Froedtert Lutheran Memorial Hospital began on September 9, 1992. As of September 30, 82 patients had been tested. By October 9, 98 patients had been tested. Because the patients processed at Froedtert were all symptomatic, a wider range of analyte values has been recorded during the testing. These data will be of great value to the program because it will allow the analysis algorithms to be tested on a range of analytes that could be found during combat conditions, as well as allowing the instrument to be optimized.

Two additional analytes have been added to the Froedtert laboratory test program: cholesterol and triglycerides.

Data Analysis and Algorithm Development

All data were stored in original form consisting of 90 light scans (actual scans of the patient), 90 dark scans (scans performed without the light source being activated), and scans of a reflective reference. Signal processing has included the following:

1. Mean filter;
2. Median filter;
3. Arterial peak;
4. Savitsky-Golay spectral filtering.

Pattern recognition methods used so far include the following:

1. Regression analysis;
2. Discriminant analysis;
3. Neural network (backpropagation) analysis;
4. Genetic algorithm analysis;
5. Neurogenetics analysis; and
6. Adaptive filter method.

Results

The following test accuracy results have been achieved as noted in the table below. While average errors for all analytes are quite satisfactory, the tracking ability of all of the algorithms need improvement. The tracking value, as expressed in the T parameter, should be at least at 2.68 to provide reliable detection of high and low values of each analytes. While algorithms will continue to be improved, the problem really lies in the lack of enough high and low values in the Bethesda data set. The Froedtert data set originating from a less healthy population is expected to correct this problem.

Analytical Results (TAMM)

Analyte	Mean Value	Average Error	Slope (b)	T	P
Calcium	9.68 mg/dl	0.235 mg/dl 2.38%	0.79	1.73	0.09
Potassium	4.08 mmol/L	0.27 mmol/L 6.66%	0.29	1.13	0.26
Sodium	139.56 mmol/L	1.39 mmol/L 0.96%	0.78	2.49	0.016
Chloride	101.22 mmol/L	1.67 mmol/L 1.65%	0.43	1.35	0.18
Bicarbonate (CO_2)	28.89 mmol/L	1.72 mmol/L 5.95%	0.54	1.50	0.15
Glucose	79.23 mg/dl	8.66 mg/dl 10.93%	0.72	1.78	0.07
Urea (BUN)	14.02 mg/dl	2.72 mg/dl 19.40%	1.04	3.39	0.0015
Hematocrit	43.36%	2.8% 6.48% of mean	0.95	2.34	0.03
Hemoglobin	14.99 g/dl	0.868 g/dl 5.79%	0.62	2.50	0.016

Field Instrument Development

The general architecture of the field instrument design has already been determined on a preliminary basis. The instrument will utilize a 64 x 1 indium gallium arsenide photodetector array and will be based on direct contact with the arm of the patient without the use of a fiber probe. Elimination of the fiber probe with its large light losses will greatly reduce electric power requirements and allow for battery operation. An instrument of the size of a portable lap-top computer is contemplated.

Diagnostic NIR-800

The original NIR-800 spectrometer was designed as a data collection instrument. Conversion to an instrument that would provide direct analyte measurements will require a significant change in the analytical and user interface software. Such software development will result in additional costs not contemplated at the time of the original Phase II SBIR proposal. A cost estimate is now in preparation along with a delivery schedule for approval by the Naval Medical Research and Development Command.

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