

THE EFFECTS OF BLOOD STORAGE TIME
ON THE ACCURACY OF
COMPREHENSIVE METABOLIC PANEL RESULTS

A Report of a Senior Thesis

by

Jessica Lynne Kitchens

Major: Biology

Maryville College

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Date Approved _____, by _____

Faculty Supervisor

_____, by _____

Editor

ABSTRACT

Blood tests are used as a diagnostic tool to evaluate one's health. A common blood test is known as the comprehensive metabolic panel or CMP. The CMP gives doctors important information pertaining to a patient's blood sugar and proteins, acid/base balance, and the status of kidney and liver function. This study seeks to assess the effects of storage time on the results of the CMP and to determine an optimal time limit for blood samples to be stored before testing. Blood samples were drawn from the antecubital vein of five volunteers and then stored at 4°C. Samples from each volunteer were tested once a day for five days. During this study, significant differences were found in sodium ($p = 0.0401$), potassium ($p < 0.0001$), glucose ($p < 0.0001$), and total protein ($p = 0.0029$). The significant changes in potassium and glucose were found as early as Day 2 of the study. These results suggest that blood samples should not be stored for more than 24 hours before testing to preserve the integrity of the analyte concentrations and to deter erroneous results, which may lead to faulty interpretations of a patient's health.

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CHAPTER I

INTRODUCTION

Blood Components

Blood is composed of both cellular and acellular factors. The cellular components include red blood cells, white blood cells, and platelets, which are all manufactured in the bone marrow. Red blood cells make up about 40% of the total volume of normal blood (Clayman, 1989). This percentage of volume made up of red blood cells, or RBCs, is known as the hematocrit. A single RBC can remain up to 120 days in the circulatory system before they are removed by the spleen. White blood cells, or WBCs, are the body's protection against invading foreign substances such as bacteria and viruses. In the blood, WBCs are outnumbered by RBCs at an average of 600 to 1. Platelets are the smallest cellular components of the blood, but they are vital because they help prevent the massive loss of blood brought about by trauma and blood vessel leakage. Platelets can only remain in the circulatory system for 9-10 days before they are removed (Shin & Bellenir, 1999).

The acellular components of blood consist of proteins, ions, and the liquid in which RBCs, WBCs, and platelets are suspended and transported through the body. Many proteins and ions are present in the blood in order to be transported throughout the

body. Some of these include calcium, glucose, albumin, sodium, potassium, and bilirubin. The liquid, which makes up about 60% of the total volume of the blood, can be referred to as plasma or serum. The liquid is called plasma when it still contains the clotting factors, which is its natural state in the body. This liquid is referred to as serum when the blood is drawn and allowed to clot, therefore removing its clotting factors (Shin & Bellenir, 1999).

Blood Testing

Examination of blood cells can reveal blood cell abnormalities, which may be characteristic of different diseases, or variation in number of cell types, which could reveal a response to infection. Blood is the major transportation system throughout the body, and with this role, it affects and is affected by all parts of the body. Therefore, blood tests can be used to determine the health of major organs as well as hormones, the immune system, respiratory function, and metabolism. There are three types of blood tests: hematological, biochemical, and microbiological (Clayman, 1989). Hematological tests examine the blood components by number, size, shape, and appearance. Examples of hematological tests include blood count, blood smear, and blood clotting tests. Biochemical tests include kidney function tests, liver function tests, and acid-base balance. These tests examine the chemicals, vitamins, gases, and drugs found in the blood. Microbiological tests are usually performed in cultures. These tests look for microorganisms in the blood, such as fungi, viruses, and bacteria.

Blood tests begin with blood being drawn, most commonly, via venipuncture or finger sticks. Venipuncture involves a technician drawing blood from a vein on the inside of the elbow after a tourniquet is wrapped around the upper arm to compress blood

vessels and limit the flow of blood in the veins back to the heart (Jatlow & Costa, 1997).

The patient is then asked to make a fist in order to make the vein stand out more prominently. The technician then cleans the area, inserts a sterile needle into the vein, and draws blood through the needle by vacuum pressure.

Finger sticks are used when only a small amount of blood is needed, such as for an anemia check, or if veins are too small or fragile (Jatlow & Costa, 1997). A technician first cleans the area and then sticks the finger with a small blade. This stick is designed to obtain blood from capillaries. Technicians will then squeeze the finger to produce drops of blood, which will then be gathered into very tiny tubes or micropipettes. This procedure is frequently performed in children and infants, and it can be also be performed on the earlobe or heel.

Comprehensive Metabolic Panel

One common blood test, known as the comprehensive metabolic panel or CMP, is frequently ordered by doctors in order to assess patient health. It is usually a common part of a medical exam or physical, but it can also be ordered to assess and elucidate disease states. The CMP gives doctors important information about the status of patient blood sugar, blood proteins, kidney function, liver function, acid/base balance, and electrolytes through a series of 14 tests. These 14 tests are for specific acellular blood components (Table 1), which include: glucose and calcium; albumin and total protein; sodium, potassium, CO₂, and chloride to check electrolytes; BUN (blood urea nitrogen) and creatinine to check kidney function; and, alkaline phosphatase, alanine amino transferase, aspartate amino transferase, and bilirubin to check liver function. Abnormal results for any of the 14 tests could indicate a problem that might need to be addressed.

For instance, the CMP can be used as a screening tool for things such as diabetes and kidney disease, as well as to monitor a current condition, like hypertension, or effects of specific medications, such as those which might produce side effects related to the kidneys or liver (American Association for Clinical Chemistry, 2004).

Table 1. Some common blood profile tests included in the Comprehensive Metabolic Panel and what the results could possibly mean (Jatlow & Costa, 1997).

Test	Increase May Mean	Decrease May Mean
Albumin	N/A	Malnutrition; liver failure; kidney failure.
Total Bilirubin	Liver disease; hemolytic anemia.	N/A
Blood Urea Nitrogen (BUN)	Kidney failure; dehydration; blood in GI tract.	Liver failure.
Calcium (Ca ⁺)	Parathyroid and thyroid gland hyperfunction; cancers; bone diseases; Vitamin D intoxication.	Kidney failure; parathyroid hypofunction; malnutrition; Vitamin D deficiency.
Chloride (Cl ⁻)	Acid-base imbalance from GI, adrenal, and renal diseases.	Kidney disease; adrenal gland hyperfunction; acid-base imbalance.
CO ₂	Acid-base imbalance from a variety of causes including respiratory failure and vomiting.	Acid-base imbalance from a variety of causes including kidney disease, diabetic acidosis, and diarrhea.
Creatinine	Kidney failure; dehydration.	N/A
Glucose	Diabetes mellitus; adrenal gland hyperfunction; intravenous glucose fluids.	Excess insulin; liver failure; adrenal gland hypofunction; starvation.
Aspartate Aminotransferase (AST)	Liver disease or damage; heart injury; muscle injury.	N/A
Alanine Aminotransferase (ALT)	Liver disease or damage.	N/A
Sodium (Na ⁺)	Dehydration; adrenal gland hyperfunction; kidney disease; diabetes insipidus.	Kidney failure; adrenal gland hypofunction; diuretics; overhydration; kidney, liver, and heart failure.
Total Protein	Multiple myeloma; chronic infection or inflammation.	Malnutrition; liver or kidney failure.
Potassium (K ⁺)	Kidney failure; adrenal gland hypofunction; acid-base imbalance.	Diuretic therapy; diarrhea; vomiting; adrenal gland hyperfunction; acid-base imbalance.

Problems in Blood Analysis

Errors in specimen collection and handling can result in inaccurate test results, which can lead to the mismanagement of a patient (Table 2). Some of the most common errors include clerical errors, hemolyzed samples, and incorrect use of anticoagulants. Hemolysis from a venipuncture can lead to erroneous results for an array of analytes including an increase in lactate dehydrogenase, AST, CK, potassium, ALT, bilirubin, acid phosphatase, and magnesium. Hemolysis may also affect counts of red blood cells, recognition of antibodies, and results of coagulation tests (Szamosi, 2001). When blood-collecting techniques are faulty, such as excessive squeezing at the puncture site, plasma K^+ and hemoglobin concentrations may be increased, especially in newborns to 13-day-old infants (Meites, Lin, & Thompson, 1981). Contribution of interstitial fluid in a sample can be determined by determining the plasma hemoglobin, K^+ , blood hemoglobin, and hematocrit. With excessive squeezing, interstitial fluid can contaminate samples with additional hemoglobin and K^+ .

Table 2. Blood analysis problems found in past research.

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Problem	Effects	Citation
Cellular		
Hemolysis	Hemoglobin, released through hemolysis, can interfere with the process of determining other analytes found in the blood including creatinine, bilirubin, total protein, albumin, and aspartate aminotransferase.	(Blank, Kroll, Ruddel, & Elin, 1985)
Plasma vs. Serum	Paired samples of plasma and serum showed that most analyte values differ from one sample to the other. Analyte concentrations of total protein, globulin, CPK, calcium, magnesium, and phosphorus were found to be higher in samples containing serum. Concentrations of albumin, A/G ratio, potassium, and chloride were found to be higher in samples containing plasma.	(Hrubec, Whichard, Larsen, & Pierson, 2002)
Acellular		
Uncentrifuged specimens	Significant changes in most analytes due to depletion of glucose, movement of water into cells, movement of analytes between cells and the fluid, and ongoing metabolism in cells.	(Boyanton, Jr., & Blick, 2002)
Microwave heating	Microwave heating of packed red blood cells to temperatures of 37°C or more showed an increase in free hemoglobin and HBDH as well as other hemolysis markers. Microwave warming of samples for transfusion can also result in overheating and hot spots within the sample.	(Hirsch, Menzebach, Welters, Dietrich, Katz, & Hempelmann, 2003)
Excessive squeezing at collection site	Sample can be contaminated with "tissue fluid," which can increase the plasma concentrations of potassium and hemoglobin, especially in newborns to 13-day-old infants.	(Meites, 1981)
Storage temperature	Analyte test results are found to be more stable when samples are refrigerated between 2-6°C.	(Hill, Johnson, Burns, Neale, Harmening, & Kenney, 2002)

Effects of Temperature and Storage Time on Blood Analysis

The temperature and time at which a sample is stored can have a great influence on prescription drug concentration, analyte values, and enzyme stability in the blood sample. For instance, Bennetto et al. (2004) found that variable temperatures and lengths of storage time can alter the stability of neviraprine, a highly prescribed HIV treatment, during processing and storage of blood samples. This drug is mainly used in resource-poor nations in Africa, so storage conditions are very important since blood samples are usually sent elsewhere to be tested. Neviraprine concentrations remained stable in plasma for up to 6 months when stored at -20°C , 15 days at 4°C , 7 days at 25°C , and 1 hour at 56°C (Bennetto, King, Turner, Stringer, & Acosta, 2004).

Analyte values for blood samples can also be affected by these variables. Rehak and Chiang (1988) found that significant differences in creatinine, glucose, phosphorus, potassium, aspartate aminotransferase, and alanine aminotransferase concentrations occurred over a range of temperatures. Glucose values suffered a drastic decrease while phosphorus values increased rapidly at temperatures greater than 22°C . Potassium concentrations spiked at 3°C and 38°C . Both aminotransferases increased after being stored at temperatures greater than 22°C , but they experienced a constant decrease at 38°C . Creatinine values increased rapidly at storage temperatures greater than 25°C (Rehak & Chiang, 1988).

Boyanton and Blick (2002) found that analyte values could be affected by storage time as well. Blood samples kept in serum or plasma at 25°C had significant changes in nine of the blood profile tests included in the comprehensive metabolic panel (Table 1). Glucose levels were significantly different after being stored for 4 hours. Potassium,

creatinine, and total protein results were significantly different when tested at 32 hours; calcium at 40 hours; albumin and alanine aminotransferase at 48 hours; and, CO₂ at 56 hours (Boyanton & Blick, 2002).

A review of the aforementioned studies suggests that most analytes kept at or below 4°C remained stable while warmer temperatures caused significant differences in analyte test results. With this knowledge in mind, the Center for Disease Control's "National Health and Nutrition Examination Survey: Laboratory Procedures Manual" requires hospitals to store processed samples in refrigerators or freezers (CDC, 2005). This is done in order to help preserve the integrity of the analytes and to suppress the possibility of hemolysis.

Purpose of Study

Recent studies have examined the combined effects of both temperature and storage time on blood analysis results. Because of this parallel research, it is difficult to discern which variable, temperature or time, is responsible for significant changes in blood analysis result values. In order to understand of the separate effects of temperature and storage time, this study seeks to solely assess the effects of storage time on blood analysis results. By keeping temperature constant and focusing on storage time effects, this study seeks to determine an optimal time limit for blood samples to be kept in a lab for further testing.

CHAPTER II

MATERIALS AND METHODS

Blood samples were drawn from the antecubital vein of four volunteers at the Blount Memorial Hospital Laboratory on 25 September 2006 following the hospital's phlebotomy protocol (Appendix B). Each volunteer's blood was placed in five 10mL "green top" Vacutainer[®] tubes, which contained the anticoagulant heparin. Because heparin was added to the samples, plasma was tested for analyte concentrations instead of serum.

On Day 1, the day of phlebotomy, one sample tube per volunteer was centrifuged while the other four sample tubes per volunteer were stored in the refrigerator at 4°C until their day of testing. Comprehensive metabolic panels (CMP) were then performed on the centrifuged samples approximately 30 minutes after collection. The comprehensive metabolic panel, which includes the tests shown in Table 1, was performed using the Synchron LX[®]20 Pro (Synchron LX Clinical Systems, 2003). For the next four days, one tube per volunteer was chosen at random from the refrigerator, centrifuged, and then tested in the same fashion and approximate time of day as those on Day 1. As a result, the changes in CMP measurements were monitored for 5 consecutive days.

A preliminary set of blood samples from one volunteer was also tested from 17 June 2006 through 21 June 2006 at a hospital laboratory following the same protocol mentioned above. Due to a confidentiality agreement, the location of the laboratory cannot be disclosed. All five volunteers signed statements of informed consent (Appendix A) and will remain anonymous throughout this study.

After analyte value results for all tubes were collected, a repeated measures Analysis of Variance (ANOVA) (Statview 5.0, 2000) was performed for each analyte in Table 1. Fisher's PLSD post hoc test (Statview) was used to determine where significant differences ($p < 0.05$) in analyte values existed among testing days.

CHAPTER III

RESULTS

According to the repeated measures ANOVA, significant differences among the 5 sampling days were found for the following analytes: sodium ($p = 0.0401$), potassium ($p < 0.0001$), glucose ($p < 0.0001$), and total protein ($p = 0.0029$). In Figures 1 through 7, the same letter shown above data points designates significance ($p < 0.05$) as determined by Fisher's PLSD.

Average concentrations of sodium (Figure 1), glucose (Figure 1), CO₂ (Figure 4), and calcium (Figure 6) decreased throughout the 5 days of testing while mean concentrations of AST (Figure 3) and potassium (Figure 4) increased throughout the testing period. The data for chloride (Figure 1) and albumin (Figure 5) stayed fairly stable, but the average concentrations of creatinine (Figure 2), ALT (Figure 3), total protein (Figure 5), BUN (Figure 6), and total bilirubin (Figure 7) did not remain constant or show a continuous pattern of increase or decrease.

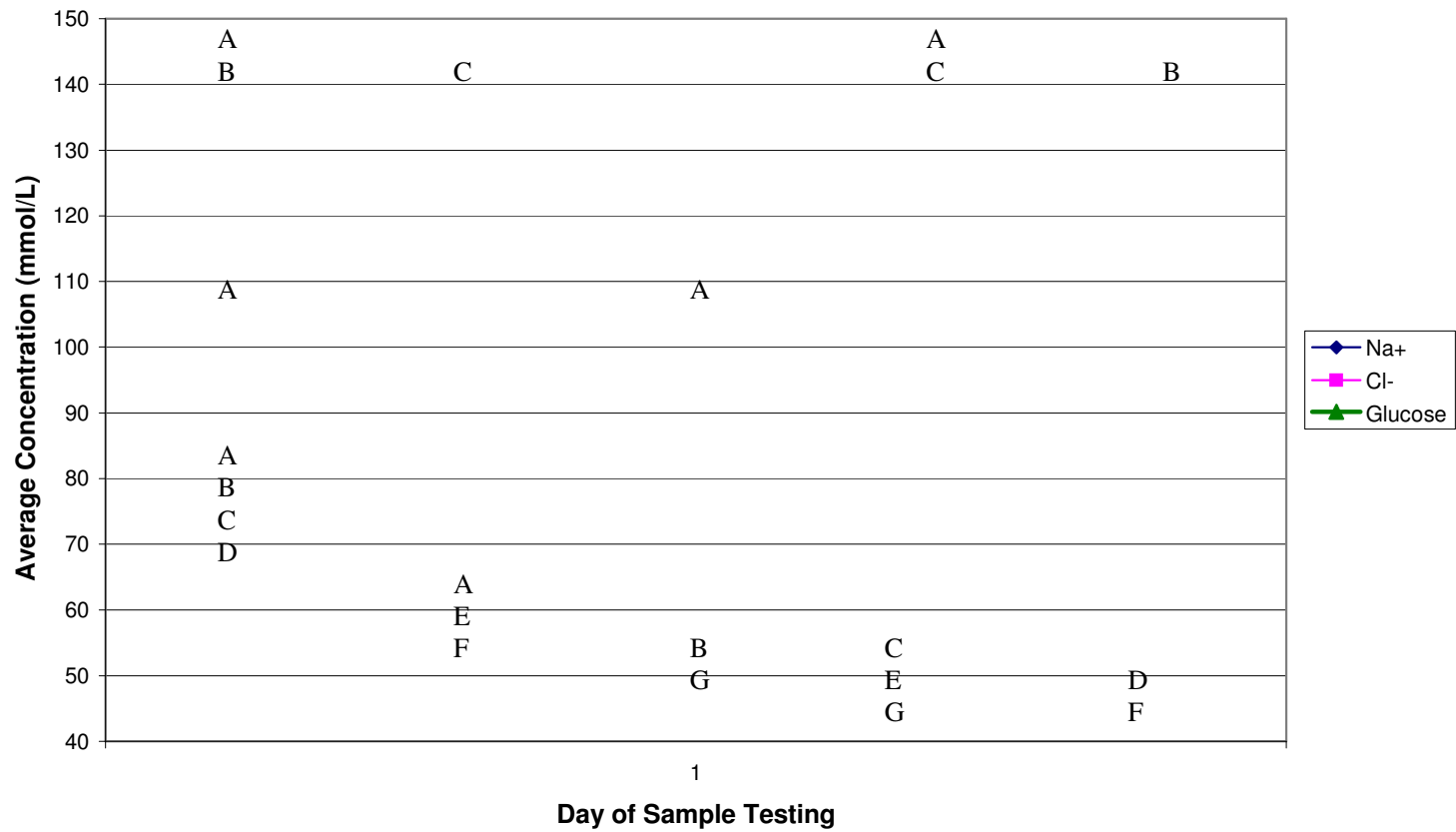


Figure 1. Average concentrations (+1 SE) for sodium, chloride, and glucose throughout the 5 days of testing. The same letter above data points indicates significant difference ($p < 0.05$).

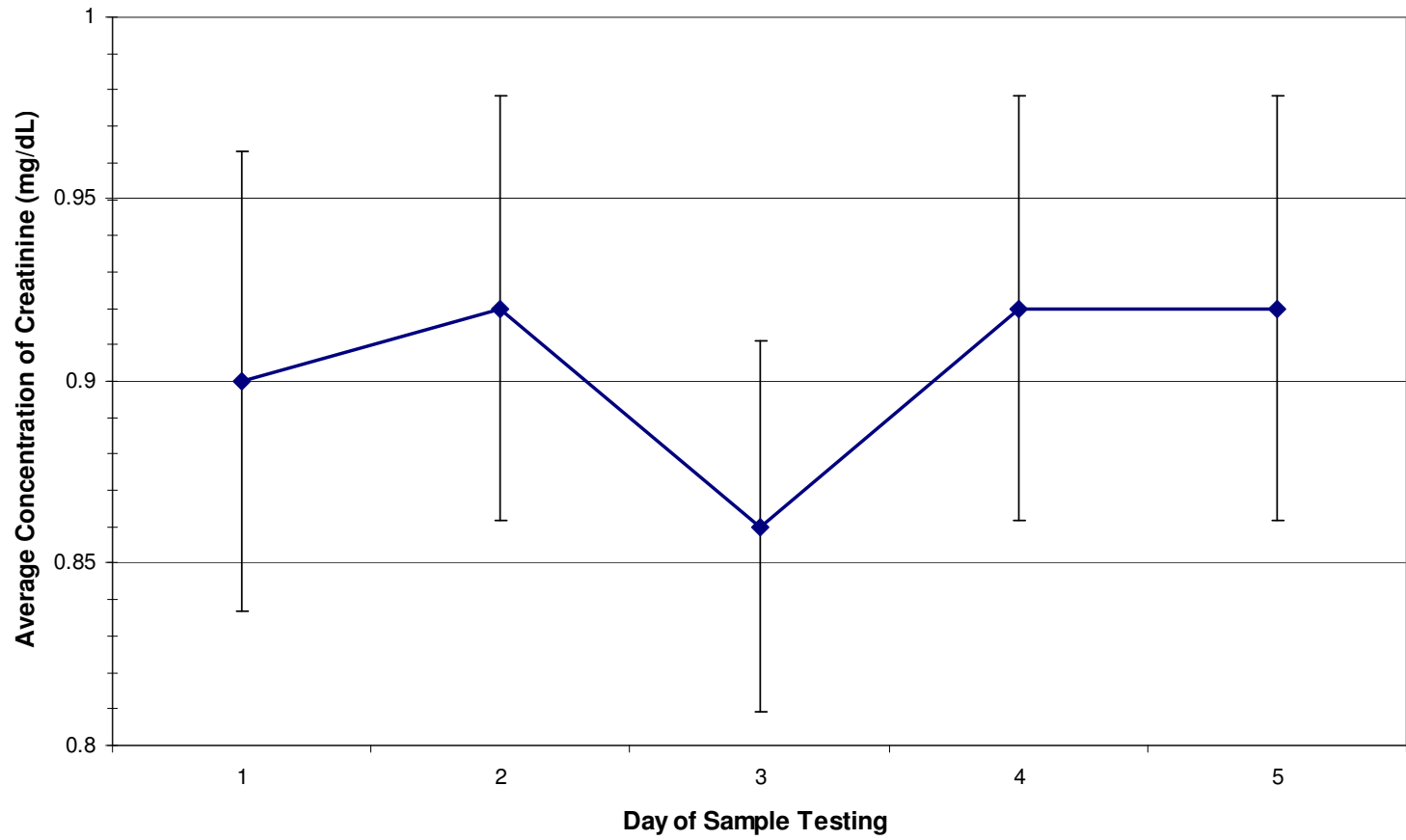


Figure 2. Average concentrations of creatinine (+1 SE) throughout the 5 days of testing.

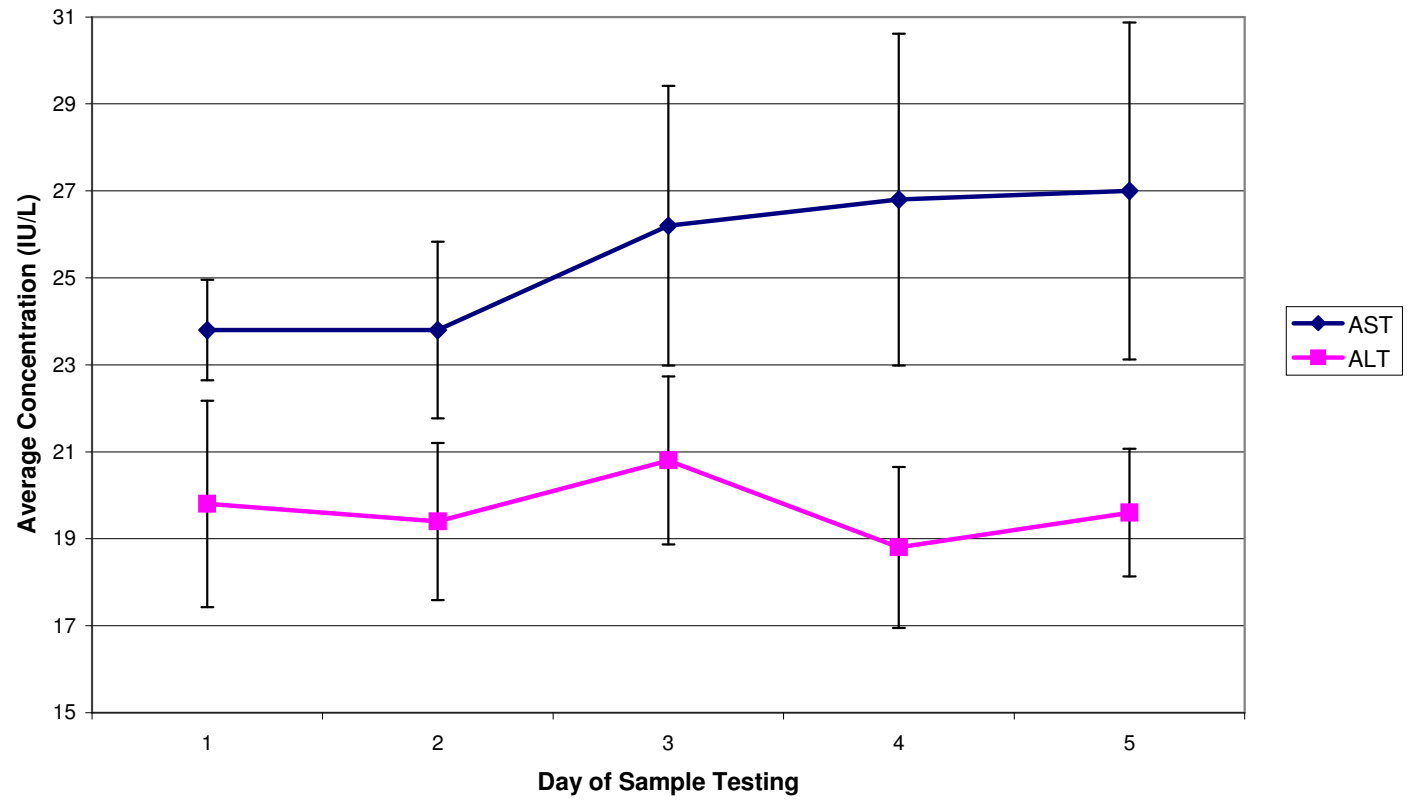


Figure 3. Average concentrations of AST and ALT (+1 SE) throughout the 5 days of testing.

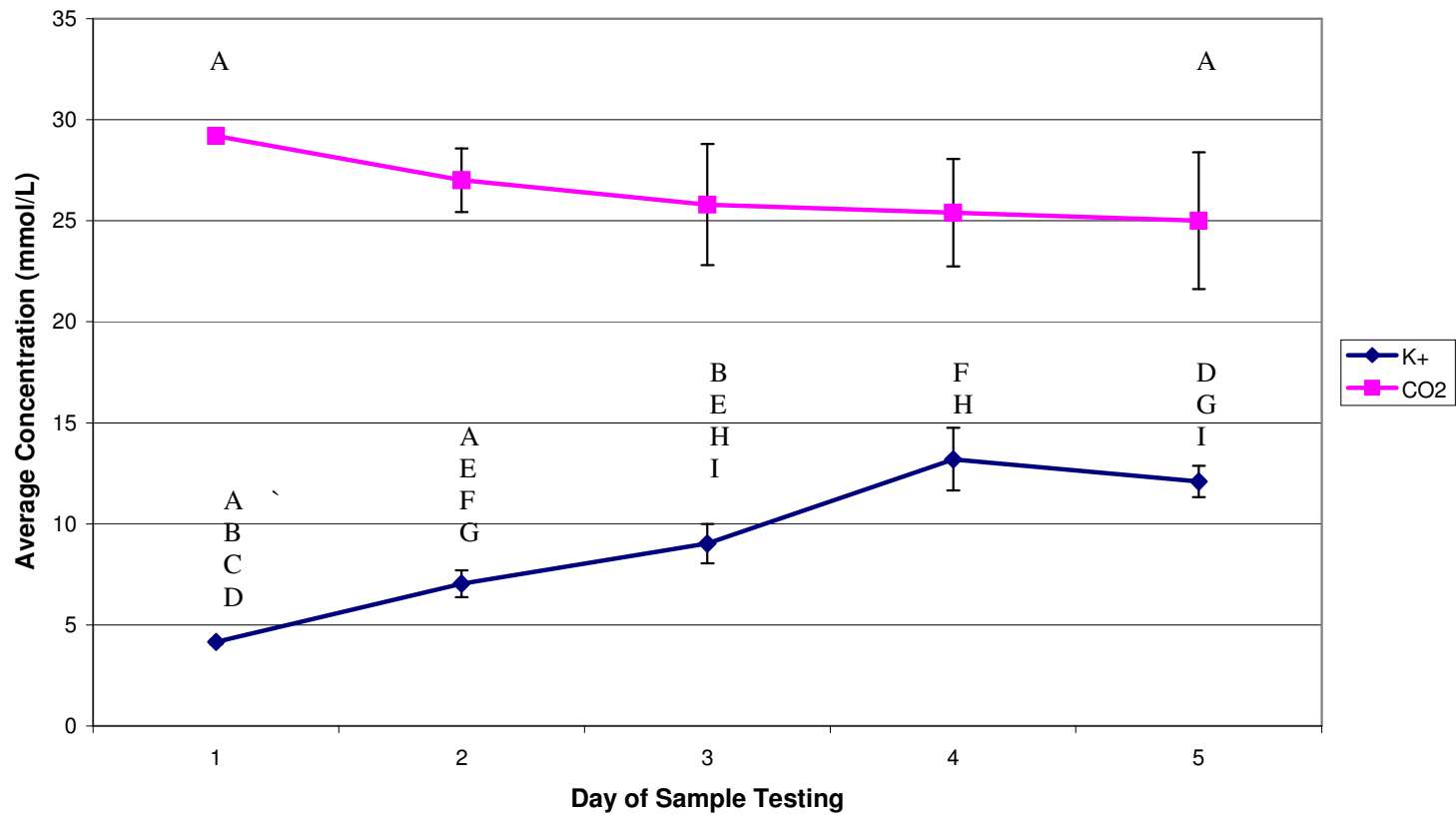


Figure 4. Average concentrations of potassium and carbon dioxide (+1 SE) throughout the 5 days of testing. The same letter above data points indicates significant difference ($p < 0.05$).

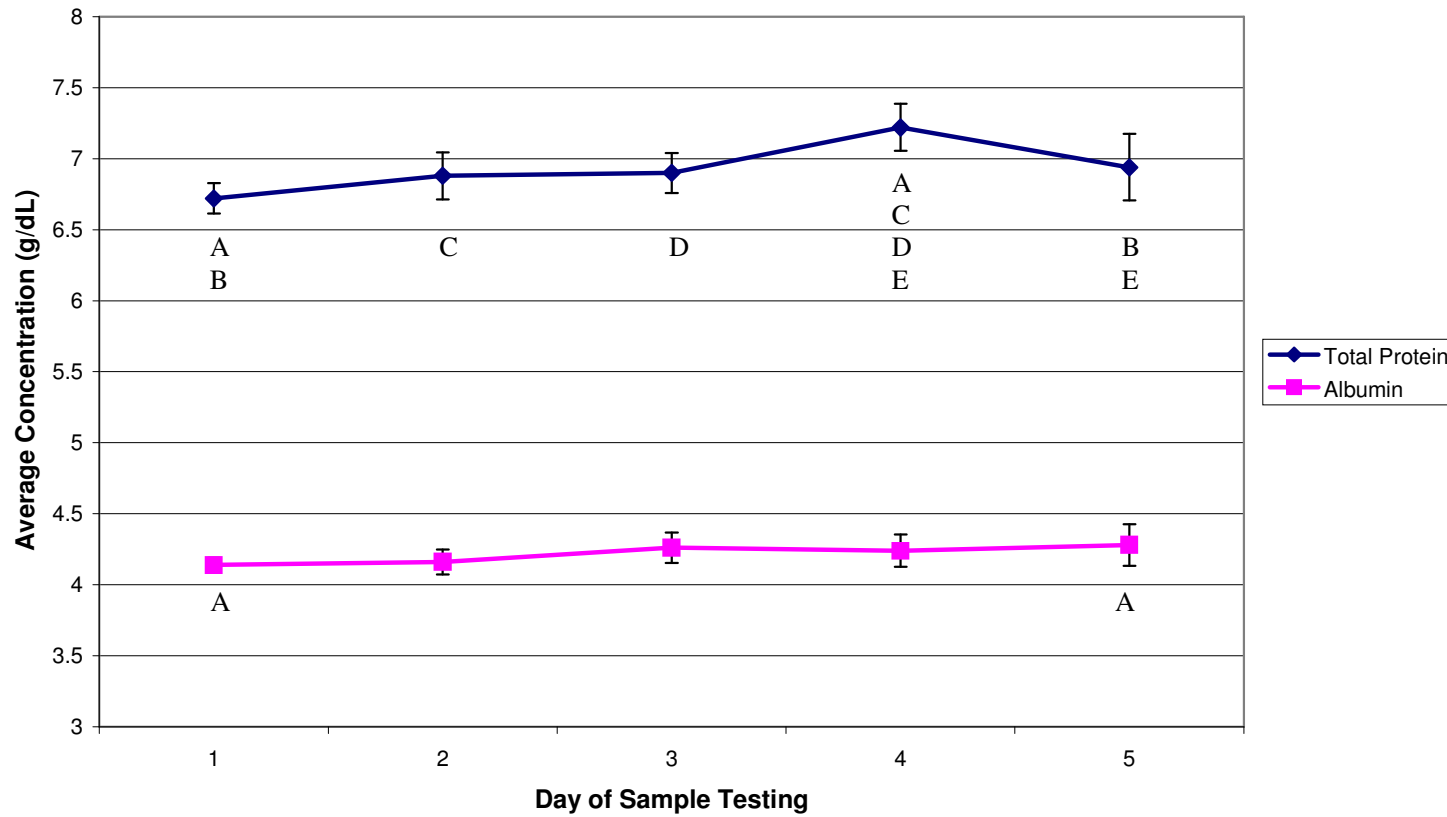


Figure 5. Average concentrations of total protein and albumin (+1 SE) throughout the 5 days of testing. The same letter above data points indicates significant difference ($p < 0.05$).

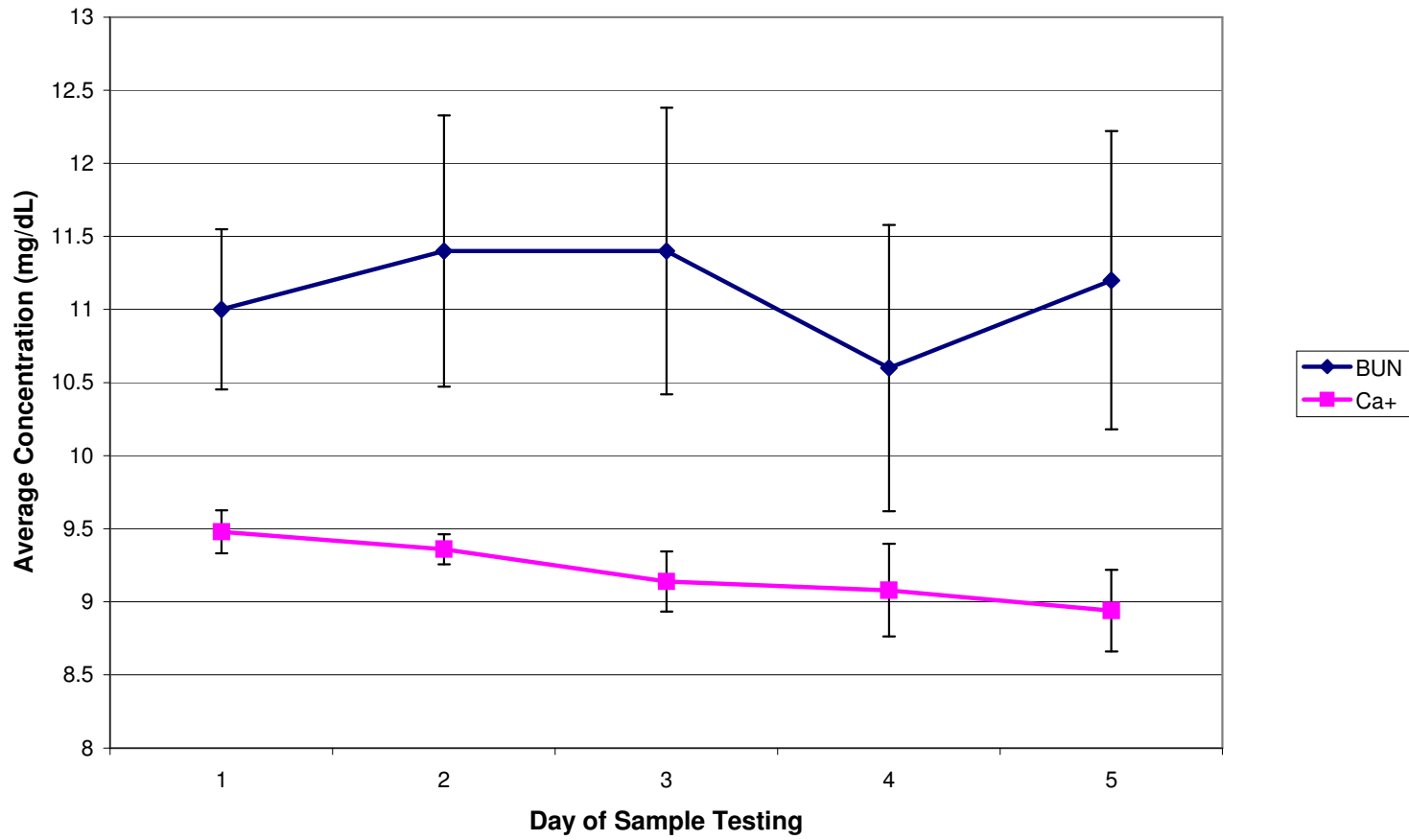


Figure 6. Average concentrations of blood urea nitrogen and calcium (+1 SE) throughout the 5 days of testing.

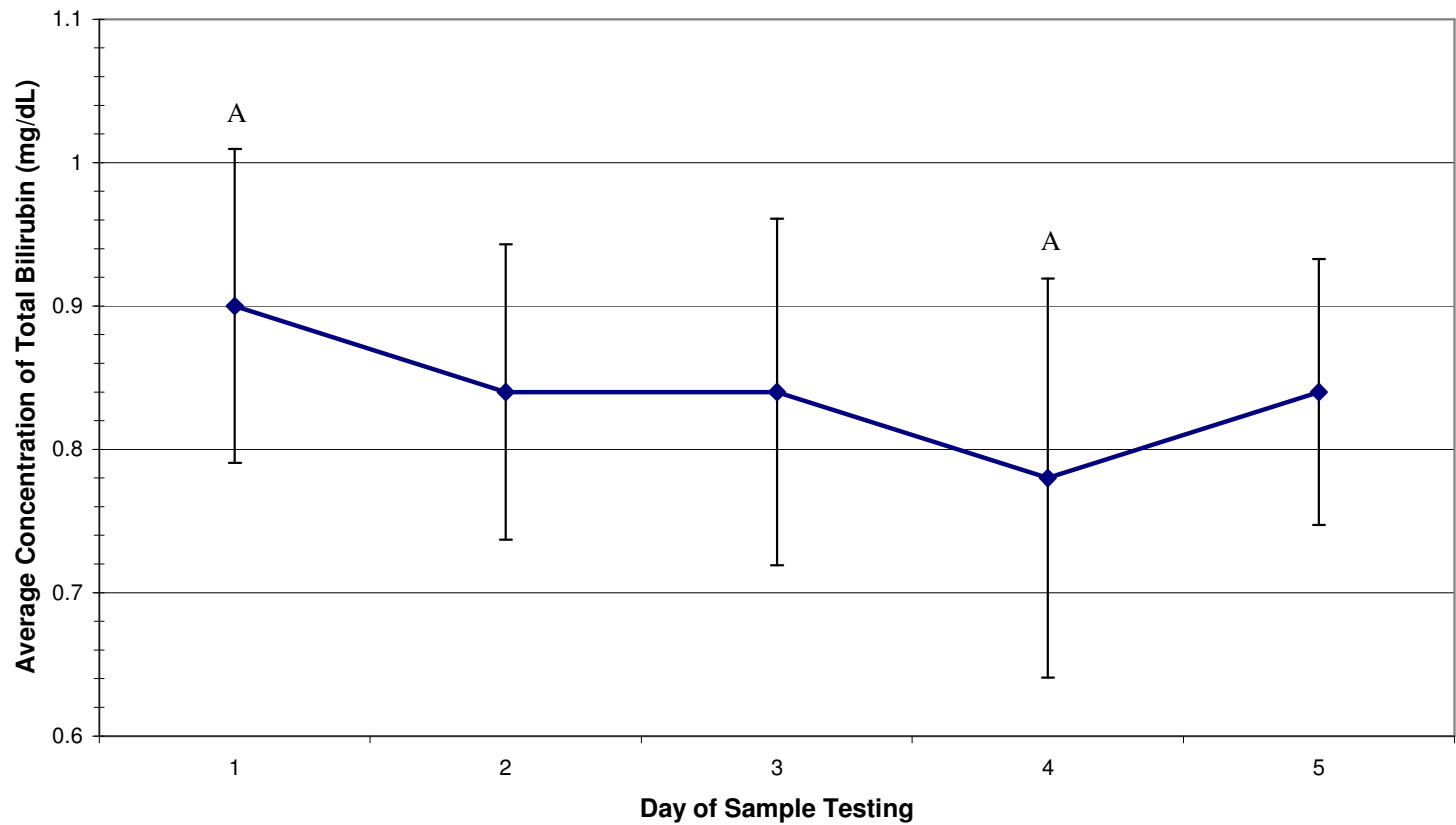


Figure 7. Average concentrations of total bilirubin (+1 SE) throughout the 5 days of testing. The same letter above data points indicates significant difference ($p < 0.05$).

CHAPTER IV

DISCUSSION

The effects of storage time on blood profile test results have not been studied separately from those produced by differing storage temperatures. Because most clinical laboratories store samples in refrigerators maintained at 4°C, I used this as my control temperature throughout the study; therefore, all changes in analyte results are due to the length of time the blood was stored before testing. Once the blood is drawn and placed into the Vacutainer tube, red blood cells begin to lyse and release their contents into the surrounding liquid, in this case the surrounding plasma. As time goes on, the rate of hemolysis increases, and this affects the concentrations of different profile tests (Robinson, 2002).

Effects of Hemolysis

The results of the present study show that plasma K^+ concentrations increase after one-day storage. Hemolysis is expected to increase a plasma analyte when there is a higher intracellular concentration of the analyte compared to the surrounding plasma (Frank et al, 1978). Potassium is such an analyte. Potassium is higher intracellularly due to Na^+/K^+ pumps on the cell membrane. These pumps help control the electrochemical balance between the inside of the cell and the extracellular fluid. For every 3 Na^+ ions

pumped out of the cell, 2 K⁺ ions are counter-transported into the cell (Guyton & Hall, 2006). These pumps also create a higher concentration of Na⁺ outside the cell. An analyte, such as Na⁺, is decreased by hemolysis when there is a higher concentration of that analyte in the plasma compared to inside the cells. When the cells lyse and release their contents, the volume of the plasma increases, and the analyte concentration is diluted (Frank et al., 1978). Indeed, the present study showed a decrease in Na⁺ after 3 days. Other examples of analytes expected to decrease include glucose and calcium.

Other Studies

Some studies have found supporting evidence for the results represented in this study. Robinson (2002), who studied the effects of in vitro hemolysis on analyte concentrations, also showed significant increases in potassium and AST concentrations and a significant decrease in CO₂. Also, Boyanton and Blick (2002), who focused on the stability of analytes in plasma and serum, also found an increase in potassium concentration and decreases in CO₂ and glucose concentrations. These studies do not entirely support the results found in this study. For example, Robinson (2002) also found a significant decrease in ALT and significant increases in glucose, total bilirubin, total protein, and albumin concentrations, which were not found in the present study. The reason for these discrepancies is unknown. Also, Boyanton and Blick's (2002) progression of analyte concentrations differed from this study for creatinine, total protein, albumin, calcium, and ALT.

Problems and Improvements

Eight of the thirteen blood profile tests monitored in this study had unusual changes in average concentrations during the last days of testing. These included sodium, glucose, and ALT increasing from Day 4 to Day 5. Creatinine decreased on Day 3, and concentrations of BUN and total bilirubin decreased on Day 4. Total protein concentrations spiked on Day 4, and potassium concentrations decreased from Day 4 to Day 5. Most of these differences occurred on Day 4, and this suggests differences in handling techniques between days of testing such as agitation, time outside of the refrigerator before testing, and so on.

Blood samples used in this study were not drawn after fasting or any other type of dietary restriction, so the range of concentrations among volunteers was greatly dispersed. Some volunteers had eaten close enough prior to the samples being drawn that their blood glucose levels were highly affected. This increase in glucose levels not only differed greatly from the other volunteers' glucose concentrations, but it could have also already caused insulin to enter the bloodstream to control the high level of glucose. If so, the insulin response, while the cells were still alive, would help decrease the amount of glucose in the sample tubes. This could be why glucose appears to decrease throughout the five days of testing.

In order to improve the accuracy and decrease the range between individual results, future studies should collect blood after fasting. Also, a larger sample size and multiple testings of each sample tube each day, such as every 4 hours, would increase the accuracy of results and provide more insight into the timeline of the processes that are occurring throughout the storage time.

Future Research

Further topics of interest could incorporate the changes of analyte concentrations in serum instead of plasma through the same procedure detailed in this study. The effects of hemolysis, temperature, and storage time on analyte concentrations in serum and plasma have been studied, but there are plenty of other variables that can also be considered. For example, the effects of certain drugs or a person's blood type on the rate of hemolysis could be examined. The effects of an individual's diet on analyte changes after storage might also be considered especially regarding glucose concentrations. An individual's age, gender, and race might have an effect on the progression of analyte concentrations during storage and these factors could be studied as well.

Clinical Significance

Because two important diagnostic profile tests, potassium and glucose, had significant changes on Day 2 followed by numerous other changes found in the following testing days, blood samples should not be stored at 4 °C for more than 24 hours. This is important in places where healthcare facilities are less equipped or in short supply and where samples must be stored and transported to facilities for testing. This is especially true for some countries in Africa, in which blood samples must be stored and sent to clinics in large cities for testing. If these samples are stored for more than 24 hours before testing, there could be significant changes in analyte values due to the storage time, and this could alter not only the results of the tests but also the way the patient is treated after the results are interpreted.

Conclusion

Although the samples were stored at 4 °C, which is recommended by the CDC to protect analyte integrity, significant changes were found in sodium, potassium, glucose, and total protein throughout the 5 days of testing. Significant changes from the original tests on Day 1 were found as early as Day 2 for potassium and glucose concentrations and Day 4 for sodium and total protein concentrations. Significant changes were also found for chloride on Day 3, total bilirubin on Day 4, and CO₂ and albumin on Day 5. Because all of these analytes can be used as a diagnostic tool (Table 1), significant changes in analyte concentrations due to storage could affect the interpretation of one's health. With this in mind and the data analysis from this study, samples should not be stored for more than 24 hours before being tested for analyte concentrations.

APPENDICES

APPENDIX A

INFORMED CONSENT

This senior study focuses on the effects of storage time on blood analyte concentrations and their corresponding results on the Comprehensive Metabolic Panel or CMP. Participation in this study requires you to have your blood drawn in a hospital laboratory following all safety precautions and hospital protocols.

This study is purely voluntary and you may withdraw from the project at any time. Minor pain, bruising, and/or swelling may result from involvement in this study. Any questions you have concerning the procedure will be answered and results of the final analysis will be available upon request. All individual results will be kept confidential.

I volunteer to participate in this senior study. I have read the above description and I have had my questions answered. I also realize that I may terminate the experimental session at any time by my request.

Date _____ Signature _____

Printed Name _____

Experimenter's Signature _____

APPENDIX B

Signed Human Participant Proposal

Proposal

APPENDIX C

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