Blood Glucose and Urine Glucose: Correlation in the Critically Ill

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INTRODUCTION: Blood glucose concentration is an important variable to control in critically ill patients. Inappropriate insulin therapy may precipitate life threatening hypoglycemic or hyperosmolar states. Uncontrolled hyperglycemia can result in osmotic diuresis with resultant dehydration. Hypoglycemia is equally important to regulate. Various body tissues require glucose as their sole energy source. Actual measurement of blood glucose is the direct method to determine levels. Blood sampling involves invasion of the patient by arterial, venous, or capillary puncture. Urine glucose analysis is a clinically accepted technique commonly used to estimate blood glucose levels and has the advantage of being a non-invasive procedure.

Clinitest (Ames Co., Elkhart, Ind.) is the most common urine glucose test routinely used as the basis for sliding scale insulin adjustments in hyperglycemic patients. An earlier study at University Hospitals, Madison, Wisconsin demonstrated that different Clinitest values occurred at unpredictable intervals for approximately the same blood glucose values ($\pm$ 5 mg%).[1] These anomalies occurred in individual patients as well as when one patient was compared to another. The purpose of the current study was to determine if the observed unpredictability of Clinitest in critically ill patients was due solely to technical error or other identifiable factors. Specifically, the hypothesis tested in the current research was that the observed unpredictability of Clinitest in the critically ill was not only due to error, but to a changing rate of renal glucose reabsorption. Given that the renal reabsorption of glucose fluctuated within the same patient, then spot urine glucose tests for estimating blood glucose would be unreliable as a basis for insulin dosage adjustment.

The current study protocol was designed to overcome deficiencies in the previous research. Drug interference and technical error with Clinitest were not evaluated in the earlier study. In addition, the current study examined if the previously cited sources of error were totally responsible for the observed deviations between Clinitest and blood glucose. Concurrent arterial blood glucose, spot urine glucose, and Clinitest analyses were performed in this study. Drug interference was monitored. Statistical analysis was performed to determine the degree of correlation between blood glucose, urine glucose, and Clinitest. To critically evaluate deviations between observed and mathematically predicted blood and urine glucose values, graphic and curve-fit analyses were done. Clinitest technical error was evaluated by comparing corresponding autoanalyzer urine glucose and Clinitest results.

EXPERIMENTAL METHODS: Patients selected for this study were required to meet the pre-existing entry criteria as listed below:

1. Arterial blood glucose determinations were previously ordered.
2. A foley catheter urine collection device was previously ordered and in place.
3. The patient had no history of juvenile onset diabetes mellitus (JODM).
4. The expected length of stay in TLC was at least 24 hours.
5. Serum creatinine was less than 2 mg%.

Six patients fulfilled the above criteria; venous blood samples had to be collected from a seventh patient who fulfilled all the remaining criteria. The complete set of criteria (Appendix 1) were established to ensure the patients had minimal impairment of renal function (normal serum creatinine is $\leq$1.2mg%), were not subjected to any additional tests or invasive procedures, were not poorly controlled (brittle) diabetics, and would be in the study long enough to generate at least six data points each.

An experimental sequence of events was outlined for nursing personnel to follow (Appendix 1). Step (1) involved arterial blood glucose sample collection and drainage of the residual urine from the foley catheter. Step (2) required nursing personnel to collect the next drained urine specimen from the foley catheter (~10ml.) within 15 minutes after arterial blood glucose sampling. In step (3), a portion of the collected urine specimen was used for a Clinitest determination following the 5-drop Clinitest method. In step (4), the remainder of the urine specimen was labeled and sent to Clinical Laboratories for an automated

quantitative urine glucose concentration determination. The results for each sampling time were collected and collated by the investigator. Appendix 2 is an example of the form used for data collection. On the reverse side of the form blood urea nitrogen (BUN), creatinine, and uric acid levels were monitored as parameters of renal function. Other physiologic and external variables monitored were toe temperature, axillary temperature, blood pressure, ventilator status, intake and output, and urinary output two hours prior to sampling. Duplicate medication and intravenous solution kardexes were created for each patient. Administration times of drugs, IV solution composition, and IV infusion rate were monitored.

Arterial blood glucose concentrations were measured by Clinical Laboratories using a glucose oxidase automated procedure. Urine glucose concentrations were semi-quantitatively measured using Clinitest (Ames Co., Elkhart, Ind.). Urine glucose concentrations were quantitatively measured in the laboratory by an automated hexokinase method.

Clinitest is a copper reduction method using glucose as a reducing agent. The basic reaction is as follows:

$$Cu^{2+} + \text{glucose} \text{ -------} \rightarrow Cu_2O + \text{oxidized glucose}^2$$

(Reaction color ranges from blue to orange)

The 5-drop Clinitest method involves placing 5 drops of urine and 10 drops of water into a clean, dry test-tube. A Clinitest reagent tablet is added to the solution and the reaction occurs. 15 seconds after the boiling subsides, the tube is gently shaken and compared to the color chart provided by the manufacturer.

The hexokinase (HK) method used by the ACA Autoanalyzer (Dupont, Wilmington, Del.) involves adding a specific volume of urine or serum to a commercial test package. The autoanalyzer then conducts the reaction under controlled conditions and computes the end-result. The abbreviated reaction sequence which takes place is:

$$\text{Glucose} + \text{ATP} \xrightarrow[Mg^{2+}]{\text{HK}} \text{Glucose-6-phosphate} + \text{ADP}$$

$$\text{Glucose-6-phosphate} + \text{NADP} \xrightarrow{\text{G6PDH}} \text{6-phosphogluconolactone} + \text{NADPH} \quad (3)$$

(NADPH concentration is computed spectrophotometrically at a specific wavelength via absorbance.)

The standard deviation for the ACA hexokinase method was $\pm$ 2.5 mg% at the 500 mg% blood glucose level.

Blood glucose concentrations were measured by the SMAC Autoanalyzer (Technicon, Tarrytown, N.J.) utilizing the glucose oxidase method. The abbreviated reaction sequence is as follows:

$$\text{Glucose} + H_2O + O_2 \xrightarrow[\text{oxidase}]{\text{glucose}} \text{gluconic acid} + H_2O_2$$

$$H_2O_2 + \text{chromagen precursor} \longrightarrow \text{chromagen} + H_2O \quad (4)$$

(The absorbance of the chromagen is concentration dependent and is measured spectrophotometrically.)

The standard deviation for the SMAC glucose oxidase method was $\pm$ 4 mg% at the 300 mg% blood glucose level.

RESULTS: Graphs 1-6 represent paired urine glucose (y-axis) versus arterial blood glucose (x-axis) values for each patient. Each set of paired data for an individual patient was analyzed for best curve fit. Geometric curve fitting consistently gave the highest coefficient of determination (r^2) for each patient. The equations of the best fit lines correspond to the general equation: $y = ab^x$. Regression correlation coefficients $(r^2)^{1/2}$ for these graphs ranged from $r = 0.22$ to $r = 0.99$. Predicted blood and urine glucose values were calculated using the geometric curve fit equation for each patient. The calculated blood and urine glucose values were compared with the corresponding observed values. Tables 1-6 give this data for each patient with arterial blood glucose samples. In 18 of 86 instances (21%), the predicted quantitative urine glucose deviated from the actual urine glucose by greater than 500 mg%. (The significance of this result will be discussed later.) In 65 of 86 (76%) instances, the predicted blood glucose concentrations were within $\pm$ 50 mg% of the observed blood glucose; 84 of 86 predicted values were within $\pm$ 100 mg%; and 2 of 86 predicted values were greater than 100 mg% of the observed blood glucose value.

A statistical analysis was performed on each patient's data. Regression correlation coefficients $(r^2)^{1/2}$ were calculated for each patient's geometric curve to determine how well the observed data fit the calculated curve. Regression correlation coefficients as previously mentioned ranged from $0.22 \leq r \leq 0.99$. Rank correlation statistical analysis was performed for each patient's blood glucose versus urine glucose values. Kendall's rank correlation was used since it does not assume linearity and approaches normality with small sample size.[5] Table 8 gives the Kendall's tau correlation coefficients (T) for each

patient; they range from $0.26 \leq T \leq 0.80$. Sample periods were divided into AM (0001-1200) and PM (1201-2400). Kendall's tau was obtained for each of these time periods. Correlation ranged from $0.00 \leq T \leq 0.81$ for the AM and $0.33 \leq T \leq 0.80$ for the PM. In 4 of 5 patients, AM analysis yielded $T \geq 0.60$, while in only 2 of 5 patients did PM analysis give $T \geq 0.60$. AM and PM analyses were not performed for patient "M" due to insufficient data points (n=5).

Quantitative urine glucose concentrations and corresponding Clinitest readings were ranked and correlated using gamma statistic analysis.[5] The gamma statistic is more useful than the Kendall's tau when a large number of ties exists. Correlation ranged from $0.20 \leq \gamma \leq 1.00$. (See Table 9) Seven patients were analyzed using this method. Patient "P" had venous blood glucose samples collected; his data was not included in the blood glucose versus urine glucose correlation. The corresponding gamma statistic for blood glucose versus urine glucose ranged from $0.26 \leq \gamma \leq 0.80$ (See Table 9).

Urine glucose concentrations were divided into specific concentration ranges corresponding to the approximate ranges for each Clinitest value. (See Tables 10 and 11) Two sets of criteria were used to categorize the quantitative urine glucose ranges. First, the product package insert states Clinitest is accurate within $\pm$ one color block (Table 10). Using this criterion, there were 10 of 89 instances (11%) where the urine glucose value did not fall within the corresponding urine glucose range assigned to Clinitest. The second criterion states Clinitest is accurate within the same color block. This is a popular belief in clinical practice. Following this criterion, 32 deviations (36%) occurred between urine glucose concentrations and Clinitest (Table 11).

All Clinitest results were monitored for drug interference. Clinitest reacts with other reducing agents besides glucose and with other urinary constituents to give false positive readings. Of the 89 readings involving Clinitest, 9 had drug interference resulting from cephalothin-Clinitest interaction. No drug interference was detected for the glucose oxidase or hexokinase tests for blood and urine glucose.[6]

A comparison of urine glucose and Clinitest was performed to determine how many false negative and false positive values Clinitest gave with respect to the quantitative urine glucose. A false negative was defined as an instance where Clinitest yielded a lower reading than would be expected for the observed urine glucose concentration. A false positive was defined as a case where Clinitest gave a higher value than was expected for the observed urine glucose concentration. Using the previous Clinitest criterion of $\pm$ one color block accuracy, one false positive and nine false negative readings were observed. If the assumed accuracy of Clinitest was within the same color block, there were eleven false positive readings and twenty-one false negative readings.

Table 12 presents the range of blood glucose values for a given Clinitest reading for each patient. This table reflects that a broad range of blood glucose concentrations occur for a specific Clinitest value. Comparison of blood glucose and Clinitest values for each patient (Tables 1-7) indicates there are the following instances where higher blood glucose values occur for a Clinitest Trace or Negative than for a Clinitest 4+ or 3+ reading:

Patient	Blood Glucose	Corresponding Clinitest
B	237 mg%	4+
	261 mg%	4+
	264 mg%	Trace
E	224 mg%	Negative
	223 mg%	3+
C	257 mg%	Negative
	256 mg%	4+

Occurrences such as these could be clinically significant when insulin therapy is based solely on Clinitest, since up to 5 units of regular insulin are customarily administered for every Clinitest plus.[13,19,28]

Observed blood and urine glucose values were compared to determine how often a small change in blood glucose would cause a large corresponding urine glucose concentration change . This comparison is important because insulin dosage adjustment based on urine glucose or Clinitest could be inappropriate in these instances when compared to the actual blood glucose concentration. The two criteria used were: 1) $\pm$ 5 mg% blood glucose range which had $\geq \pm$ 500 mg% urine glucose range; and 2) $\pm$ 10 mg% blood glucose range which gave a corresponding $\geq \pm$ 1000 mg% urine glucose range. Table 13 presents this comparison. Six instances of $\geq \pm$ 500 mg% urine glucose for $\pm$ 5 mg% blood glucose occurred while there were eight occurences of $\geq \pm$ 1000 mg% urine glucose for $\pm$ 10 mg% blood glucose.

The "pass-through" phenomenon with Clinitest is well documented.[7,18,28] The data gathered provided an opportunity for six instances of pass-through. The phenomenon can occur when urine glucose exceeds 3000 mg% and the characteristic orange color (4+) is missed, giving a false 2+ or 3+ end result.[7] This apparently occurred with one sample and was not documented by nursing personnel in the nursing notes.

Kendall's tau correlation coefficients for blood glucose versus urine glucose were ranked from the highest to the lowest value. Average axillary temperature, toe temperature, diastolic and systolic blood pressure, and age were calculated and ranked. Kendall's tau analysis was performed on the resulting ranked pairs to determine if there was a correlation between blood-urine glucose correlation and some other physical parameter. The results of the ranked correlation tests are as follows:

Blood-urine glucose (tau) compared with:	tau
Increased axillary temperature	0.33
Decreased toe temperature	0.07
Increased toe temperature	-0.07
Increased diastolic blood pressure	0.69
Increased systolic blood pressure	0.60
Increasing age	0.20

No correlation was observed between blood-urine glucose correlation and fluid intake versus output, mechanically ventilated versus non-ventilated patients, inotropic agent administration (no pressor agents were administered), diuretic administration, or insulin administration.

DISCUSSION: In the referenced unpublished study it was found that there was a wide range of blood glucose values for a given Clinitest reading in the same patient.[1] Quite different Clinitest readings were observed for approximately the same blood glucose values, e.g. 256 mg% blood glucose gave a 4+ Clinitest while 257 mg% blood glucose gave a negative Clinitest. The unpublished study was a retrospective review and had limitations in the amount of data that could be extracted. Its primary deficiency was that quantitative urine glucose determinations were not done to establish the accuracy of the Clinitest technique being performed.

It was the hypothesis of the current research that the renal glucose spillage rate and renal threshold are not stable as had been previously observed.[8] This hypothetical instability could account for the unpredictable Clinitest results. However, nursing error could not be discounted as a possibility for producing the observed deviations.

In the current study quantitative single-catch urine samples were collected within 15 minutes after arterial blood sampling. It has been reported that 15-20 minutes is a reasonable time for passage of urine from the kidneys to the bladder.[8,23] Quantitative urine determinations yielded two distinct benefits as opposed to Clinitest alone: 1) the hexokinase quantitative test is subject to different drug interferences than the copper reduction method (Clinitest),[3,6] and 2) the quantitative test assigns an exact number to the urine glucose concentration which can be easily ranked and compared with the arterial blood glucose. Quantitative arterial blood glucoses and quantitative urine glucoses provided the opportunity to quantitate the hypothesized changing renal glucose spillage.

Urine glucose testing systems base their reliability on the assumption that as the blood glucose concentration varies above the renal threshold, the urine glucose concentration also changes predictably. Approximately 40 years ago, Goldring, et al, demonstrated in humans that there was a maximal reabsorption rate (T_{max}) for glucose filtered through the kidney. Above the T_{max}, glucose was spilled into the urine[8] and approximately 150-180 mg% was the blood glucose concentration at which spillage occurred.[10] In 1953, Gray reported that the renal threshold of most people is 180 mg% and defined the blood glucose ranges where one should see negative through 4+ Clinitest readings. Gray defined the ranges of blood glucose for a given Clinitest as follows: Negative = 0-180 mg%, Trace = 180-200 mg%, 1+ to 3+ = 200-300 mg%, and 4+ = 300 mg% or greater. Gray noted that there existed conditions where the previous definitions would not be true, e.g. renal glycosuria where the renal threshold is lowered or diabetes where the renal threshold is elevated.[9] Tune and Burg demonstrated a renal T_{max} for glucose in rabbits and showed that the glucose reabsorption rate changed as the concentration of the perfusate or the perfusion rate changed. They concluded that there must be a saturable transport system in the rabbit kidney for glucose reabsorption.[11]

Service, et al, concluded from their data for humans that as the urine glucose concentration increased, so did the blood glucose concentration but not predictably.[12] Several other investigators have reported unpredictable deviations in simultaneous blood glucose and urine glucose readings.[13,14,15,16,17] In the above referenced studies, the patients were primarily insulin dependent diabetics. No critically ill non-juvenile onset diabetic patients were included in these references.

The basis of all urine glucose testing systems is the concept that above the renal glucose T_{max}, glucose is spilled into the urine at a rate dependent upon the blood glucose concentration. Three basic assumptions seem to be made: 1) the renal threshold (T_{max}) does not vary from time to time for an individual patient, 2) as blood glucose varies above the renal threshold urine glucose follows blood glucose in a predictable and proportionate manner, and 3) urine volume does not change significantly.

Clinitest has been compared to other urine tests and has remained the standard for management of diabetic patients requiring sliding scale insulin adjustments.[18,19] Other commercial tests available are TesTape (Lilly), Diastix (Ames), and Clinistix (Ames). TesTape (glucose oxidase paper test) is specific for glucose and more sensitive than Clinitest. TesTape is used primarily to detect glycosuria in non-insulin dependent diabetics and is used to double check suspected Clinitest false positive results.[18]

The reliability of Clinitest with respect to quantitative urine glucose determinations has been reported in the literature frequently. The urine glucose and Clinitest are consistent in most cases. The reported accuracy in the literature is within $\pm$ 1-2 color blocks.[7,20,21,22,24,2] One study reported a 22% significant error rate (e.g. $\geq$1000 mg% difference between Clinitest and autoanalyzer urine glucose) when Clinitest was used by hospital personnel.[26] Logan and Haight reported a 48% error rate (Clinitest was considered accurate within the same color block) when Clinitest was used by trained laboratory personnel.[27] The current study's data using nursing personnel demonstrated an 11% error rate between quantitative urine glucose values and corresponding

Clinitest for ± one color block deviation, and 36% deviation for accuracy within the same color block.

Clinitest as a urine glucose testing method has several potential errors in testing technique of which a partial listing is given below:

Drug interference
Water drop size
Urine drop size
Age of tablet/reagent
Timing of reaction
Pass-through phenomenon
Color interpretation
Other reducing agents
Wrong number of drops
Wet reaction tube
Single versus double-voided specimen
Urine concentration

The drug interference associated with Clinitest is a result of the presence of urinary reducing substances and constituents, e.g. reducing sugars, cephalothin, and large doses of ascorbic acid.[18] Dilute urine also gives false positive reactions with Clinitest.[18,25] The Clinitest "pass-through" phenomenon is reported to occur when the urine glucose is ≥ 3000 mg%.[7] The phenomenon is observed as a very rapid color change from blue (negative) to orange (4+), and then the color progresses to a final green (2+) or brown (3+) hue.[18,28]

Clinically, Clinitest is treated as accurate within the same color block and sliding scale insulin therapy is based on the Clinitest result. Commonly 5 units of regular insulin are administered for each plus of Clinitest, e.g. 2+ Clinitest would result in the administration of 10 units of regular insulin.[13,19,28] The Clinitest package insert states the accuracy of Clinitest is ± one color block which implies that a range of 10 units of regular insulin is determined by the Clinitest result. As stated previously, the results of this study showed that Clinitest was 89% accurate within ± one color block. Of the 11%

exceptions there were four instances where a Clinitest 4+ or 3+ corresponded to a blood glucose which was less than the blood glucose for a corresponding negative or trace observed in the same patient. This could have meant a difference of up to 20 units of insulin administered based solely upon Clinitest results which did not mirror the blood glucose values. Quantitative urine glucose values in these four instances verify that Clinitest was not in error.

The current research demonstrated for the sample population that Clinitest gave false negative results more often than false positive results. Within the $\pm$ one color block criterion, there were nine false negatives and one false positive. If one assumes Clinitest accuracy to be within the same color block, there were eleven false positives and twenty-one false negatives.

The results of this study show a poor to moderate correlation between urine glucose and blood glucose, $0.26 \leq T \leq 0.80$ (Kendall's tau analysis, $0.26 \leq \gamma \leq 0.80$ (gamma statistic analysis) and $0.22 \leq r \leq 0.99$ (geometric curve-fit analysis). The results of each patient were not combined for an overall tau, gamma or linear regression correlation coefficient due to the individual variations of each patient, i.e. each patient has characteristic reabsorption and threshold parameters. Using best-curve fit equations for each patient, urine glucose could be used to predict the arterial blood glucose within $\pm$ 50 mg% in 65 of 86 cases (76%), $\pm$ 100 mg% in 84 of 86 cases (98%), and $>$100 mg% in 2 of 86 predictions (2%). In the current study there were no instances where the actual blood glucose was less than 100 mg% while the corresponding Clinitest was 3+ or 4+.

The unpublished study had instances where the blood glucose was less than 100 mg% and the corresponding Clinitest was 3+ or 4+.[1] The individuals who exhibited this behavior had not history of renal glycosuria or Fanconi's Syndrome.

Blood and urine glucose correlation was analyzed with respect to the physical parameters of age, axillary temperature, and toe temperature. The correlation between these parameters and blood versus urine glucose ranged from $-0.07 \leq T \leq 0.33$. Average blood pressure correlated most closely with blood and urine glucose correlations: $T = 0.69$ for increasing average diastolic blood pressure, and $T = 0.60$ for increasing average systolic blood pressure. The degree of renal perfusion could be one possible explanation for the correlation with average blood pressure. The analysis revealed that as blood pressure increased the correlation also increased. This would suggest that as the renal perfusion improves, the glucose reabsorption mechanism becomes more stable.

Diurnal variation was observed in the correlation of urine and blood glucose for the study population. Correlation was $T \geq 0.60$ for 4 of 5 patients in the AM period (0001-1200) while in the PM (1201-2400) there were 2 of 5 patients where $T \geq 0.60$. There may be two possible explanations for this behavior. First, the duration of external stimuli in each period was different. The PM period contained 60% more waking hours than did the AM period. The second possibility is the maximum release of endogenous adrenocortical steroids occurred during the AM sample period. Exactly how increased steroid level would favorably affect the blood versus urine glucose correlation is uncertain. The sample size in this study is too small to draw meaningful conclusions about the AM versus PM differences.

Clinitest and urine glucose correlate relatively well: $0.20 \leq \gamma \leq 1.00$. As previously mentioned, there is a difference between the accuracy of Clinitest as it is clinically viewed and the accuracy as reported in the literature. If Clinitest is accepted as accurate within the same color block, then a 36% difference between the actual urine glucose and Clinitest occurred. Two patients, using the above criterion, had perfect correlation between urine glucose and Clinitest. Using the $\pm$ one color block criterion, Clinitest was 89% accurate. Three patients had perfect correlation within the $\pm$ one color block accuracy.

A brief overview of Tables 1-6, reveals that although there is a statistical correlation between blood glucose and urine glucose, a wide range in urine glucose values exists for a given small range of blood glucose values. Technical error could account for a portion of the observed deviations in urine glucose but the consistency of the variation suggests that other factors are influencing the urine glucose spillage. In the hypothesis, it was proposed that the renal threshold for glucose was not constant from time to time within an individual. In a recent article, Malone, et al, found that while correlation existed between urine and blood glucose for diabetic patients ($r = 0.92$), there was a significant scatter of urine glucose points for a narrow range of capillary blood glucose values. When compared with Clinitest, the range of blood glucose was 131 mg% $\pm$ 63(S.D.) for negative Clinitest and 389 mg% $\pm$ 116(S.D) for 4+ Clinitest.[13]

Malone observed that not all people have the same renal threshold values,[13] and this project's data confirms that finding. The renal threshold values for the six critically ill patients and standard errors are listed on the following page:

Patient	Renal Threshold Value ± Standard Error
A	232 mg% ± 23
M	264 mg% ± 52
C	214 mg% ± 23
Z	248 mg% ± 39
E	205 mg% ± 4
B	216 mg% ± 9

The renal threshold valueswere calculated via linear regression analysis on all blood and urine glucose pairs with greater than 179 mg% blood glucose levels. Malone's renal threshold values for diabetic patients ranged from a blood glucose of 96 mg% ± 21(S.D.) to 233 mg% ± 51 (S.D.). Combination of Malone's entire data revealed a 30 mg% blood glucose range for a Clinitest range from negative to 4+.[13] Combining all data for the current study showed a minus 20 mg% blood glucose range from negative to 4+ Clinitest. Individually the blood glucose range for Clinitest negative to 4+ was 230 mg% for patient "M" and minus 1 mg% for patient "C". (See Table 12)

Malone, et al, attributed their observations to the brittle diabetic patients studied and to possible changes in renal tubular reabsorption.[13] The current study population of critically ill patients had no juvenile onset diabetics. Hyperglycemia in the critically ill study population was a result of iatrogenic causes, e.g. hypertonic glucose solutions, steroids, and stress/trauma induced hyperglycemia. Patients A, B, C, and M were receiving hypertonic glucose total parenteral nutrition (TPN) solutions which contributed to their hyperglycemia. The TPN solutions were controlled by IVAC infusion pumps, therefore no large momentary variations of glucose input should have occurred in the hyperalimented patients. Insulin dose response is reported to be affected by conditions such as trauma.[17] Stress and trauma have been reported to induce hyperglycemia by elevating levels of contrainsulin hormones.[29] Known hormones which

antagonize insulin are glucagon, epinephrine, cortisol, and growth hormone.[29]

It is important to control hyperglycemia for several reasons. The hyperglycemic state is associated with ketoacidosis, hyperosmolar coma, osmotic diuresis, and decreased antibody formation and phagocytosis.[30] In addition, hypoglycemia is a condition which should be quickly corrected. Glucose is the only nutrient that can be utilized by the retina, brain, and germinal epithelium.[31]

The results of this project suggest that the observed variations in urine glucose and the unpredictability could be in large part due to changes in renal tubular reabsorption of glucose by the kidney. Several studies in laboratory animals have demonstrated that various factors influence the renal glucose reabsorption. Robson, et al, demonstrated in rats that renal glucose reabsorption was inversely related to the extracellular fluid (ECF) volume status. As the ECF volume was expanded with saline solution, the T_{max} decreased. In addition, Robson postulated there was a common carrier for active transport of sodium and glucose from the renal tubule to the blood.[32] Canine studies revealed that as sodium reabsorption increased so did glucose reabsorption,[33] and that as glomerular filtration rate (GFR) increased so did glucose reabsorption.[33,34] Wen demonstrated in dogs that 90% of glucose reabsorption occurs in the proximal tubule and that the remainder is reabsorbed in the distal portion. He suggests that glycosuria is a result of the saturation of the distal tubular transport system. Wen's study reaffirmed a close relationship between sodium and glucose transport in the proximal tubule.[35] In humans, it has been demonstrated that as insulin concentration increases

sodium excretion decreases, and that there appears to be no correlation between the amount of glucose metabolized and urinary sodium excretion.[36] In summary, changes such as GFR, extracellular fluid volume changes, sodium load, and insulin levels are all dynamic processes which can occur in the critically ill patient and could contribute to momentary changes in glucose excretion.

CONCLUSIONS: Nursing error with Clinitest was not shown to be a major problem using the ± one color block criterion as stated by company literature. The unpredictable nature of urine glucose concentration is significant, although urine glucose does correlate statistically with blood glucose in the critically ill study population. It is concluded that urine glucose concentrations can not be relied upon to mirror blood glucose levels in the critically ill. Insulin dosage adjustments in critically ill patients should be based on blood glucose levels.

Clinitest is not accurate within the same color block as is clinically accepted. The error in Clinitest technique was 11% of the total samples using the criterion of ± one color block accuracy. However, if one considers Clinitest to be accurate within the same color block, a 36% difference was observed between Clinitest and quantitative urine glucose values. The importance of the 36% figure is that clinically, patients are treated as if Clinitest is accurate within the same color block. Using this criterion, the study population could have received inappropriate insulin therapy with 36% frequency if therapy adjustments were solely based on Clinitest, as opposed to quantitative urine glucose values.

Kendall's tau, gamma statistic, and geometric curve regression analysis applied to 86 pairs of corresponding arterial blood and urine glucose samples demonstrated a poor to moderate correlation. To determine the clinical significance of the observed correlation, geometric curve analyses ($y = ab^x$) were performed. The result of these calculations showed that urine glucose could be used to predict blood glucose within ± 50 mg% in 65 of 86 instances (76%), within ± 100 mg%

in 84 of 86 instances (98%), but in 2 of 86 cases (2%) the difference exceeded 100 mg%. Axillary temperature, toe temperature, ventilator versus non-ventilator status, age, inotropic drugs, insulin infusion rate, and fluid intake versus output indicated no significant correlation ($T \leq 0.34$) with blood and urine glucose correlation. However, when the blood and urine glucose tau correlation coefficients were ranked versus average diastolic and systolic blood pressure for each patient, a moderately good correlation was observed: $T = 0.69$ for increasing diastolic blood pressure, and $T = 0.60$ for increasing systolic blood pressure. The significance of this observation is that increased renal perfusion seems to reflect better correlation between blood and urine glucose values. This corresponds with the finding in animals that as the GFR increases, so does the glucose reabsorption rate.[33,34]

Diurnal variations were observed in the correlation coefficients for AM and PM sample times. Four of six patients (67%) had $T \geq 0.60$ in the AM compared to two of six patients (33%) in the PM who had $T \geq 0.60$. The possible reasons for this occurence are diurnal variations in adrenocortical steroid secretions and the external stimuli differences resulting from different amounts of waking time in the AM and PM.

Blood glucose could be predicted fairly accurately from urine glucose using a geometric curve fit analysis. The converse demonstrated that urine glucose predictions show a wide variation from observed values. In 18 of 86 samples (21%) there existed a difference of greater than 500 mg% (greater the $\pm$ one Clinitest color block) between the observed and predicted urine glucose values.

Clinitest should be performed by properly trained staff who rigidly adhere to test procedures to minimize error. Clinitest is susceptible

to many potential errors: drug interference, dilutional errors, reaction with other reducing substances, reaction end-color interpretation, and the pass-through phenomenon. Drug-laboratory test interference was monitored. In 9 samples (10%) there was possible interference by cephalothin with Clinitest. Hexokinase urine glucose values compared to Clinitest in these nine cases indicated that probably cephalothin did cause false positive Clinitest values. No drug interference was observed with the hexokinase or glucose oxidase methods. The pass-through phenomenon with Clinitest was possible in six instances where the quantitative urine glucose values (hexokinase) exceeded 3000 mg%. In only one of these cases did the urine glucose and Clinitest disagree. Pass-through was not documented in the nursing notes for this one occurence.

Blood and quantitative urine glucose concentrations do not correspond well enough to base insulin therapy adjustments solely on urine glucose testing for the sample population. There were 6 occurences (7%) where the urine glucose value varied greater than $\pm$ 500 mg% for a blood glucose range of $\pm$ 5 mg%, and 8 occurences (9%) where the urine glucose varied greater than $\pm$ 1000 mg% for a $\pm$ 10 mg% blood glucose range. It seems highly improbable that the explanation for these large differences as well as the many small variations lie solely with testing error. It is proposed that the "renal threshold" for glucose is dynamic and fluctuates in critically ill patients. Several investigators have referred to various influences which are known to cause changes in glucose reabsorption in experimental animals. Among these influences are sodium load, extracellular fluid volume, glomerular filtration rate, and the concentration of the perfusate.[11,32,33,34] In humans, insulin levels have been shown to influence sodium excretion.[36] Other factors which might influence

the glucose concentration are those which affect the concentration of the urine. These factors include aldosterone, anti-diuretic hormone, diuretics, and osmotic agents. Critically ill patients could have any one or a combination of the above cited factors influencing their glucose reabsorption rate, thus rendering urine glucose concentration unreliable as an indicator of the blood glucose level.

APPENDIX 1

CLINITEST STUDY

I. Entry criteria: The patient must have the following preexisting criteria.

A. Serum creatinine (Cr) less than 2.0.
B. Must not have juvenile onset diabetes mellitus.
C. Foley catheter previously ordered and in place.
D. Blood glucoses Q4H previously ordered.
E. Expected length of stay in 6-TLC at least 24 hours.

II. Study Protocol: This patient has been selected for the Clinitest study having fulfilled the above criteria. The following procedures are necessary to generate the needed data.

A. Collect a clean catch urine (5-10 ml.) from the patient's Foley catheter within 15 minutes of the Q4H blood glucose collection.

B. Perform a Clinitest analysis on the collected urine (2 or 5 drop method). Record this value and the time performed in the nursing notes along with an annotation as to whether the 2 or 5 drop method was used.

C. Send the remaining clean-catch urine specimen to clinical laboratories with a Miscellaneous Test card (UWH 708) and "Requisition Form for Research Work - U.W. Clinical Labs" form. (The card and sheet are necessary so the patient will not be charged for the test.)

D. Please annotate also whether the blood sample was an arterial or venous sample and the location of collection, e.g. left antecubital.

E. The laboratory urine glucose values will not be reported back to TLC, but will be compiled weekly by Labs for our records.

F. Any questions on the procedure, please page Dale Smith or call at home 255-6002.

APPENDIX 2

CLINITEST^{R} DATA

COLLECTION FORM

ADDRESSOGRAPH

DATE & TIME	SITE DRAWN	LABORATORY GLUCOSE	DEXTROSTIX GLUCOSE	URINE GLUCOSE	CLINITEST	MISCELLANEOUS

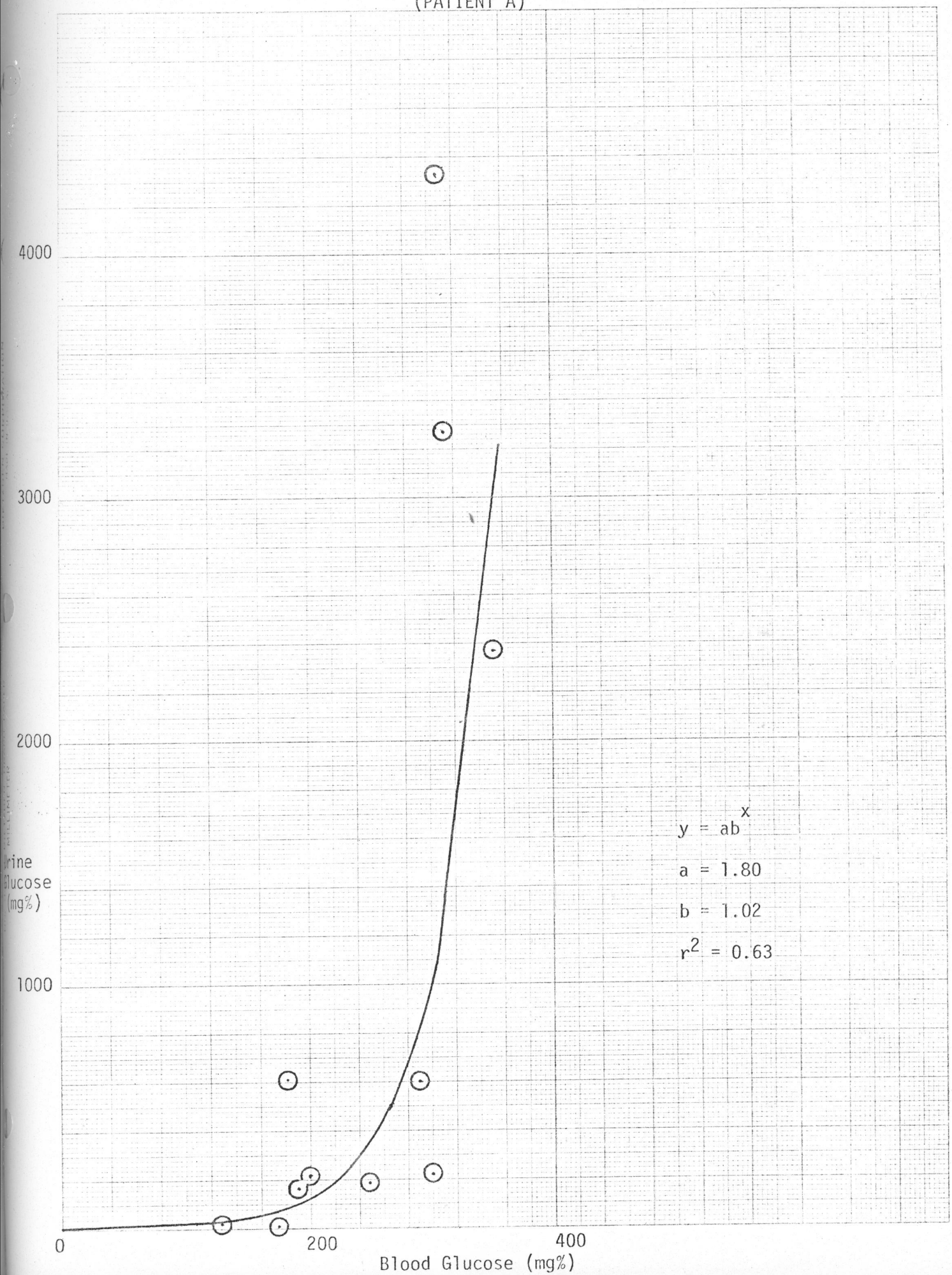
BLOOD PRODUCTS

START DATE & TIME	STOP DATE & TIME	COMPOSITION	SITE INJECTED	MISCELLANEOUS

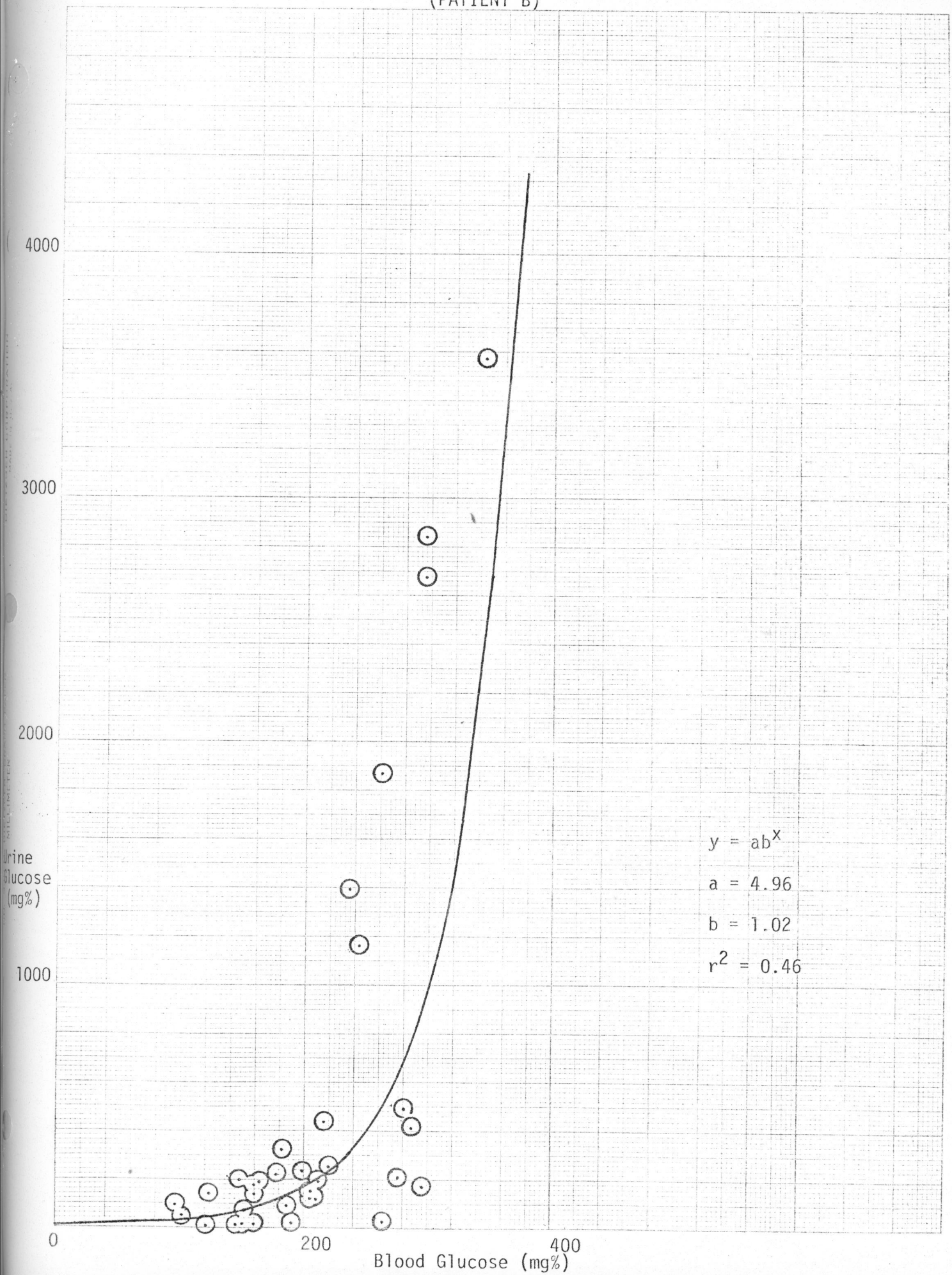
LABORATORY VALUES

DATE & TIME	Cr	URIC ACID	BUN

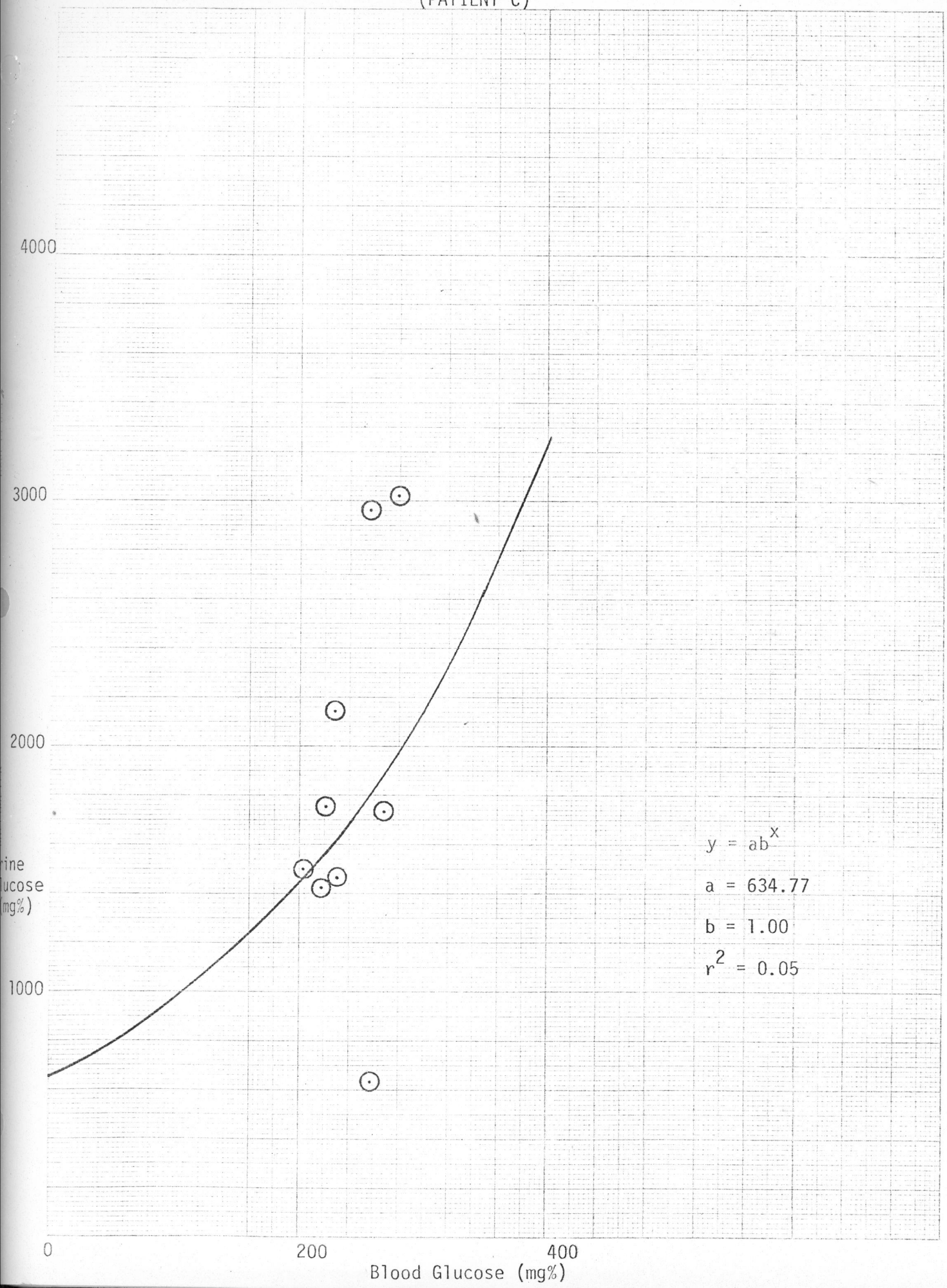
GRAPH 1
(PATIENT A)



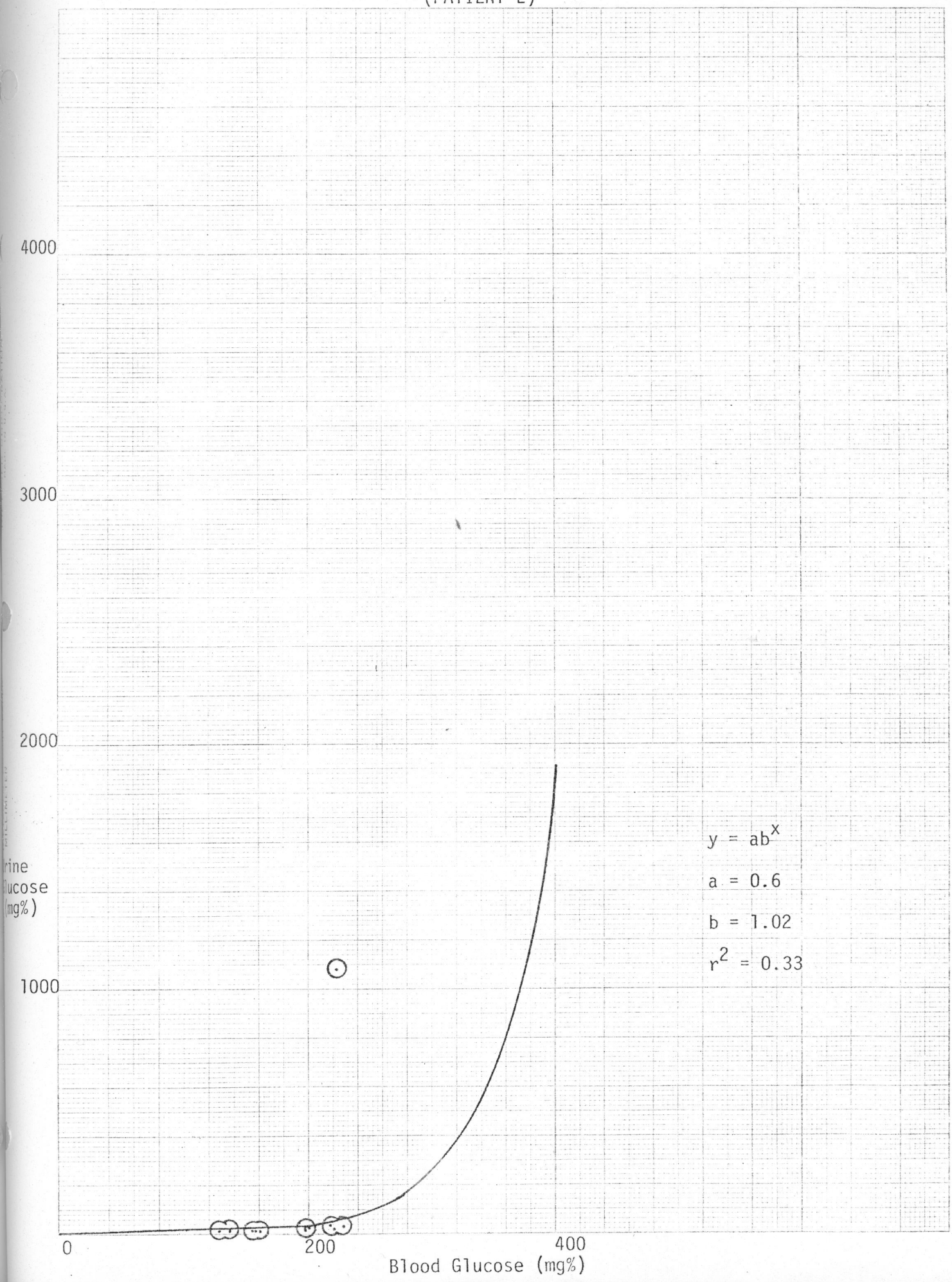
GRAPH 2
(PATIENT B)



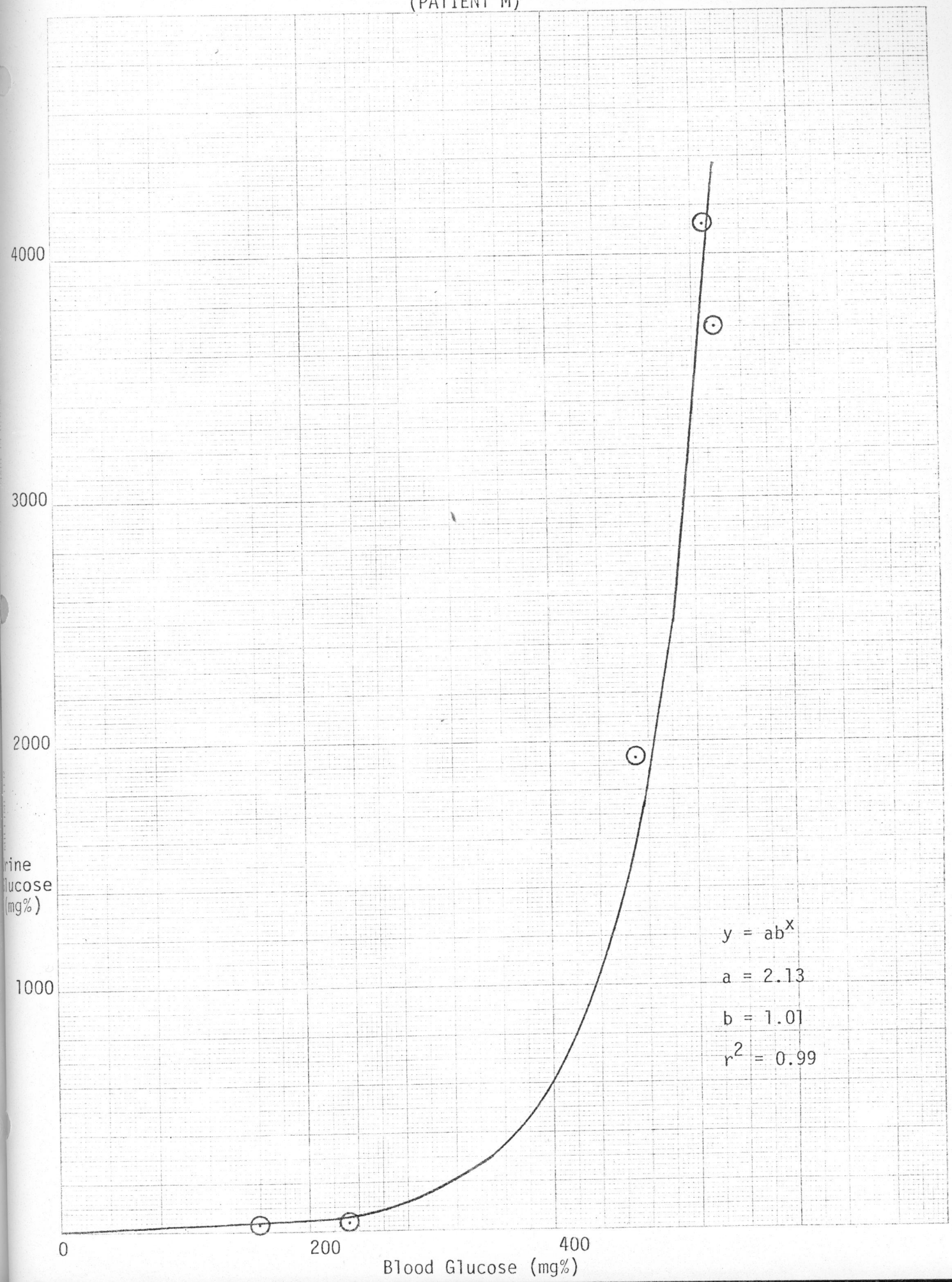
GRAPH 3
(PATIENT C)



GRAPH 4
(PATIENT E)



GRAPH 5
(PATIENT M)



GRAPH 6
(PATIENT Z)

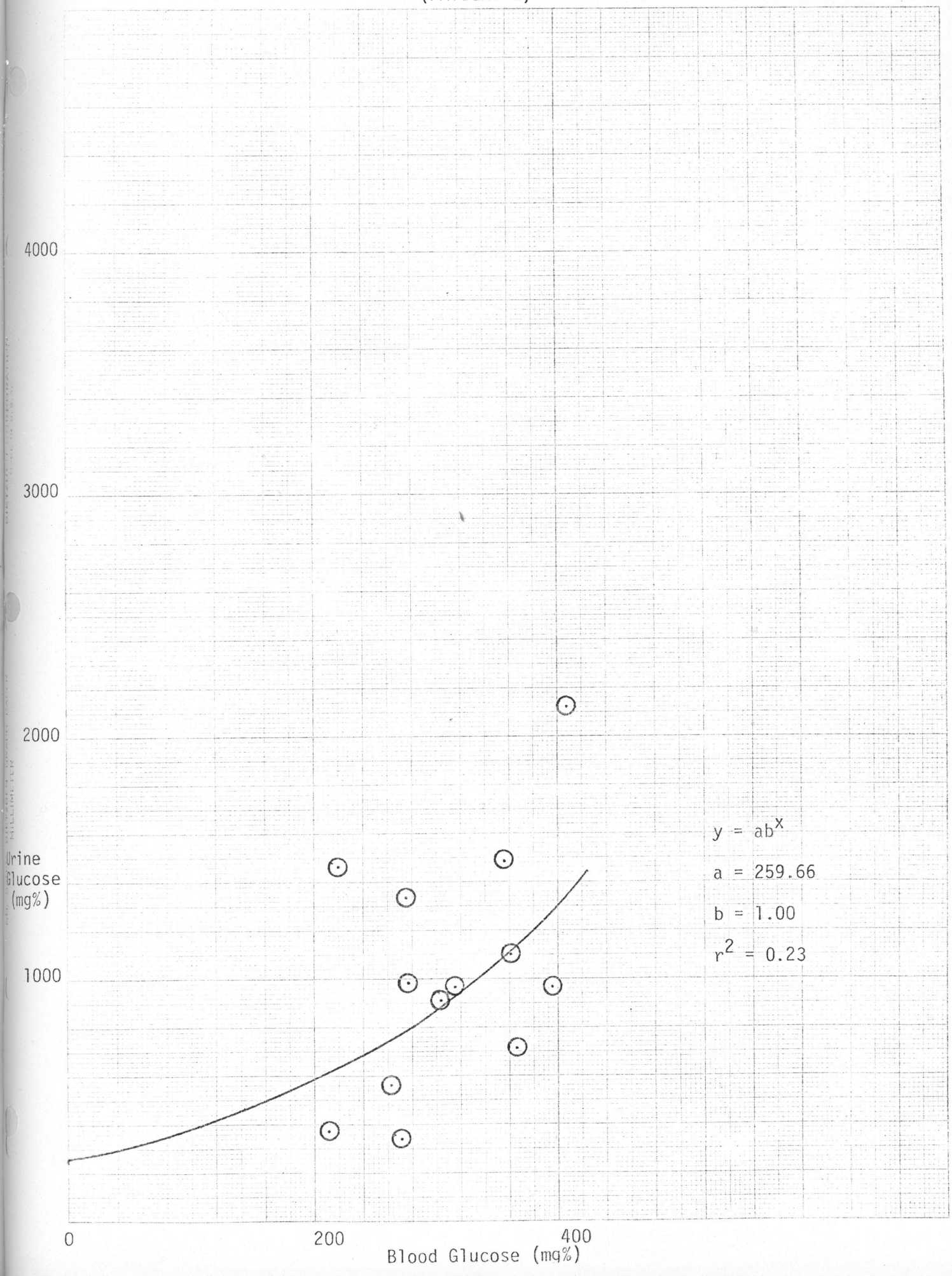


TABLE 1

(PATIENT A)

Observed Arterial Blood Glucose	Observed Urine Glucose	Clinitest	Calculated Blood Glucose	Calculated Urine Glucose
182 mg%	610 mg%	2+	219 mg%	86 mg%
190	160	--	206	102
312	3270	4+	313	1368
308	4330	3+	361	1257
351	2370	4+	277	3135
299	220	--	207	1038
128	23	--	202	27
290	597	1+	218	857
199	216	Neg	207	124
174	9	Neg	202	73
248	190	--	207	351

TABLE 2

(PATIENT B)

Observed Arterial Blood Glucose	Observed Urine Glucose	Clinitest	Calculated Blood Glucose	Calculated Urine Glucose
261 mg%	1865 mg%	4+	260 mg%	457 mg%
281	493	4+(K)	194	647
344	3570	4+	373	1929
297	2840	4+	319	854
297	2670	3+	308	854
237	1390	4+	234	301
123	139	Neg	180	42
121	5	Neg	175	40
187	99	Neg	178	127
216	430	1+	191	210
148	200	1+	182	64
182	321	2+(K)	187	116
160	174	1+	181	79
145	8	Neg	175	61
150	17	Neg	175	67
210	114	Neg	179	189
220	250	2+(K)	184	225
206	152	1+	180	176
178	222	Trace	183	108
264	29	Trace	176	482
190	23	Trace	175	134
205	120	Trace	179	173

TABLE 2 (cont.)

Observed Arterial Blood Glucose	Observed Urine Glucose	Clinitest	Calculated Blood Glucose	Calculated Urine Glucose
199 mg%	236 mg%	3+(K)	183 mg%	156 mg%
102	55	1+(K)	176	29
152	72	Neg	177	69
226	--	Neg	--	--
159	14	--	175	78
211	189	--	182	192
296	172	2+(K)	181	839
164	188	2+(K)	182	85
244	1158	Trace	223	341
276	206	3+(K)	182	593
160	138	1+	180	79
95	96	Trace	178	26
--	118	Trace	--	--
287	408	3+(K)	190	718

K = Cephalothin-Clinitest interference

TABLE 3

(PATIENT C)

Observed Arterial Blood Glucose	Observed Urine Glucose	Clinitest	Calculated Blood Glucose	Calculated Urine Glucose
230 mg%	1460 mg%	3+	234 mg%	1625 mg%
279	3020	4+	255	1985
268	1730	2+	237	1898
217	1420	3+	233	1541
256	2960	4+	254	1807
228	2140	3+	243	1612
203	1500	Neg	234	1455
221	1750	1+	237	1566
257	630	Neg	223	1814

TABLE 4

(PATIENT E)

Observed Arterial Blood Glucose	Observed Urine Glucose	Clinitest	Calculated Blood Glucose	Calculated Urine Glucose
128 mg%	12 mg%	Neg	180 mg%	8 mg%
154	12	Neg	180	13
136	15	Neg	180	9
196	18	Neg	180	31
--	13	Neg	180	--
160	10	Neg	180	15
199	22	Neg	180	33
196	22	Neg	180	31
224	30	Neg	181	54
157	14	Neg	180	14
217	40	Neg	181	47
197	25	Neg	180	32
221	22	Neg	180	51
223	1080	3+	226	53
197	24	Neg	180	32

TABLE 5

(PATIENT M)

Observed Arterial Blood Glucose	Observed Urine Glucose	Clinitest	Calculated Blood Glucose	Calculated Urine Glucose
105 mg%	--	Neg	--	9 mg%
152	--	Trace	--	18
168	--	Neg	--	23
159	28 mg%	Neg	208 mg%	20
232	36	Neg	209	56
470	1935	4+	343	1625
530	4120	4+	607	3792
538	3700	4+	544	4246
582	--	4+	--	7903
572	--	4+	--	6862
462	--	4+	--	1452
202	--	Neg	--	37

TABLE 6

(PATIENT Z)

Observed Arterial Blood Glucose	Observed Urine Glucose	Clinitest	Calculated Blood Glucose	Calculated Urine Glucose
408 mg%	2120 mg%	4+	372 mg%	1353 mg%
366	710	2+	286	1141
361	1100	3+	307	1118
395	965	3+	300	1283
444	--	4+	--	1565
379	--	4+	--	1203
176	--	1+	--	529
220	1460	1+	329	632
263	560	2+	278	752
271	344	1+	267	777
355	1476	3+	330	1092
275	1330	2+	321	790
315	966	Trace	300	929
275	981	Trace	301	790
304	906	Trace	296	888
211	370	Neg	268	610

TABLE 7

(PATIENT P)

Observed Venous Blood Glucose	Observed Urine Glucose	Clinitest
334 mg%	800 mg%	3+
316	800	Trace
209	132	Trace
177	115	Trace
276	558	1+
250	43	Neg
241	82	Neg

NOTE: This patient had venous blood samples drawn. This data was not included in the arterial blood versus urine glucose correlation analysis and curve fitting.

TABLE 8

Rank Correlation Coefficients
Urine Glucose versus Blood Glucose
(Kendall's Tau Analysis)

Patient	Overall Tau	AM Tau	PM Tau
P(Venous)	--	--	--
A	0.60 ($P < 0.02$)	0.81	0.33
M	0.80 ($P < 0.09$)	--	--
C	0.28 ($P < 0.28$)	0	0.33
Z	0.26 ($P < 0.24$)	0.60	0.33
E	0.67 ($P < 0.01$)	0.62	0.62
B	0.55 ($P < 0.01$)	0.61	0.80

TABLE 9

Rank Correlation Coefficients
Urine Glucose versus Clinitest &
Urine Glucose versus Blood Glucose
(Gamma Statistic Analysis)

Patient	Urine Glucose versus Clinitest (Gamma)	Urine Glucose versus Blood Glucose (Gamma)
P	0.56	--
A	0.79	0.60
M	1.00	0.80
C	0.55	0.26
Z	0.20	0.26
E	1.00	0.69
B	0.56	0.55

TABLE 10

Urine Glucose and Clinitest
(± 1 Color Block Accuracy)

0-375 mg% Negative	0-625 mg% Trace	126-875 mg% 1+	376-1500 mg% 2+	626 mg% - 3+	876 mg% - 4+
43	132	558	710	800	2120
82	115	344	560	1100	1935
370	222	430	1330	965	4120
28	29	200	610	1476	3700
36	23	174		2670	1865
139	120	152		1080	3570
5	96	138		1460	2840
99	118	597		1420	1390
8				2140	3020
17				4330	2960
114					3270
72					2370
12					
12					
15					
18					
13					
10					
22					
22					
30					
14					
40					
25					
22					
24					
216					
9					

Exceptions:

Urine Glucose	Clinitest	Urine Glucose	Clinitest
800 mg%	Trace	188 mg%	2+(K)
1460	1+	1158	Trace
966	Trace	206	3+(K)
981	Trace	408	3+(K)
906	Trace	1720	2+
493	4+(K)	1500	Neg
321	2+(K)	1750	1+
250	2+(K)	630	Neg
236	3+(K)		
55	1+(K)		
172	2+(K)		

K = Cephalothin-Clinitest Interference

TABLE 11

Urine Glucose and Clinitest
(Same color block accuracy)

0-125 mg% Negative	126-375 mg% Trace	376-625 mg% 1+	626-875 mg% 2+	876-1500 mg% 3+	1501 mg% - 4+
43 mg%	132 mg%	558 mg%	710 mg%	1100 mg%	2120 mg%
82	222	430		965	1935
28		597		1476	4120
36				1080	3700
5				1420	1865
99				1460	3570
8					2840
17					3020
114					2960
72					3270
12					2370
12					
15					
18					
13					
10					
22					
22					
30					
14					
40					
25					
22					
24					
9					

Exceptions:

Urine Glucose	Clinitest	Urine Glucose	Clinitest
115 mg%	Trace	96 mg%	Trace
800	3+	118	Trace
800	Trace	200	1+
370	Neg	174	1+
344	1+	152	1+
560	2+	138	1+
1330	2+	2670	3+
1460	1+	1390	4+
966	Trace	493	4+(K)
981	Trace	321	2+(K)
906	Trace	250	2+(K)
139	Neg	236	3+(K)
29	Trace	55	1+(K)
23	Trace	172	2+(K)
120	Trace	188	2+(K)

(Continued on next page)

TABLE 11 (cont.)

Urine Glucose	Clinitest
1158 mg%	Trace
206	3+(K)
408	3+(K)
1730	2+
1500	Neg
1750	1+
630	Neg
2140	3+
216	Neg
610	2+
4330	3+

K = Cephalothin-Clinitest Interference

TABLE 12

Blood Glucose Range for a Given Clinitest Value

Patient	4+	3+	2+	1+	Trace	Negative
P(Venous)	--	334 mg%[1]	--	276 mg%[1]	316-117 mg%	250-241 mg%
Z	444-379 mg%	395-355 mg%	366-263 mg%	271-176 mg%	315-275 mg%	211 mg%[1]
B	344-237 mg%	297 mg%[1]	--	216-148 mg%	264-95 mg%	226-121 mg%
A	351-312 mg%	308 mg%[1]	182 mg%[1]	290 mg%[1]	--	199-174 mg%
E	--	223 mg%[1]	--	--	--	224-128 mg%
M	582-462 mg%	--	--	--	152mg%[1]	232-105 mg%
C	279-256 mg%	230-217 mg%	268 mg%[1]	221 mg%[1]	--	257-203 mg%

Legend: 1 = Only one sample had that corresponding Clinitest value.

TABLE 13

Blood Glucose and
Urine Glucose Deviations

Patient	Observed Arterial Blood Glucose	Observed Urine Glucose	Observed Urine Glucose Deviation
B	297 mg% 296 mg%	2670 mg% 172 mg%	2498 mg%
	264 mg% 261 mg%	29 mg% 1865 mg%	1836 mg%
Z	220 mg% 211 mg%	1460 mg% 370 mg%	1090 mg%
E	224 mg% 223 mg%	30 mg% 1080 mg%	1050 mg%
A	312 mg% 308 mg%	3270 mg% 4330 mg%	1060 mg%
	308 mg% 299 mg%	4330 mg% 299 mg%	4031 mg%
C	257 mg% 256 mg%	630 mg% 2960 mg%	2330 mg%
	230 mg% 228 mg%	1460 mg% 2140 mg%	680 mg%

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