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Human voluntary control of fasting blood glucose by glucose feedback and autogenic training

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HUMAN VOLUNTARY CONTROL OF FASTING BLOOD GLUCOSE BY GLUCOSE FEEDBACK AND AUTOGENIC TRAINING

by

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DISSERTATION

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ABSTRACT

Using direct feedback, humans have demonstrated voluntary control (operant conditioning) of such functions as heart rate, blood pressure, skin temperature, and brain waves. Lack of suitable instrumentation to provide feedback has prevented attempts at voluntary glucose control until now. The analyzer portion of the Biostator^{R} (Glucose Controlled Insulin Infusion System) is suitable for providing a continuous glucose feedback signal. This is accomplished by electrically modifying the analyzer voltage output in order to feed a high resolution glucose signal to a strip chart monitor. Unfortunately the Biostator glucose signal is delayed 90 sec., unlike conventional feedback signals which are nearly instantaneous. Glucose differential effects were calculated on a digital computer by a non-parametric method of Lehmann.

To determine the effect of relaxation alone on glucose levels, a group of subjects (2 normals and one insulin dependent diabetic) practiced whole body relaxation using EMG feedback during control periods, with no attempt to alter glucose. Glucose increased in 7 of 9 trials ($P=0.18$). Values in mg/dl of whole blood ranged from -3.7 to 5.5 with a median of 1.3. These results suggest that relaxation alone causes a small increase in fasting glucose levels. Another group of subjects (three normals) relaxed and attended to changing their glucose levels for periods of about 15 minutes, while viewing the monitor. Occasionally standard autogenic suggestions, which have been reported to increase blood sugar levels, were employed as an aid. These suggestions evoke feelings of relaxation and warmth in the extremities and abdomen,

regularity of breathing and heart rate, and forehead coolness. Glucose increased in 13 of 15 trials ($P < 0.01$), during regulation periods, of one subject who was highly trained in several feedback modes. The range was -1.8 to 7.6 with median 2.9. Glucose increased during regulation periods of the second subject in 7 of 11 trials ($P=0.34$). Range was -1.3 to 5.1 with 2.4 median. The third subject was available for only two trials which showed glucose increases of 2.5 and 6.5. Learning sessions were included in the trials. The conclusion is that glucose increased during regulation periods of three out of three subjects. The increases were statistically significant for one subject. False positives can occur if the subject tenses arm muscles in the region of the i.v. catheter during regulatory periods. One regulatory period, during which glucose increased, was monitored via EMG. There was no evidence of increased muscle tension during that time. Autocorrelation analysis of baseline data from six subjects indicated that there may be natural glucose rhythms varying from 0.5 to 1 hr. or more and of a magnitude comparable to the voluntary glucose regulation changes. Such natural rhythms could conceivably increase or decrease the significance of voluntary changes.

APPRECIATION

In carrying out this project, I have been impressed with the vast resources, such as are found at the University of California, which are necessary for research. Particularly important are the people there, who have such a wide range of expertise. In this regard, my Dissertation Committee has been especially valuable. Dr. Peter Forsham made available the resources of the Metabolic Research Unit where this research was conducted. His role has been both paternal and incisive. Professor Gerold Grodsky has influenced my career since its beginning here, setting the highest standards of excellence in research. Professor Joe Kamiya -- who stayed up all one night reviewing the manuscript -- made available the resources of the psychophysiology laboratory. Many profitable and enjoyable hours have been spent in his laboratory and home working out the details of this study. The committee members are all men of eminent good will and generosity.

Of particular mention is the encouragement received from Professor Harold Harper. I am fortunate to have been here while he was Dean of the Graduate Division. His assistant, Nellie Cady has also been very helpful.

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1. INTRODUCTION

1.1 Biofeedback background: The term biofeedback was coined in 1969 at the first meeting of what is now called the Biofeedback Society of America. Other terms such as self-regulation, auto-regulation, and feedback control were preferred, but as it turned out the less precise term took hold. Biofeedback is a form of human instrumental conditioning where a signal proportional to a psychophysiological variable, such as heart rate, is generated. This signal is amplified and presented to the subject, usually in the form of a tone or visual display. The subject uses this information to influence the psychophysiological variable.

The work of Pavlov (see for example, Pavlov, 1957) demonstrated that salivation and other physiological processes could be elicited by a neutral stimulus which had been paired with the repeated presentation of food. This type of conditioning of autonomic processes served to demonstrate functional connections between the autonomic and central nervous systems. There have been only limited applications of this method to the study of metabolic processes. Meanwhile a kind of conditioning distinct from the classical or Pavlovian type was developed. This was known as instrumental or operant conditioning (Skinner, 1938). Operant conditioning, initially applied to the training of overt voluntary behavior, uses the premise that behavior which is rewarded tends to be repeated.

Kamiya (1969, 1971), who was training humans to discriminate the presence or absence of electroencephalograph (EEG) alpha rhythm, devised a system for direct control of the rhythm. This innovation consisted of presenting to the subject instanteous feedback on the alpha activity in the form of a tone. Basmajian (1963) applied feedback training to the skeletal motor system. Operant conditioning of heart rate was accomplished by Weiss and

Engel (1971) in eight patients with premature ventricular contractions (PVCs). All of the patients showed some degree of heart rate control. Five of these patients showed a decrease in PVCs related to learning heart rate control. Four patients have shown persistence of a low PVC frequency after the study, the longest follow-up being 21 months. Pharmacologic studies suggested that decreased PVC frequency was mediated by diminished sympathetic tone and increased vagal tone.

Peripheral blood flow was studied by Taub (Schwartz and Beatty, 1977). After recording baseline temperatures of left and right hands on four successive days, subjects received visual feedback in the form of a light whose intensity was proportional to increases or decreases in hand temperature. Out of 21 consecutive subjects, 19 were able to change hand surface temperature from 8 to 15 deg. F. Rarely were more than four 15 minute training periods required to learn this. These techniques were successfully applied to the treatment of certain forms of Raynaud's disease.

In a preliminary report by Gorman (1974), stomach acid secretion seems subject to voluntary control. Using a 0.1 N solution of sodium bicarbonate, intragastric pH was maintained at 3.5 by automatically controlled titration through a stomach tube in three fasting subjects. These subjects were given feedback reflecting the rate of acid secretion along with periodic quantification of performance and reward; all gave evidence of some ability to alter the secretory pattern in the appropriate manner. To learn this only took three to twelve trials at 15 minutes per trial.

In another novel study, four subjects were given breath by breath feedback, in the form of a tone, proportional to their alveolar CO_2 tension. Subjects were instructed not to manipulate their breathing in the control of CO_2 tension. When all trials were averaged together, it was found that the subjects could raise CO_2 tension 2.7 standard deviations above baseline values. They were unable on the average to lower their levels below baseline, (Naifeh and Kamiya, 1979).

Successful feedback control of such a wide variety of physiological processes has led some to postulate that, "any physiological process which can be monitored, amplified, and made visible to an individual can be voluntarily controlled by that individual" (Pelletier, 1975).

1.2 Blood glucose background: Michael Bauch (1935) observed a significant decrease in blood sugar of diabetics which did not occur in normal control subjects with certain relaxation exercises. Autogenic training (Luthe 1969-1973) was developed by J. H. Schultz in Germany based on observations of naturally occurring events (such as arm relaxation and hand warming) during hypnotic induction. Marchand (1956) reported that he was able to reduce the insulin requirements of a young diabetic by 20 units with autogenic training. Subsequently, he reported a significant increase in blood sugar levels of normal subjects during standard autogenic training exercises (Marchand, 1961). Daily EMG relaxation feedback training has been claimed to aid a diabetic in reducing insulin requirements over a period of

weeks (Fowler et. al., 1976). Classically conditioned drops in human blood sugar by as much as 30 to 50 mg/dl have been reported (reviewed by Woods and Kulkosky, 1976).

Blood sugar is finely regulated by homeostatic mechanisms involving a variety of hormones and the nervous system. A certain minimal level of sugar is required to supply body energy, the brain's requirement being pre-eminent. Also blood sugar must not exceed maximum limits for any length of time, as shown by the devastating effects of untreated diabetes. The endocrine pancreas secretes insulin in response to rises in blood sugar, and glucagon in response to falls in blood sugar, into the blood stream. Insulin lowers blood sugar by expediting glucose absorption into body tissues. Glucagon and the catecholamine epinephrine act on the liver to release glucose and thus raise blood sugar. Somatostatin which is released from the hypothalamus of the brain inhibits the release of both glucagon and insulin. Its net effect is usually to lower blood sugar. There is a long list of other hormones which tend to modulate the effects of those just described. These include pituitary, thyroid, gastrointestinal, adrenal, gonadal, and other hormones most of which stimulate glucagon and insulin secretion. The pancreas is supplied with both sympathetic and parasympathetic nerves which can modify the secretion of insulin and glucagon. These hormonal and neural influences are reviewed by Gerich et. al. (1976).

Equipment for operant conditioning of blood glucose has not been available until the recent development of membrane bound enzyme

technology which provides rapid measurement of glucose levels. The present study is the first utilization of the new technology for short term controlled experiments on psychological conditioning of blood glucose by means of continuous glucose feedback. Of serious concern from the outset, was the unavoidable 90 second delay in returning the glucose signal to the subject. The subject of delayed feedback has received scant attention in the literature, because investigators of other modalities have been able to supply nearly instantaneous feedback to their subjects. There is one report by Laye (1976) that 9 sec. delays in alpha wave feedback, decreases performance to baseline levels. This suggests the following modification of the control postulate, "any physiological process that can be fed back can be controlled provided the feedback delay is less than the response time of the variable being controlled." As blood sugar regulating hormones reach effective blood levels within minutes, the conditions of the modified postulate were met. In view of these considerations, a series of experiments was performed with a small group of dedicated subjects, to test the feasibility of instrumental conditioning of blood glucose.

2. METHODS

Initially there was only a clinical glucose analyzer available for feedback studies. Blood samples were withdrawn periodically from the subject who sat in front of the analyzer. The samples were fed into the analyzer which displayed the glucose level digitally to the subject within 90 sec. This is termed discrete feedback. When the Biostator became available, it was possible to give the subject a continuous feedback display of glucose level on a strip chart, although there was still a 90 sec. delay in the signal. The continuous method thus supplanted the discrete method. Experiments usually were conducted in the morning after an overnight fast by the subject. Afternoon experiments were conducted after at least a five hour fast. In the course of the study afternoon experiments were avoided, when it was found that the glucose baselines often displayed a linear (declining) trend. In both types of feedback, blood was withdrawn from forearm or antecubital veins. With discrete feedback, at least 30 min. elapsed after catheterization before the subject attempted regulation. This was extended to at least an hour with the continuous system. To allow for adaptation of the subjects to catheterization, often a saline drip was begun prior to connection of blood flow to the Biostator. This adaptation period is necessary to avoid sympathetic effects associated with the trauma of venipuncture. These effects alone can raise blood sugar (Woods and Kulkosky, 1976). Subjects were given the option of lying or sitting during the continuous feedback. Most preferred sitting.

A continuous or discrete feedback session was divided into separate trials of baseline (B) and regulation periods (R), see fig. 1 for example. During baseline and regulation periods, the subject could see the glucose feedback levels. During baseline periods the subject was instructed not to influence the levels; reading or talking was permitted while remaining as physically quiet as possible. During regulation periods, the subject was asked to influence the glucose level by whatever mental processes seemed effective. In some sessions the subject practiced autogenic training during regulation periods. The length of a regulation period was specified before it began. Occasionally a subject requested a brief extension during the regulation period which was granted. The length of a regulation period was usually 10 to 15 minutes with extensions around 3 minutes. A regulation period was initiated when observation showed that sufficiently good quality baseline had elapsed. In the initial subject instructions, no direction of desired glucose change was specified during regulation periods. After a few trials showed that glucose was increasing during regulation periods, the instructions were modified. In

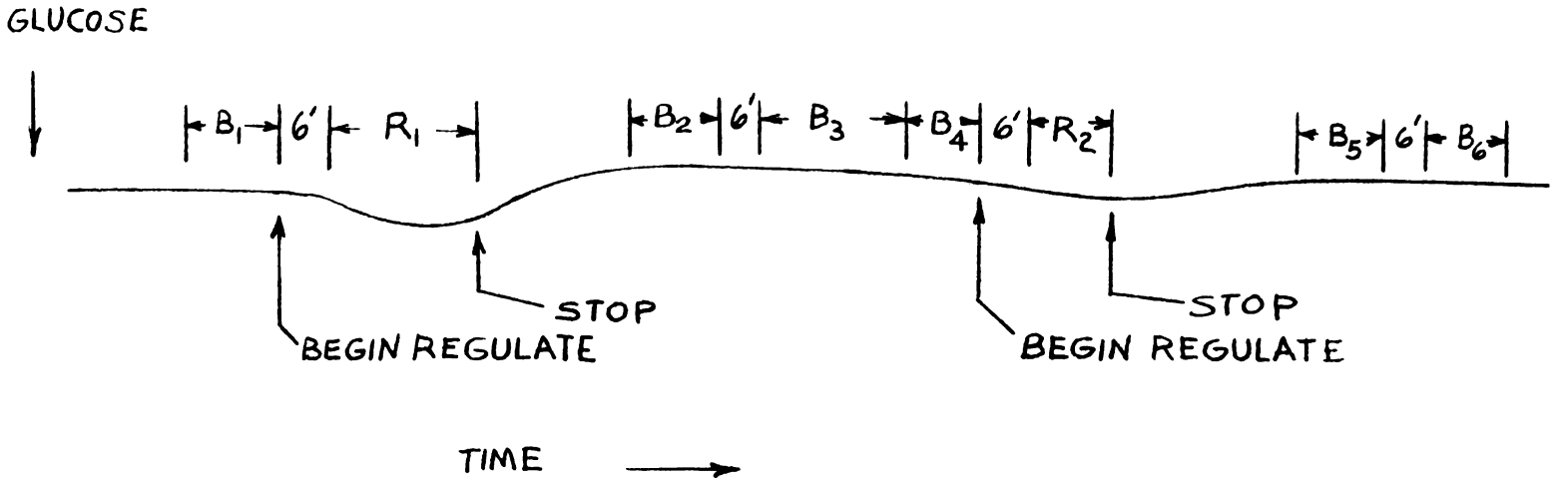

Fig. 1. Allocation of glucose signal for estimation of differential effects.

subsequent regulation periods, the subjects were asked to continue whatever they were doing to cause the increases. In the case of subject C.C., this was to continue practicing the autogenic training.

2.1 Discrete glucose feedback: Blood samples of 0.3 cc size were obtained from an indwelling 19G butterfly catheter using a 1 cc syringe. The catheter was flushed periodically with around 2 cc of heparinized saline to prevent clotting. The blood was transferred into anticoagulant coated microfuge tubes. In some experiments samples were frozen for later assay. In the case of the Beckman glucose analyzer which uses plasma, the blood was centrifuged for 15 sec. before being pipetted into the analyzer. A clinical Beckman glucose analyzer was used for discrete feedback; glucose levels were displayed within one minute after

sampling. Using a 100 mg/dl standard, the accuracy of the analyzer was found to be 4 mg/dl with a precision=1.7 mg/dl. A clinical Yellow Springs Instruments (YSI) glucose analyzer was used in some of the later discrete feedback sessions. The Yellow Springs Instrument reads whole blood, so centrifugation was not necessary. YSI processing time was about 90 sec., so samples were taken at two minute intervals. The accuracy of the YSI was found to be 0.5 mg/dl with a precision=0.9 mg/dl. Sample volume is 60 µl. Sample volume of the Beckman instrument is 15 µl. The smaller sample volume probably contributed to the lower precision of the Beckman analyzer.

Sources of error with the discrete system were dilution of the samples by the flushing procedure, non uniform sample collection times (times could sometimes be off by as much as 0.5 min.), uneven handling of stored samples (such as the development of a backlog in removing plasma from cells), and pipetting errors. Only an air displacement pipette was available to transfer a sample to the analyzer, whereas a positive displacement pipette would have been preferred. An effort was made to minimize the dilution effect by flushing immediately after taking a sample and discarding one syringe of blood before taking the next sample.

2.2 Continuous glucose feedback: The continuous system used an indwelling double lumen catheter supplied by the Biostator^{R} manufacturer (Miles Labs., Inc., Elkhart, Indiana). The catheter was inserted using an 18G Medicut syringe. Anticoagulant fluid was pumped into the outer lumen at the same pressure at which

blood was withdrawn from the inner lumen, which prevented any of the anticoagulant from entering the subject's bloodstream. The blood entered the Biostator via small bore tubing; consequently the total blood withdrawn by the continuous system (approx. 2 ml/hr.) was only a fraction of that of the discrete system. The blood was diluted by a buffer solution at a selected pump-ratio before transfer to the analyzer. The analyzer measures glucose by means of a chemical reaction on a glucose oxidase membrane. The reaction releases H_2O_2 which is sensed by a platinum electrode. Sources of error for the continuous system include pump dilution ratio drift, and platelet build up at the catheter tip and on the glucose oxidase membrane. Whole blood data provided by the manufacturer (Fogt et. al., 1978, 1979) indicate that the Biostator analyzer is most accurate in the range of normal fasting glucose with very good linearity. Accuracy is 0.4 mg/dl with a precision (standard deviation of difference between readings and true values)=5.2 mg/dl. The pump-ratio (number of parts of diluent added per part of sample) variation was 4% over six hrs.

The subject can see the magnitude of his glucose level on a Biostator digital display which is updated several times per minute. Relative glucose levels are continuously displayed on a strip chart visible to the subject. In order to obtain high resolution glucose readings, the Biostator voltage output was fed into a voltage divider and current bucking device which was designed and built at the University of California. The output from this device was fed into a three channel Honeywell strip

chart recorder which allowed simultaneous monitoring of skin temperature and EMG. The recorder response time under the damping and gain settings used was between 2 to 3 sec. full scale, which is well within the glucose response time. Fig. 2 shows the setting of a feedback session. The other physiological measures shown were usually not used during learning sessions as they could be distracting to the subject.

Future feedback experiments could utilize the insulin and glucose infusion option of the Biostator to clamp blood sugar at a desired level. A feedback signal could be the amount of insulin or glucose necessary to maintain the desired blood sugar level as determined by an algorithm programmed into the Biostator's digital computer.

2.3 Biostator calibration procedure: The Biostator manufacturer has worked out an accurate calibration procedure which is not dependent on an external analyzer. As relative accuracy is more important than absolute accuracy in these experiments, the following more rapid procedures were developed. Initially baseline solution is pumped through the Biostator at slow speed for at least one hour before the subject is connected. The pump speed is turned to high and the digital glucose readout is set at zero mg/dl using the baseline knob. The current output is recorded and must be less than five milliamp. The standard glucose solution is then pumped through the machine and the current output is again recorded. The difference in current from baseline to standard

Fig. 2. Experimental setting of a feedback session. The investigator is adjusting the Biostator. The catheter is barely visible in the region of the subject's left antecubital vein. An EMG electrode is shown attached to her left forearm. Her left hand lies on the heating pad which has been opened out. The telethermometer sits on top center of the Biostator. To the right is the stripchart recorder. Temperature and glucose is being recorded on the left channel and EMG on the right channel. The electromyograph sits on top of the strip chart recorder; the voltage divider on top of that. Photograph courtesy of Barbara Frankel.

is a measure of the sensitivity of the glucose oxidase membrane and must be at least 15 milliamp, or the membrane must be replaced. If the membrane is acceptable, the digital glucose readout is set to the standard value (around 200 mg/dl) by means of the calibrate knob.

Two standard glucose solutions (usually 80 and 100 mg/dl) are used to calibrate the strip chart recorder. These are made from alpha-D glucose in isotonic saline. If absolute glucose accuracy were required, the standard solutions would require viscosity adjustment due to the streaming potential effect on the membrane. Streaming potential of ions in solution is analogous to the Van de Graaff effect of ions in gases. Viscosity adjustment of the solutions was not done because streaming potential does not affect relative glucose readings.

The glucose standards are placed in separate tubes into which a Biostator catheter is alternately placed for about 2 minutes. The outer lumen of the catheter is connected via the pump to isotonic saline representing the anticoagulant solution. The inner lumen is connected to the Biostator blood intake port. Then the strip chart recorder is adjusted to a span of 40 mg/dl full scale by means of the voltage divider and current bucking device.

The subject is catheterized and a sample of venous blood is taken for assay by a clinical glucose analyzer. With the Biostator reading the subject's glucose levels, the Biostator

digital readout is set to correspond to the glucose value determined by the clinical analyzer. This value is reduced approximately 15% if the clinical analyzer is fed only plasma in order to adjust for hematocrit. A final blood sample is taken at the end of the experiment for independent assay to check for Biostator drift.

2.4 Subjects

Selection: All subjects who participated in the glucose feedback experiments were referred through colleagues. They were motivated by the novelty of the challenge. All were offered renumeration for their time and discomfort. One, J.K., elected not to accept compensation. Bonuses were given for successful regulation of glucose.

Background: Table 1 presents a brief summary of the subjects. At the time of their first experiment their ages were from 20 to 37 years. There was approximately the same number of men as women. One of the subjects used daily insulin to regulate blood sugar. While it is not known that one type of feedback training facilitates another, it was felt that previous feedback experience would be helpful. Accordingly, each (with the exception of J.K. who already was trained) was given electromyograph (EMG) feedback (using an Autogen 1700) sufficient to achieve relaxation of major muscle groups. The number

TABLE I

Subject Summary

Subj.	Age	Sex	Insulin Units/day	Hours EMG. Training	Other† Feedback	No. Disc. Feedback	No. Cont. Feedback
R.	31	M		0			0
C.B.	33	M		2			1
R.B.	34	F	32	6			1
C.C.	27	F		0.5	T, ∝	1	11
T.H.	20	M		1.5	∝, C		11
J.K.	37	F		7*	T, ∝, E, C, G	12	10
L.S.	36	M		1.5			2
M.L.S.	30	F		1.5			5
A.T.	26	F		0			0

* Estimated hours of EMG practiced independent of this study.

† T = Temperature, ∝ = alpha wave, E = other EEG frequencies and cortical specialization, C = carbon dioxide, G = galvanic skin response.

of hours of EMG training given is shown in table 1. Types of feedback training the subjects experienced in other contexts is also shown. The feedback background of J.K. was exceptional. For example, she has practiced over 1000 hours of EEG feedback.

The last two columns of table 1 show the total number of discrete or continuous glucose feedback sessions. There was only one session for a given subject per day. There may have been several trials in a given session. The number of sessions refers to experiments in which glucose data were recorded irrespective of acceptability. The number of baseline sessions (no glucose feedback) is not shown. Subjects R., A.T., and M.L.S. produced baseline data only. Subjects C.B., R.B., and L.S. participated in the EMG relaxation study only.

2.5 Autogenic training: The subjects were given the following autogenic suggestions to practice at home for a few minutes for only a few days before trying them for glucose regulation. Therefore subjects who tried the autogenic training methods, C.C., J.K., and T.H., were relatively inexperienced in their use. The suggestions were:

1. My arms and legs are heavy.
2. My arms and legs are warm.
3. My heart beat is calm and regular.
4. My body breathes freely and comfortably.
5. My solar plexus (liver, abdominal area) is warm.
6. My forehead is cool.

Each suggestion was to be dwelled upon during a regulation period on the Biostator. The idea was not merely to repeat the suggestions, rather to use them to slowly scan the different parts of their body, evoking sensations as they did so. For example, instruction number one tends to promote muscle relaxation, instruction number two encourages surface vasodilation. Some subjects went through the suggestion cycle repeatedly during a regulation period, others only once.

3. RESULTS

3.1 Data analysis: For convenience of analysis, the continuous data were sampled at 40 sec. intervals. Acceptance criteria were uniformly applied to all recorded data in order to eliminate from analysis data which were excessively noisy,and to avoid the pitfall of selecting only data which gave a desired effect. A method of data analysis was selected which reduced the effects of random fluctuations or linear trends in the underlying glucose baseline, in order to estimate the extent to which a subject influenced glucose. This estimate is termed the differential effect. Finally autocorrelation studies were conducted in order to determine if there were natural oscillations in blood glucose. Such oscillations are of concern for they could simulate voluntary regulation. These procedures are discussed in the following paragraphs; the mathematical details are given in the appendices.

3.2 Data acceptance criteria: There were two criteria to which all runs were subjected before data were accepted for analysis: a stability requirement on baseline data, and restrictions on the

allowable noise level of the data.

(1). The glucose baseline must remain within a 5 mg/dl bandwidth.

(2). There must be less than 15% spurious points in a baseline or regulation period.

Spurious data points are points which differ by 2 or more mg/dl from an immediately adjacent point provided that the points are not part of a linear progression. This is illustrated in fig. 3 where X_4, X_7, and X_8, would be rejected, but not X_{12}, or X_{13}. In order for a regulation period to be acceptable, the immediately preceding baseline must meet the criteria.

3.3 Differential effect estimate: Data were eliminated from analysis for six minutes after the beginning of a regulation period in order to allow for the 90 sec. feedback delay and the time it takes for a subject to generate an effect. Baselines were divided into sub baseline periods with similar 6 minute data lags. These arbitrary divisions are shown in fig. 1.

To determine if the subject was able to influence glucose, the change from B_1 to R_1 was compared with a change from B_2 to B_3. This will be called an estimated linear differential effect (L). Computing L values tends to compensate for random fluctuations, or linear trends in the underlying glucose baseline, which a comparison of baseline to regulation alone wouldn't do. Similarly in the second trial an L value is computed by comparing a change from B_4 to R_2 to a change from B_5 to B_6. The reference baseline pair may either precede or follow the regulation period.

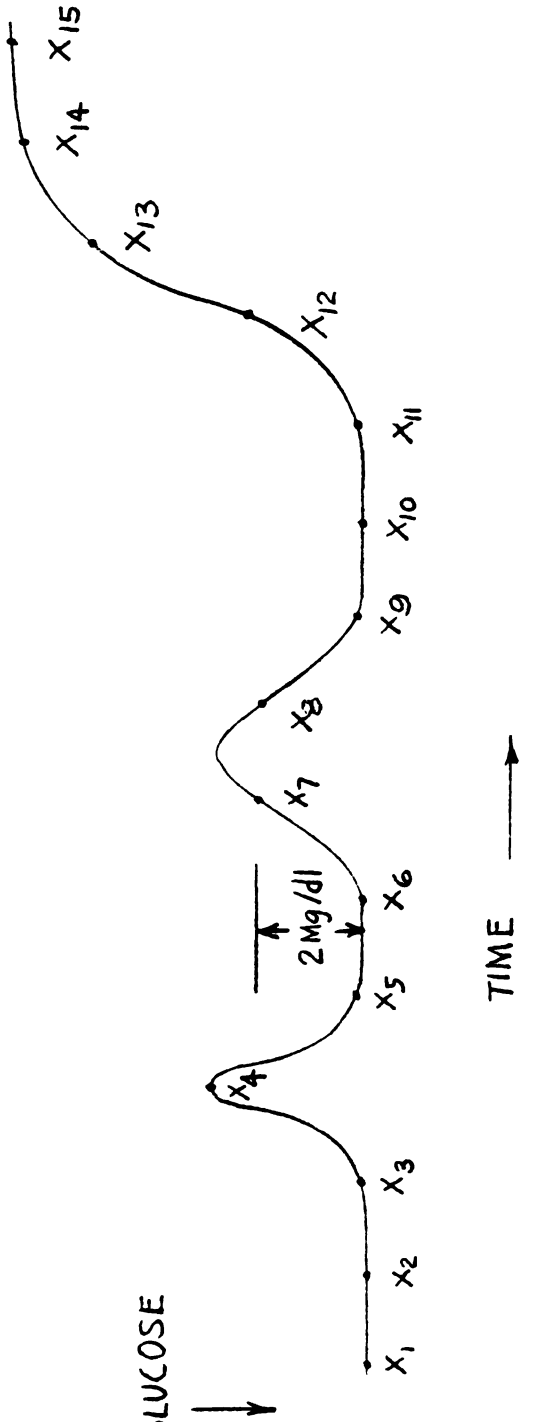

Fig. 3. Data acceptance criterion.

For example, B_2 and B_3 could have been compared to B_4 and R_2. A problem, called carryover, occurs with this method when due to limited baseline length, it was necessary to place the beginning of B_2 closer to the end of R_1 than shown in fig. 1. If in the presence of carryover, B_2 and B_3 were used as reference pair for the second trial, the L value could indicate an increase in glucose where none existed. Carryover (in the opposite direction) could also reduce the size of L (indicate no change when one actually existed). Therefore to aid in interpreting the differential effects, the tables in the results section give Δ values, which are components of the L values. A Δ value is either a comparison of baseline to regulation, or baseline to baseline. The median values in each period (B_1, R_1, B_2, B_3, etc.) will be given for reference. Referring to the symbols indicates whether a baseline pair preceded or followed a regulation period, and if (rarely) the same baseline pair was used for two regulation periods. Because the data distribution in some of the periods tended to be skewed, non parametric methods were used to compute L and Δ values. Because the carryover effect tended to reduce the quantitative significance of some L values, probability (P) values were computed by the sign test.

3.4 Discrete glucose feedback: Of 17 sessions using a clinical glucose analyzer for feedback, virtually all failed the rigorous criteria which were adopted after the superior Biostator data were obtained. Therefore none of the discrete data was tested for

statistically significant evidence of glucose regulation. However these sessions may have aided in training the subject for subsequent continuous glucose feedback.

3.5 Continuous glucose feedback: Sufficient data to test for statistical significance were obtained from two subjects. These data were analyzed independently in order to allow for individual differences in the subjects' abilities. It must be emphasized that the data were gathered from sessions while the subjects were in training for the task. That is, learning may have occurred during the sessions. Therefore it would be expected that if subsequent to training, a number of regulation sessions had been conducted, the subjects' significance levels would have improved.

Results for the eight sessions (15 trials) of J.K. are shown in table 2. The table shows the sessions chronologically with date. Change in glucose during regulation with respect to a baseline set is given under L (glucose differential effect). For subject J.K., the L values ranged from -1.8 to 7.6 with a median of 2.9 mg glucose/dl whole blood. There was less than one chance in a hundred that the increases of glucose during regulation periods were random ($P < 0.01$).

Changes in glucose between two baseline periods, or between a baseline and regulation period are given under Δ. The median glucose values of each period are given, followed by the number of data points (N) in each period. The periods are identified by subscript so as to document their order. For example in trial

TABLE 2

Glucose Feedback Results for J.K.

Trial	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N
1	7-14-77	2.2	1.4	77.3	B_1	13
				79.0	B_2	13
			3.6	77.4	B_3	13
				81.2	R_1	13
2	8-24-77	4.4	0.7	84.5	B_1	10
				85.1	R_1	19
			-3.7	85.4	B_2	11
				81.6	B_3	18
3	8-24-77	6.0	1.6	80.1	B_4	4
				81.7	R_2	20
			-4.6	81.4	B_5	10
				76.7	B_6	14
4	8-24-77	0.1	-0.3	76.8	B_7	6
				76.5	R_3	22
			-0.4	76.8	B_8	14
				76.5	B_9	14
5	8-30-77	1.8	-0.1	86.7	B_1	4
				86.7	R_1	7
			-2.1	85.8	B_2	6
				83.9	B_3	5

TABLE 2
Continued

Trial	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N
6	9-8-77	4.5	1.5	75.9	B_1	11
				77.5	R_1	14
			-3.0	76.5	B_2	11
				73.7	B_3	14
7	9-8-77	7.6	4.7	72.6	B_4	7
				77.3	R_2	13
			-3.0	77.1	B_5	9
				74.1	B_6	11
8	10-18-77	-0.7	-0.5	80.0	B_1	7
				79.6	B_2	12
			-1.2	78.1	B_3	7
				76.9	R_1	12
9	10-18-77	2.9	1.5	74.2	B_4	10
				75.5	R_2	25
			-1.4	75.5	B_5	10
				74.1	B_6	25
10	11-1-77	-1.8	0.6	76.4	B_1	8
				77.1	B_2	21
			-1.1	76.7	B_3	7
				75.4	R_1	22

TABLE 2
Continued

Trial	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N
				73.9	B_4	12
			-1.8			
				72.2	B_5	13
11	11-1-77	0.9				
				71.0	B_6	11
			-0.9			
				70.1	R_2	14
				73.4	B_1	12
			-7.0			
				66.4	R_1	42
12	3-17-78	3.4				
				58.4	B_2	12
			-10.5			
				47.6	B_3	41
				90.0	B_1	6
			-1.0			
				89.0	B_2	9
13*	5-5-78	7.4				
				88.2	B_3	5
			6.4			
				94.4	R_1	10
				88.4	B_4	15
			6.1			
				94.3	R_2	13
14*	5-5-78	6.5				
				88.3	B_5	13
			-0.6			
				87.5	B_6	15
				88.2	B_7	10
			1.3			
				89.2	R_3	18
15*	5-5-78	2.0				
				88.3	B_5	13
			-0.6			
				87.5	B_6	15

* Subject used autogenic training with Glucose Feedback.

1 of table 2, the reference baseline set B_1 and B_2 preceded the regulation period R_1 with its baseline B_3. In some cases, due to limited availability of baseline data, it was necessary to use the same reference baseline set for different regulation periods for a given session. For example the session of 5-5-78 used the same baseline reference set, B_5 and B_6, for the second and third regulation periods (trials 14 and 15). A tracing from part of the glucose data for trial 14 is shown in figure 4. This shows a relatively large increase in glucose during R_2. Note that glucose increases are shown by the downward direction in the figure.

Table 3 presents the results of the seven sessions (11 trials) of subject C.C. The L values ranged from -1.3 mg/dl to 5.1 mg/dl with 2.4 mg/dl median. Again the results favor an increase in glucose, but not significantly (P=0.34). Fig. 5 shows a tracing from trial 3. This shows a small increase in glucose during R_2. One source of artifacts of the type shown, is electrostatic discharge which was noted to occur when someone brushed against the subject's clothing.

Table 4 shows results of one session with a third subject. The two favorable trials (1 and 2) with T.H. came after a series of disappointing sessions where regulation was not attempted, because an adequate glucose baseline could not be established. The subject would have liked to repeat his feat, but it was necessary for him to leave the country.

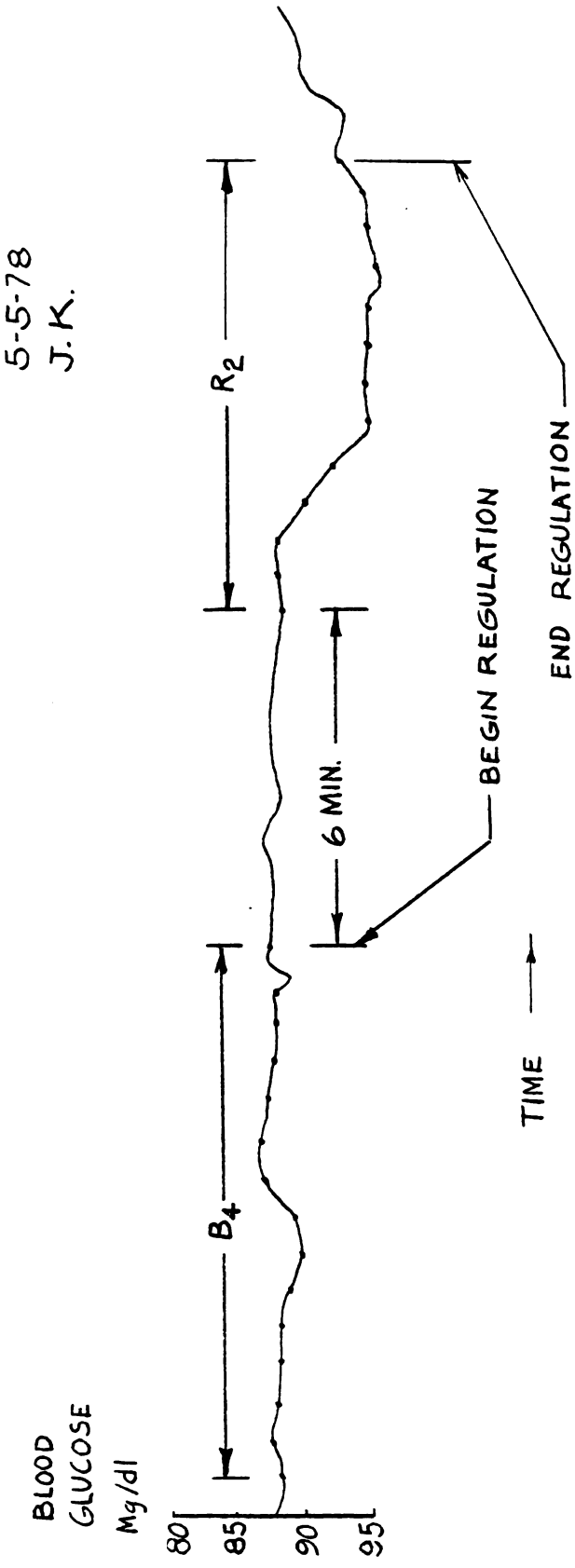

Fig. 4. Example of regulation (R_2) and baseline (B_4) periods (high effect). Figure is reduced 64% from actual size.

Table 3

Glucose Feedback Results For C.C.

Trial	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N
1	10-21-77	-1.3		80.5	B_1	6
			1.7	82.0	B_2	11
				81.6	B_3	6
			0.3	82.1	R_1	11
2	12-8-77	5.1		78.4	B_1	10
			3.0	81.4	R_1	23
				81.6	B_2	16
			-2.1	79.6	B_3	17
3*	12-8-77	3.0		81.6	B_2	16
			-2.1	79.6	B_3	17
				82.9	B_4	8
			0.9	83.8	R_2	25
4*	12-14-77	5.0		74.7	B_1	7
			2.2	77.0	R_1	15
				77.5	B_2	7
			-2.8	74.8	B_3	15
5*	12-14-77	3.3		75.2	B_4	8
			0.4	75.5	R_2	14
				77.5	B_2	7
			-2.8	74.8	B_3	15

TABLE 3
Continued

Trial	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N
				91.5	B_1	5
			-3.7			
				87.7	B_2	21
6*	1-23-78	0.0				
				85.4	B_3	5
			-3.8			
				81.7	R_1	21
				79.4	B_4	5
			-5.8			
				73.4	B_5	14
7*	1-23-78	-0.2				
				67.8	B_6	5
			-5.6			
				62.8	R_2	14
				86.0	B_1	7
			-0.4			
				85.6	B_2	10
8*	1-31-78	-0.2				
				85.0	B_3	4
			-0.6			
				84.3	R_1	12
				80.5	B_1	6
			1.4			
				81.9	R_1	22
9*	4-28-78	2.7				
				80.4	B_2	14
			-1.3			
				78.9	B_3	14
				84.2	B_1	11
			0.5			
				84.7	B_2	10
10*	5-16-78	1.0				
				84.2	B_3	6
			1.5			
				85.7	R_1	15

TABLE 3
Continued

Trial	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N
				88.1	B_4	11
			1.0			
				89.1	R_2	13
11*	5-16-78	2.4				
				88.4	B_5	12
			-1.4			
				87.1	B_6	12

* Subject used autogenic training with Glucose Feedback.

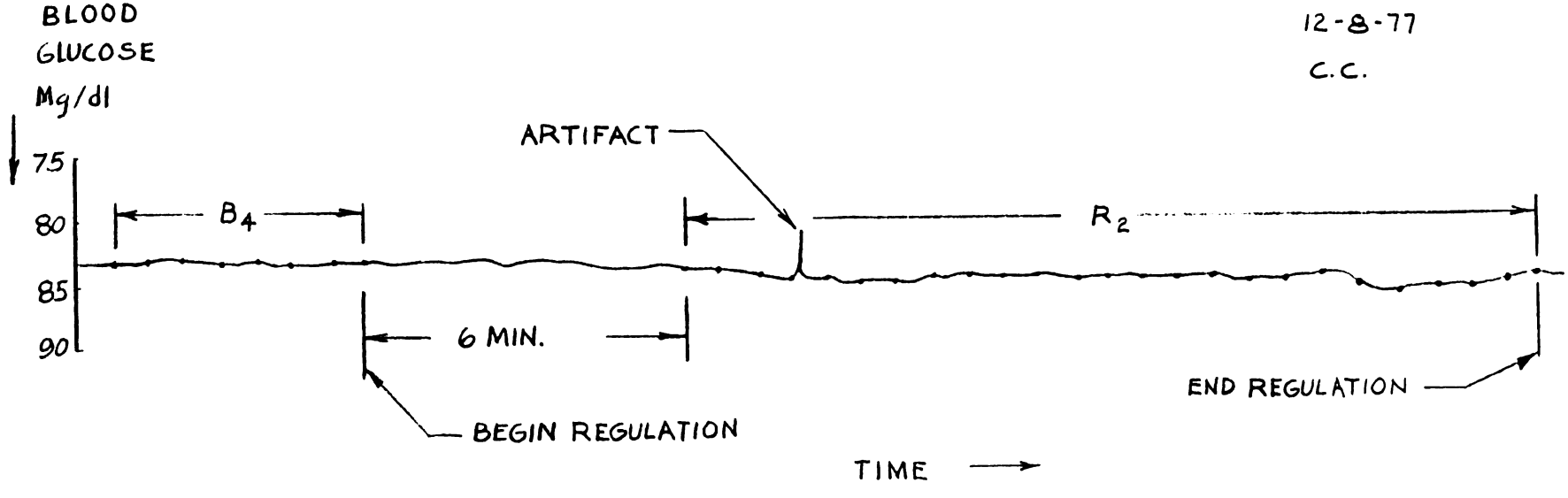

Fig. 5. Example of regulation (R_2) and baseline (B_4) periods (low effect). Figure is reduced 64% from actual size.

TABLE 4

Glucose Feedback Results

Trial	Subject	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N
					85.3	B_1	13
				1.2			
					86.5	R_1	20
1*	T.H.	6-8-78	2.1				
					86.2	B_2	13
				-0.9			
					85.4	B_3	20
					85.6	B_4	11
				3.3			
					88.4	R_2	15
2*	T.H.	6-8-78	6.5				
					88.3	B_5	11
				-3.2			
					84.6	B_6	15

* Subject used autogenic training with Glucose Feedback.

The subjects practiced autogenic training during the regulation periods of trials marked with an asterisk in tables 2 to 4. It is of interest to know if these trials had a different effect on glucose than those trials where there was no autogenic training. Neglecting individual differences, there were 13 trials wherein the subjects practiced glucose feedback with autogenic training, and 14 trials of glucose feedback without autogenic training. With autogenic training, the glucose change (L) ranged from -0.2 to 7.4 with a median value of 2.4 mg/dl (P=0.02). Without autogenic training, L ranged from -1.8 to 7.6 with a median value of 2.6 (P=0.06). A reasonable conclusion is that the two types of trials gave similar results across subjects. There was a small significant increase in glucose.

Prior to beginning the continuous feedback experiments, a few sessions with different subjects were devoted to discovering the effect of muscle relaxation on blood glucose. There were four sessions with three subjects (nine trials total). Subject R.B. required daily insulin. During the sessions the subjects received both EMG and glucose feedback. During regulation periods they were instructed to lower their EMG; there was no instructions to regulate glucose. Results are shown in table 5. The up arrows under the electromyograph column indicate an ordinary degree of muscle tension (see example in fig. 6). Down arrows indicate a relaxed state which is characterized by a lower and steadier EMG voltage. Glucose L values ranged from -3.7 to 5.5 with 1.3 median. A positive influence on glucose is sug-

TABLE 5

Effect of Relaxation on Blood Glucose

Example	Subj.	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N	EMG
1	L.S.	5-20-77	-0.7		61.0	B_1	3	↑
				2.6	63.8	B_2	3	↑
					64.0	B_3	3	↑
				1.9	65.9	R_1	3	↓
2	L.S.	5-31-77	0.3		56.2	B_1	5	↑
				1.0	57.1	R_1	5	↓
					57.9	B_2	5	↑
				0.7	58.6	B_3	5	↑
3	L.S.	5-31-77	4.4		61.2	B_4	12	↑
				1.5	62.6	R_2	12	↓
					62.6	B_5	12	↑
				-3.0	59.3	B_6	12	↑
4	C.B.	6-6-77	5.5		89.6	B_1	5	↑
				-1.8	87.7	B_2	7	↑
					87.3	B_3	5	↑
				3.7	91.0	R_1	7	↓
5	C.B.	6-6-77	1.0		81.4	B_4	12	↑
				1.6	83.0	B_5	17	↑
					83.8	B_6	11	↑
				2.5	86.3	R_2	18	↓

TABLE 5
Continued

Example	Subj.	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N	EMG
					299.9	B_1	15	↑
				-0.8				
					299.0	R_1	15	↓
6	R.B.	5-31-77	-3.7					
					298.1	B_2	15	↑
				2.9				
					300.9	B_3	15	↑
					302.8	B_4	8	↑
				1.5				
					304.3	R_2	21	↓
7	R.B.	5-31-77	1.3					
					301.8	B_5	15	↑
				0.1				
					301.8	B_6	14	↑
					301.8	B_7	13	↑
				2.0				
					304.1	R_3	13	↓
8	R.B.	5-31-77	2.7					
					304.4	B_8	13	↑
				-0.7				
					303.7	B_9	13	↑
					298.8	B_{10}*	6	↑
				-3.6				
					295.2	R_4	6	↓
9	R.B.	5-31-77	1.3					
					294.1	B_{11}	6	↑
				-4.9				
					289.1	P_{12}	6	↑

* 29 minutes after subject received 5 units of regular insulin (i.m.), her first since the previous day.

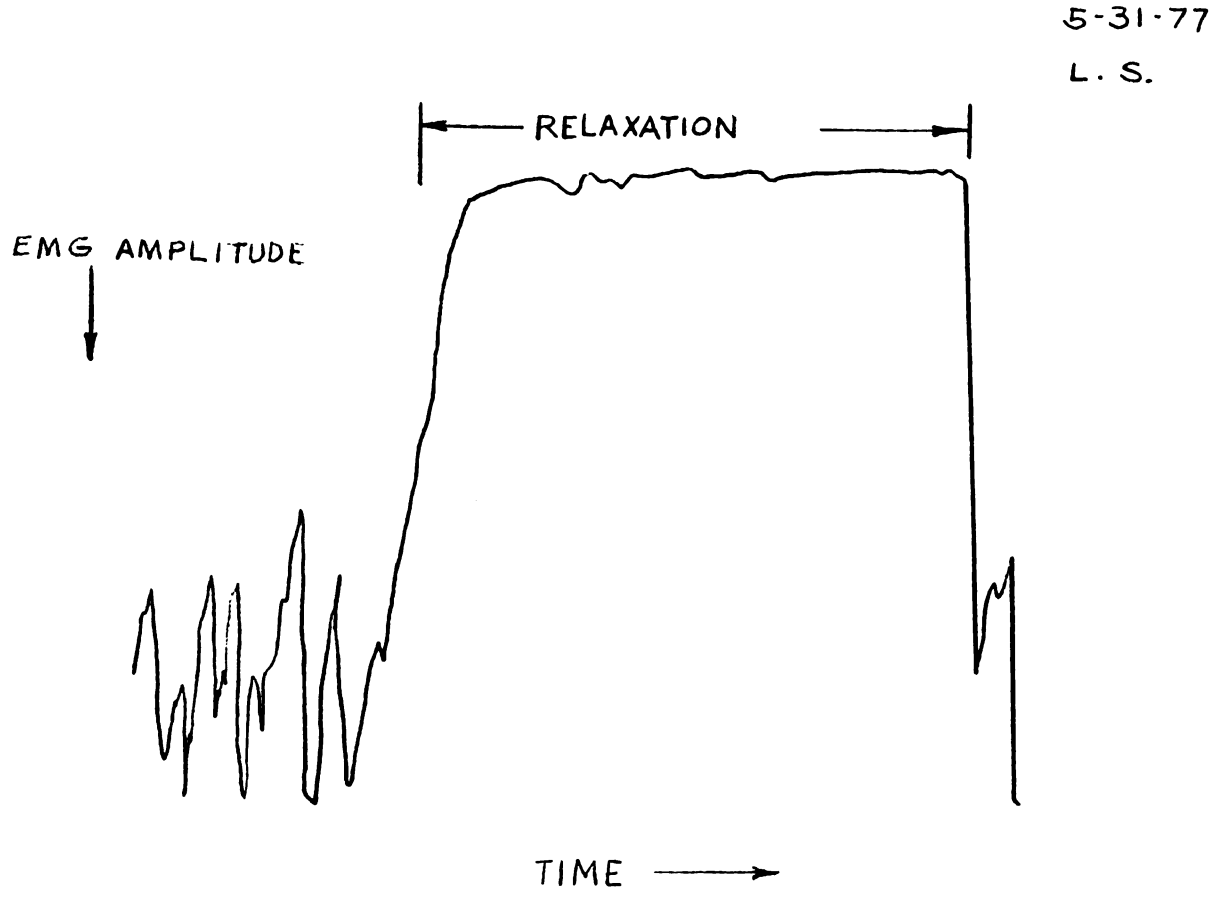

Fig. 6. Characteristic EMG. Reduced 64% from actual size.

gested (P=0.18); therefore relaxation may be of value during voluntary glucose regulation trials.

To give an estimate of the magnitude of the glucose changes in all the feedback experiments, a histogram summarizing the L values from tables 2 to 5 is shown in fig. 7. The histogram is approximately normally distributed with mean glucose increase of 2.6 mg/dl and standard deviation of 1.0 mg/dl. The kurtosis of the histogram (peakendness)=2.6, compared to the kurtosis of a normal distribution which is 3. The skewness of the histogram=0.06 in the direction of a positive glucose change. The skewness of a normal distribution is between $\pm$ 0.5.

3.6 Control experiments: An early strategy for glucose regulation attempted by the subjects was to use food fantasies. This did not seem useful, so was abandoned. To verify this, a control experiment was performed using a strong psychic stimulus -- tasting food that was either desirable or aversive. There was no attempt to regulate glucose during the R' periods. The food was tasted during the R´periods. The results shown in examples 1 and 2 of table 6 show scant glucose effect and are further evidence that food fantasies are ineffective.

A second control experiment concerned an alternative explanation to glucose regulation. Perhaps the subjects were not actually changing their glucose levels, but because they were competent in other types of feedback, they were raising their hand temperature. This could conceivably shunt arterial blood, having

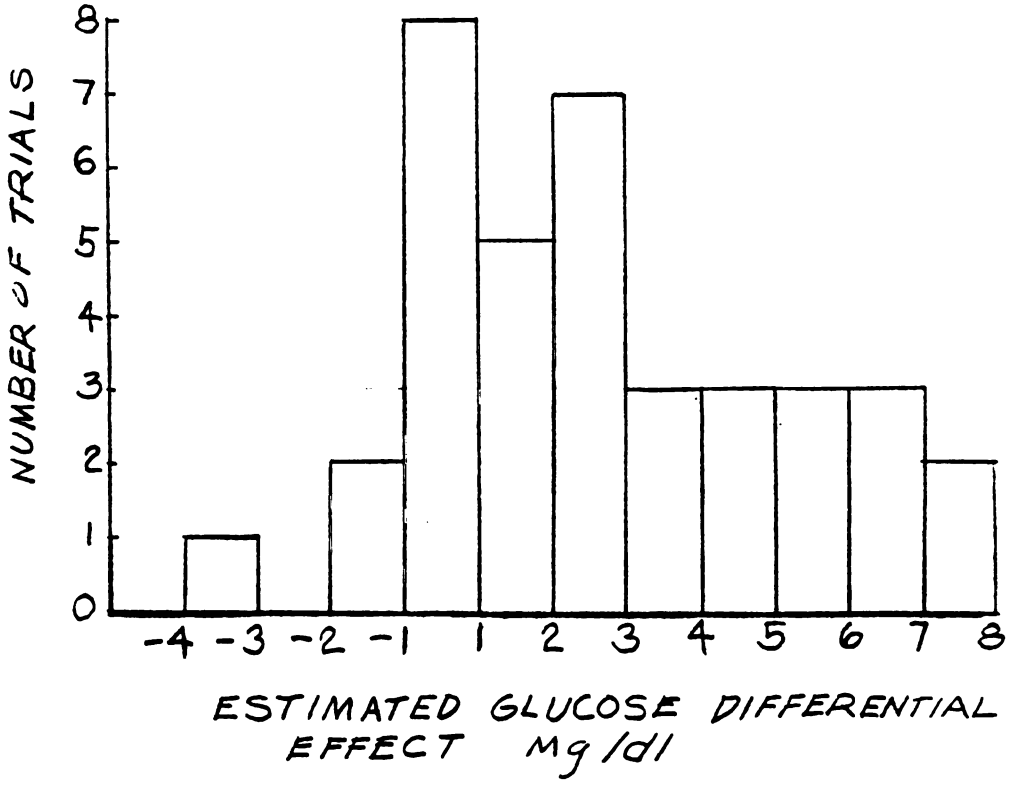

Fig. 7. Summary of glucose regulation and relaxation experiments, showing distribution of L values.

TABLE 6

Control Experiments

Example	Subj.	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N	EMG	T deg.C.	Description
					81.0	B_1'	10			
				-0.8						
					80.5	B_2'	10			
1	M.L.S.	8-12-78	0.1							
					80.7	B_3'	5			
				-0.7						
					80.0	R_1'	15			Taste favorable food
					81.0	B_1'	10			
				-0.8						
					80.5	B_2'	10			
2	M.L.S.	8-12-78	-0.6							
					80.2	B_4'	6			
				-1.3						
					78.6	R_2'	15			Taste averse food
					91.4	B_1'	5		28	
				-2.6						
					88.9	B_2'	3		27	
3	C.C.	1-23-78	0.0							
					89.0	B_3'	3		27	
				-2.6						
					86.4	R_1'	5		40	Raise ambient hand temp.
					86.3	B_2'	11		32	
				-0.9						
					85.5	B_3'	15		32	
4	T.H.	6-8-78	4.2							
					85.6	B_4	11		39	Raise ambient hand temp.
				3.3						
					88.4	R_2	15		39	
					79.4	B_1'	8	↓		
				-0.1						
					79.3	B_2'	8	↑ sl.		Straighten fingers
5	T.H.	3-14-78	1.9							
					79.4	B_3'	7	↓		
				1.8						
					81.2	R_1'	9	↑		Lift arm

TABLE 6
Continued

Example	Subj.	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N	EMG	T deg.C.	Description
					88.1	B_4	11	↑		
				1.0						
					89.1	R_2	13	↓		Regulate
6	C.C.	5-16-78	2.4							Glucose
					88.4	B_5	12	↑		
				-1.4						
					87.1	B_6	12	↑		

a higher glucose level, into the forearm venous system and give an apparent glucose increase. An experiment (example 3, table 6) was performed to determine if raising ambient hand temperature had a glucose effect. The hand of the catheterized arm was in a thermostatically controlled chamber throughout the experiment. The hand was at room temp. in B_1', B_2', and B_3'. The hand temp. was raised 13 deg. C during R_1'. There was no attempt to regulate glucose during R_1'. Note that increasing hand temp. had no effect on glucose.

Another experiment (ex. 4, table 6) was performed to see if a subject could voluntarily raise glucose after hand temperature had been increased by direct application of heat. The subject's hand temperature was, by means of a commercial heating pad, held at a constant 7 deg. C. above baseline during B_4' and R_2' periods. However, glucose increased 3.3 mg/dl during R_2' over B_4'. These two experiments indicate that the glucose increases found during voluntary regulation periods could not have been due to shunting of arterial blood to veins. Hand temperature in these experiments was taken by a telethermometer with the sensor taped to the thenar eminence.

Another alternative explanation to glucose regulation is that venous blood pressure increases could be transferred to the Biostator analyzer membrane and cause an apparent glucose change. It was known from observing pump artifact on the strip chart recorder that the membrane was pressure sensitive (the recorder pen moved a perceptible amount in synchrony with the Biostator peristatic pump). Exerting strong manual pressure on a glucose filled syringe connected to the Biostator blood

inlet port gave a 7 mg/dl glucose rise in 20 sec. Five experiments (table 7) were conducted to determine if lower levels of pressure change could affect glucose readings. Pressure was varied by raising or lowering a gravity suspension system. A water filled U tube manometer was attached to measure the pressure. Tests 1, 2, and 3 used glucose solutions in normal saline in the gravity chamber. Tests 4 and 5 used heparinized blood. The chamber holding the blood was agitated periodically to keep the cells from settling. Pressure was held relatively constant between the baseline set, and increased slightly in the regulation set. Increases in glucose under these circumstances appeared to be random (P=0.5).

To further search for a pressure sensitive artifact, an experiment was conducted to determine the effect of muscle contraction in the vicinity of the indwelling venous catheter. This is shown in example 5 of table 6. The subject relaxed during B_1'. During B_2' he stretched his fingers enough to slightly raise his EMG level (only about a 7 uv. change). He continued relaxing during B_3'. During R_1', without any attempt to regulate glucose, he raised his arm just enough to significantly alter his EMG. This increased his glucose nearly 2 mg/dl.

It remained to be verified that the subject's arm was relaxed during an actual regulation experiment. This is shown in example 6 of table 6. The EMG was recorded, but not displayed to the subject. It was shown that the subject's arm remained relaxed during

TABLE 7

Biostator Pressure Tests

Test	Date	L mg/dl	Δ mg/dl	Med. mg/dl		N	$\bar{P}$ cm H_2O
1	3-5-78	1.3	-0.6	60.0	B_1'	5	0
				59.4	B_2'	10	1
			0.7	61.7	B_3'	5	0
				62.0	R_1'	10	5
2	3-23-78	-0.1	0.3	98.8	B_1'	3	0
				99.1	B_2'	4	1
			0.3	99.1	B_3'	3	8
				99.3	R_1'	4	15
3	3-23-78	-0.9	0.8	101.2	B_4'	2	0
				102.0	B_5'	3	0
			0.0	101.7	B_6'	2	5
				101.6	R_2'	3	20
4	6-9-78	1.6	-1.1	66.3	B_1'	6	0
				65.3	B_2'	3	0
			0.6	64.4	B_3'	6	7
				65.0	R_1'	8	19
5	6-9-78	0.9	-0.6	52.1	B_4'	3	4
				51.6	B_5'	6	4
			0.3	51.8	B_6'	3	4
				52.1	R_2'	6	7

R_2, and was in a usual state of tension during the baseline periods.

A final experiment sought to determine if somehow sympathetic tone increased during a regulation period. If so, this should be reflected in decreased hand temperature. Table 8 shows two such trials during a glucose regulation experiment. Here L refers to the differential effect on temperature. Comparing this to examples 4 and 5 of table 3 shows that hand temperature dropped 0.6 deg. in one case while glucose increased 5 mg/dl. In the second instance, hand temperature increased 0.8 deg. while glucose increased slightly over 3 mg/dl. These results suggest no significant change in sympathetic tone during glucose regulation.

3.7 Natural blood sugar rhythms: Discrete and continuous subject baseline glucose data were analyzed for periodic trends by autocorrelation. Such trends, if present, are of interest in aiding interpretation of glucose feedback data, and also from a glucose control system viewpoint. Details of the analysis are provided in appendix C. Results of the analysis are summarized in table 9. To give an estimate of the size of baseline glucose changes, the standard deviation (S) and mean ($\bar{X}$) of the data samples are given. The last columns show two estimates of the periodic trends in the data (T_1, T_2). Neither estimate is considered better than the other. In some cases a value for T_2 could not be calculated because there were too few data points available, or the data showed little evidence of periodicity.

TABLE 8

Effect of Voluntary Glucose Regulation

on Hand Temperature

Example	Subj.	Date	L deg. F.	Δ deg. F.	Med. deg. F.		N
1	C.C.	12-14-77	-0.6	-0.7	90.4	B_1	7
					89.6	R_1	15
				-0.1	89.1	B_2	7
					88.9	B_3	15
2	C.C.	12-14-77	0.8	0.7	88.3	B_4	8
					89.0	R_2	14
				-0.1	89.1	B_2	7
					88.9	B_3	15

TABLE 9

Periodic Trends in Baseline Glucose Data

Example	Figure	N	Sample Interval min.	Instrument	Subj.	Date of Exp.	S mg/dl	$\bar{X}$ mg/dl	Estimated period T_1 min.	Estimated period T_2 min.
1	13	30	1	Beck.	Base	2-2-77	1.7	96	15	13
2	14	64	2	"	R.	6-2-76	1.9	89	12	-
3	14	65	2	"	R.	7-8-76	2.8	90	10	-
4	15	30	2	YSI	Base.	2-2-77	0.9	100	34	38
5	15	62	2	"	C.C.	1-24-77	4.0	100	45	37
6	16	80	2/3	Biost.	A.T.	11-3-77	0.7	78	76	-
7	16	48	2	"	A.T.	11-3-77	0.9	79	31	30
8	17	80	2/3	"	A.T.	11-10-77	0.1	70	25	-
9	17	59	2	"	A.T.	11-10-77	1.1	69	44	45
10	18	40	2	"	T.H.	10-27-77	2.1	79	66	-

TABLE 9
Continued

Example	Figure	N	Sample Interval min.	Instrument	Subj.	Date of Exp.	S mg/dl	$\bar{X}$ mg/dl	Estimated period T_1 min.	Estimated period T_2 min.
11	18	62	2	Biost.	T.H.	11-7-77	1.4	76	68	-
12	19	48	2	"	T.H.	12-5-77	1.5	77	40	44
13	19	38	2	"	M.L.S.	7-20-77	0.7	80	21	44
14	20	33	2	"	M.L.S.	8-2-77	3.2	95	77	-
15	20	45	2	"	M.L.S.	8-12-77	1.0	79	61	61
16	21	40	2	"	J.K.	4-13-78	0.6	83	38	45
17	22	42	2/3	"	J.K.	3-17-78	0.8	66	18	-
18	22	41	2/3	"	J.K.	3-17-78	1.3	47	12	10

Most of the data were sampled at 2 minute intervals. Samples taken at 40 sec. intervals from some sessions are given for comparison. It is seen that data for the faster sampling rate gives different periodicity estimates for the same session. This is a consequence of noise in the data, and the fact that the number (N) of 40 sec. samples was more than the number of 2 min. samples. Baseline tests of the clinical analyzers using glucose standards are given in examples 1 and 4. Future studies should include autocorrelation analysis of Biostator baseline data in order to determine if baseline drift introduces any artificial rhythms in the data.

With the exception of example 13, the paired estimates of the periods for each subject are reasonably close, suggesting that there may be natural rhythms in baseline blood glucose. These rhythms may have periods ranging from 30 to 60 minutes. Some of the Biostator data for which only one estimate of the period was available, indicates there may be periods exceeding one hour. As pointed out in Appendix C, these results are very tentative in that the length of the data sequences analyzed were too short in relation to the cycles involved. The high noise level of the data prohibits good estimates of the periods under these circumstances.

Examples 17 and 18 are given for comparison. They are the R_1 and B_1 periods respectively of a glucose regulation experiment. The periods are shorter than for pure baseline runs for the same or other subjects.

4. DISCUSSION

Median glucose levels increased a few mg/dl during regulation periods in all three subjects tested. There were a sufficient number of trials to test for statistical significance in two of the subjects. The one subject (J.K.) whose results were significant was a highly sophisticated person in many types of biofeedback. There are no known studies on the effect of one type of feedback training on learning another, but it is presumed that there is an enhancement effect. Though the two subjects had about the same number (10 and 11) of continuous feedback sessions;* in addition J.K. had 12 sessions of discrete glucose feedback over a period of a year. This also may have contributed to her higher significance levels. All the glucose feedback sessions were evaluated with equal weight including those wherein the subjects were learning the task. Both subjects exhibited fatigue by the end of a long and difficult series of experiments. Two trials were conducted with a third subject. Both showed a positive effect on glucose.

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* See Table 1. Note There may be more than one trial per session, also some trials did not meet acceptance criteria and were not analyzed though they may have contributed to learning.

It was suggested in this study that relaxation helps to increase glucose levels. This tends to confirm a hypothesis (Pelletier, 1975), that "a meditative state of deep relaxation is conducive to the establishment of voluntary control ... ." Therefore, the intuitive strategy of training the subjects in EMG relaxation prior to glucose feedback training may have been helpful. It should be noted that each of the glucose regulation subjects had experience with EEG alpha wave feedback which should also enhance relaxation skills. Autogenic training may be conducive to similar internal states that the subjects learned to induce with glucose feedback. It is difficult to attribute any clinical significance to the levels of glucose increases reported here.

Certain control experiments were performed. The effect of food taste was found to have no effect on blood sugar. This is in accord with reports of other investigators that sight and smell (Parra-Covarrubias, 1971), and taste (Penick et al., 1966) of food didn't affect blood glucose levels. Goldfine et al. (1970) found similar results with hypnotic suggestions of hunger or food.

There was concern that the subjects could be causing an apparent glucose change by raising their hand temperature. McGuire et. al. (1976) have reported a 3 mg/dl arteriovenous difference in glucose in fasting humans. By warming the hand in a 68 deg. C air chamber, arterial blood was shunted to a dorsal hand vein. Venous blood thus arterialized was found to be 2 mg/dl higher than venous blood. In one control experiment in the present study, it was shown that there was no glucose change due to raising the ambient hand temperature. Dorsal hand veins were never used for blood sampling in glucose regulation experiments. Another control experiment demonstrated that glucose increased during a regulation period, despite the previous raising of ambient hand temperature. Thus shunting of blood was not considered to be an artifact in this study.

Of more concern was the finding that the Biostator membrane was pressure sensitive. This was determined to be unimportant at antecubital pressure levels of venous blood which are around 7 mm of Hg. However, muscular contractions

in the vicinity of the catheter, that might cause changes in blood flow to the Biostator, were shown to increase apparent glucose readings. A control experiment was performed in which it was demonstrated that a subject could raise blood sugar while maintaining muscle relaxation. Similar EMG controls should probably be applied to all glucose regulation experiments. An electromyograph was not available for most of the experiments reported here. To simultaneously give EMG with glucose feedback could interfere with the learning phase of glucose regulation.

Finally, evidence was presented that there may be natural cycles of glucose change. Periodic secretion has been reported in humans for luteinizing hormone (Nankin and Troen, 1971), growth hormone (Sassin et. al., 1969), and ACTH (Liddle, 1966) from the pituitary, and melatonin (Lynch et. al., 1975) from the pineal. Secretion of the later three hormones seems to be related to sleep cycles. Goodner et. al. (1977) using autocorrelation, reported oscillations in monkeys of a 9 min. period for fasting insulin, glucagon, and glucose. Glucose analysis was by ferricyanide reduction (Technicon Instruments). The amplitude of the reported glucose changes was on the same order as found here.

The length of possible glucose cycles reported here, with 6 subjects, was variable and ranged from 0.5 to 1 hr. or more. This raises the possibility that such cycles could be simulating

glucose regulation. Great care was taken in the development of an analytical technique for the glucose regulation data, to negate the influence of random glucose fluctuations. It would be expected that any systematic fluctuation in blood glucose would not always be synchronized with glucose regulation periods. Three out of three subjects showed glucose changes in predominantly one direction. It would be expected that natural glucose cycles of greater than 30 minutes would tend to influence a regulation period and its baseline (of about 15 minutes each) in both directions about equally. The probability of the influence being in only one direction for the two subjects tested, is P=0.01 and 0.34.

An argument in favor of natural rhythms masking as regulation is the observation that the glucose changes found in the baseline studies are on the same order of magnitude as changes found during regulation experiments. Such natural rhythms could also be working against actual regulation by a subject. The question of the authenticity of voluntary glucose regulation could be settled in future experiments if allowance is made for enough glucose baseline runs (to be statistically significant) prior to feedback training. The data could be analyzed for differential effects as in a regulation experiment, but with L composed of four baseline periods instead of three baseline periods and a regulation period.

There are several mechanisms by which the rise in glucose observed during regulation periods could have occurred. Associated with sympathetic activation, a rise in glucose is generally observed. In their review, Woods and Kulkosky (1976) warn that venipuncture is associated with sympathetic activation. Thus, care was taken in these experiments to allow the subjects to adapt to such effects. Two glucose regulation trials were conducted while hand temperature was monitored. Sympathetic activation should have caused a drop in hand temperature. No consistent drop was observed. The relaxed state induced by the subjects, accompanied by a rise in glucose appears paradoxically to be associated with reduced sympathetic tone or parasympathetic effects. Vagal stimulation increases both insulin and glucagon secretion. Conditioned insulin release is abolished by vagotomy or atropine. No comparable data are available for glucagon (reviewed by Gerich et. al., 1976). Thus we are left with the possibility that circulating hypothalamic factors could play a role in conditioned blood sugar increases. These include somatostatin, neurotensin, and substance P. The last two substances have been shown to stimulate glucagon and inhibit insulin release which should raise blood sugar. Another unnamed substance released from the ventromedial hypothalamus exhibits similar effects (Moltz, et. al., 1977).

APPENDIX A

CALCULATION OF DIFFERENTIAL EFFECTS

An estimate (Lehmann, 1975) of the difference between two groups of data is given by the median difference

$$\Delta_{ij} = \text{med}\ (X_{ia} - X_{jb}).$$

In this case there are four groups, therefore

$$i,j = 1,2,3, \text{ or } 4.$$

The data points are subscripted

$$a = 1,2, \ldots, n_i$$
$$b = 1,2, \ldots, n_j$$

where n_i or n_j is the total number of points in a particular group. The estimates have the property

$$\Delta_{ij} = -\Delta_{ji}$$
$$\Delta_{ii} = 0.$$

An example of the estimated differences between the first two groups, with three points in the first group and four points in the second group, is given by the median in the following array of differences

$$\Delta_{12} = \text{med} \begin{bmatrix} X_{11} - X_{21}, & X_{12} - X_{21}, & X_{13} - X_{21} \\ X_{11} - X_{22}, & X_{12} - X_{22}, & X_{13} - X_{22} \\ X_{11} - X_{23}, & X_{12} - X_{23}, & X_{13} - X_{23} \\ X_{11} - X_{24}, & X_{12} - X_{24}, & X_{13} - X_{24} \end{bmatrix}.$$

An estimate useful in this case for finding a linear contrast between

four groups containing unequal number of data points is the weighted average

$$\Delta_{i*} = \frac{1}{N} \sum_{j=1}^{4} n_j \Delta_{ij}$$

where N = sum of number of points in all four groups. For example (recalling that $\Delta_{11} = 0$)

$$\Delta_{1*} = \frac{n_2 \Delta_{12} + n_3 \Delta_{13} + n_4 \Delta_{14}}{N} .$$

Using these estimates, a linear contrast (L) between the four groups can be calculated. For example

$$L = (\Delta_{2*} - \Delta_{1*}) - (\Delta_{4*} - \Delta_{3*}).$$

In the context of this report for example

$$\Delta_{2*} = R_1$$

$$\Delta_{1*} = B_1$$

$$\Delta_{4*} = B_3$$

$$\Delta_{3*} = B_2 .$$

The analytic method for discrete data just described assumes that the data points are mutually independent. This assumption is inherent in most statistical analyses of discrete data whether parametric or non parametric. Scheffe' (1959) reports there is a marked increase in type 1 error (the probability of finding a result significant when there is no true difference) with autocorrelations (of lag k=1) as high as $\pm$ 0.4. Samples of such correlations of the Biostator data usually exceeded this (on the order of 0.7 to 0.9). This is common for time series data. For this reason no attempt was made to specify confidence intervals for the L values.

APPENDIX B

CALCULATION OF P VALUES

The null hypothesis tested was that the L values have a probability distribution of zero mean. Due to the previously described effects of carryover and autocorrelation, the null hypothesis was tested by a method based on the sign and independent of the magnitude of the L values. The P values given in the results section are the probability of rejecting the null hypothesis based on a two sided sign test applied to the L values obtained. For purposes of the sign test, L values were calculated to one decimal point; L values $|\pm 0.05|$ or less were excluded from the test. Tables for the sign test were from Lehmann (1975). Two of the assumptions on which the sign test is based are fulfilled in this study: (1) Each of the four groups composing a single L value were made under similar conditions, and (2) that different L values were made at different times. That the conditions of the third assumption (different trials were independent) were fulfilled is dependent on how much a regulation trial influenced baseline periods of later trials. Such an influence occurred occasionally. However, the net effect in such cases would have been an underestimate of the effect of regulation.

APPENDIX C

AUTOCORRELATION ANALYSIS

To determine if there were natural rhythmic fluctuations which might have obscured the interpretation of glucose regulation data, baseline data were subjected to autocorrelation analysis. This determines the degree to which a series of data points shifted with respect to the entire series tend to co-vary over time. This is done for a series of progressively increasing shifts (or lags) beginning with zero. The successive values of the covariations taken over the time lags (k) reveal any tendency of the time series to oscillate periodically.

The measure of the degree of autocorrelation is the autocorrelation coefficient (r_k). This is analogous to a standard correlation coefficient which compares two distinct series. Similarly, the values of r_k range from one, for high positive correlation, through zero for no correlation, to negative one for negative correlation.

The values of r_k reveal how the correlation changes as the data points are shifted. This process is illustrated in table 10 for a set of 13 data points. More points would be required for an actual calculation because a point is dropped from the end of the series for each increment in k. If the data series were compared point by point with itself, the lag (k) would be zero, and $r_0 = 1$. Now if the series is compared with the data points once removed (lag k=1), a slight positive correlation (r_1) is obtained. For k=2, the data set is shifted twice to the right,

TABLE 10

Illustrative Autocorrelation Calculations

for time series data with a period = 4

r_k	k	DATA												
1.000	0	1	2	3	2	1	2	3	2	1	2	3	2	1
0.010	1		1	2	3	2	1	2	3	2	1	2	3	2
-0.857	2			1	2	3	2	1	2	3	2	1	2	3
-0.014	3				1	2	3	2	1	2	3	2	1	2
0.708	4					1	2	3	2	1	2	3	2	1
0.007	5						1	2	3	2	1	2	3	2

and is at maximum apposition to the first set. The value of r_2 reaches a maximum negative. For k=3, the negative correlation declines. When k=4, the data are again in register with the first set. The value of r_k has declined however from 1 to 0.708 because four terms have been dropped from the series.

Calculation of the autocorrelation function: It has been concluded (Box and Jenkins, 1970) that the most satisfactory estimate of the kth lag autocorrelation is

$$r_k = \frac{C_K}{C_0}$$

where the estimate of the autocovariance is given by the algorithm

$$C_k = \frac{1}{N} \sum_{t=1}^{N-k} (X_t - \bar{X})\,(X_{t-k} - \bar{X}),\ k=0,1,2,\ldots,K.$$

$\bar{X}$ is the arithmetic mean of the data points (X_t) in the time series, and N is the total number of points in the series. The variance is C_0. Therefore setting k=0 in the above expression for r_k gives r_0=1. The usual nature of the function as computed above is to dampen with increasing k. In order to accommodate the available data, the requirement of Box and Jenkins (1970) that $N \geq 50$, and $K \leq N/4$ was relaxed. The effect of small N is discussed later in this appendix. To perform the autocorrelation calculations, programs were written for a Texas Instruments (TI) 59 calculator.

A convenient method of displaying the results is to plot r_k versus k. This plot is called the (estimated) autocorrelation function. As an aid in interpretation, autocorrelation functions (a.c.f.s.) of periodic (sine wave) and random data were computed. To simulate glucose data if periodic trends were present, noise was added to the sine wave data. The noise was in the form of randomly distributed random numbers added to the amplitude and phase of the sine wave. The amplitude noise was noncumulative, the phase noise was cumulative. Amplitude noise was generated by serially adding random numbers of standard deviation σa, which were normally distributed about 88 (to represent fasting glucose levels), to values of the sine function. That is the first random number was added to the sine of μ_ϕ, the second random number was added to the sine of $2\,\mu_\phi$, etc. Phase noise was generated by calculating random numbers of standard deviation σ_ϕ, normally distributed about μ_ϕ. The first data point was obtained by taking the sine of the first random number, the second data point was obtained by taking the sine of the sum of the first two random numbers, etc. To simulate periodic glucose data, autocorrelation functions of amplitude and phase noise data were calculated. The seeds used to generate random numbers in the TI program were 55 for phase and 13.5 for amplitude random numbers throughout.

Fig. 8 shows the a.c.f. of 60 data points generated by incrementing the sine function at 45 deg. intervals (μ_ϕ=45 deg.). The dashed

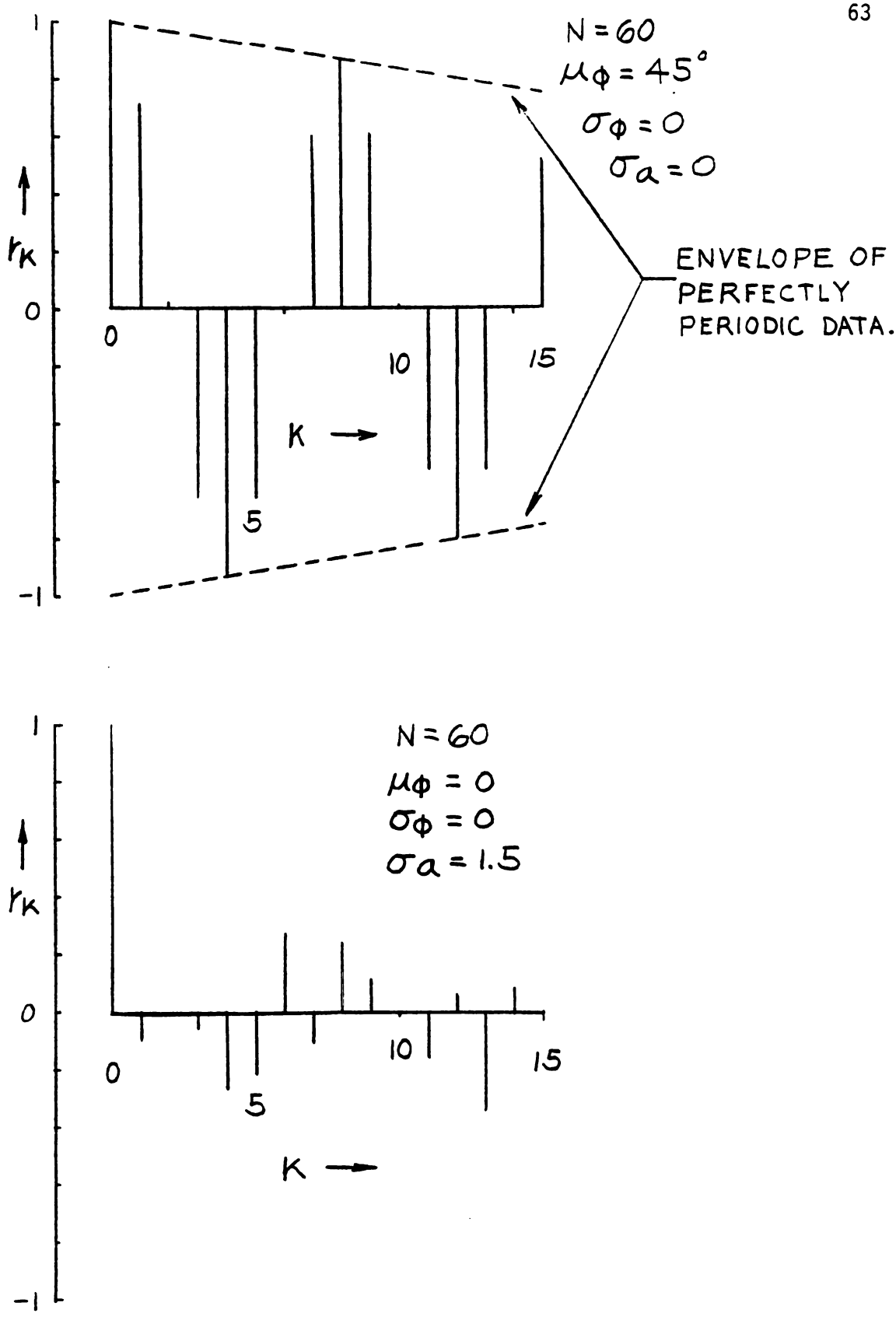


Fig. 8. Autocorrelation functions of data having a period of 8 (top), and random data (bottom).

line shows the reduction in magnitude of the correlation coefficient (r_k) at its peak values for increasing k. This reduction in magnitude of r_k is due to successive dropping of data points with increasing k by the algorithm used to generate the autocorrelation function. A periodic trend is evident from the regular recurrence of peak values of r_k. The period may be calculated by noting the k interval between peaks. In this case the actual period is 8. That is, a sine curve generated at 45 deg. intervals repeats itself every 8 points. Multiplying the period (8 points) times the frequency (45 deg/point) gives a full cycle of 360 deg. Now contrast the periodic function with the a.c.f. of normally distributed random numbers of standard deviation 1.5 shown in the bottom of fig. 8. The absence of periodic trends is evident from the lack of any systematic grouping of r_k values and their tendence to repeatedly change sign.

A more precise way of finding periodicities in the data can be determined by finding the k value of the autocorrelation function where r_k crosses zero as it changes sign. This k value is determined by linear interpolation of the two encompassing r_k values. An estimate (T_1) of the period is found by multiplying the k value of the first zero crossing by four times the sampling frequency of the data. Another estimate of the period (T_2) is obtained by multiplying the k value of the second zero crossing by 4/3 times the sampling frequency of the data. This is illustrated for the perfect (noiseless) sign wave in ex. 1 of table II. The first crossing of the abscissa occurs around k=2, the second crossing around k=6. This

TABLE II

Parametric Analysis of Wave Model

Example	Figure	N	μ_ϕ deg.	σ_ϕ deg.	σ_a	Estimated Period* T_1	Estimated Period* T_2	Actual Period*
1	8	60	45	0	0	8	8	8
2	9	60	18	0	0	21	20	20
3	9	60	18	9	0.5	18	21	20
4	10	60	18	9	0	22	21	20
5	10	30	18	9	0	24	26	20
6	11	60	18	0	0.5	19	19	20
7	11	30	18	0	0.5	17	16	20
8	12	60	18	36	0	25	17	20
9	12	60	18	0	1.5	13	7	20
10	8	60	0	0	1.5	4	7	-

* In minutes.

gives values of T_1 and T_2=8.

Example 2 of table 11 shows a similar calculation for a perfect sine curve incremented at 18 deg. intervals. Such a curve has an actual period of 20 (18 X 20=360 deg.). The T_1 estimate of 21 would have improved for larger N.

Example 3 shows that relatively low values of combined phase and amplitude noise slightly distort the estimates of the period.

Example 4 shows the effect of low phase noise ($\sigma_\phi = \frac{\mu_\phi}{2}$) alone on the period estimates. Reducing the number of data points (N) in the calculation of the autocorrelation function accentuates the effect of the phase noise (ex. 5). Example 6 shows the effect of low amplitude noise (σa=0.5) alone which is intensified by reduction in N (ex. 7). Example 8 gives the effect of relatively high phase noise ($\sigma_\phi = 2\mu_\phi$) and example 9 is high amplitude noise. Example 10 shows the effect of the noise of example 9 without any built in periodicity.

Note the similarity of the autocorrelation function of ex. 9 (fig. 12 bottom) to the imagined combination of the a.c.f.s. of ex. 2 (fig. 9 top) and ex. 10 (fig. 8 bottom). If the number of data points (N) in the sample is not increased, the a.c.f. of periodic data would approach pure noise with increasing σa. Conversely, periodic behavior if present, can be elicited from noise, if the N is increased sufficiently.

Prior to calculation of the autocorrelation functions of a set of

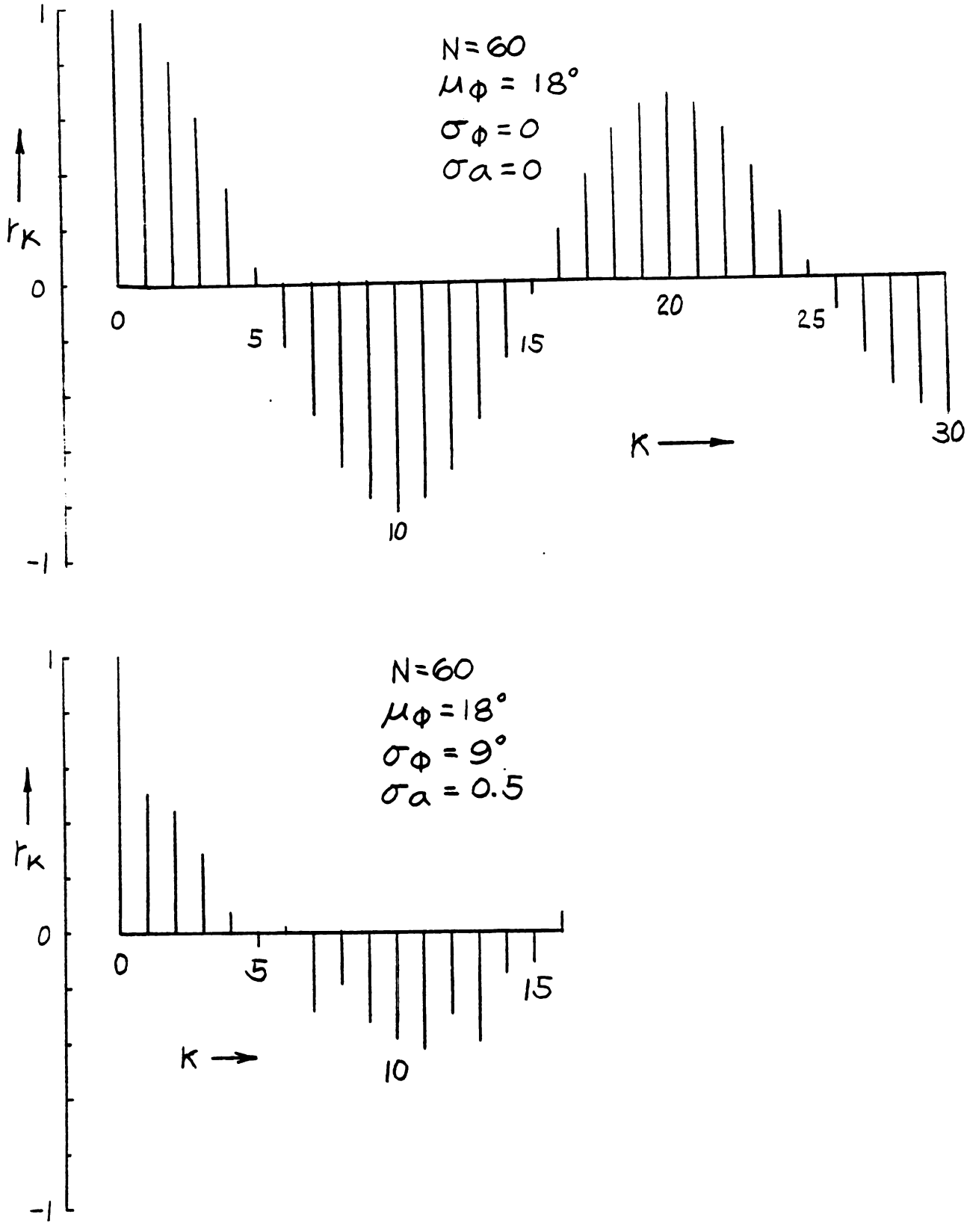


Fig. 9. Autocorrelation functions of data of period=20, with k carried out to N/2 (top), and with low phase and amplitude noise added (bottom).

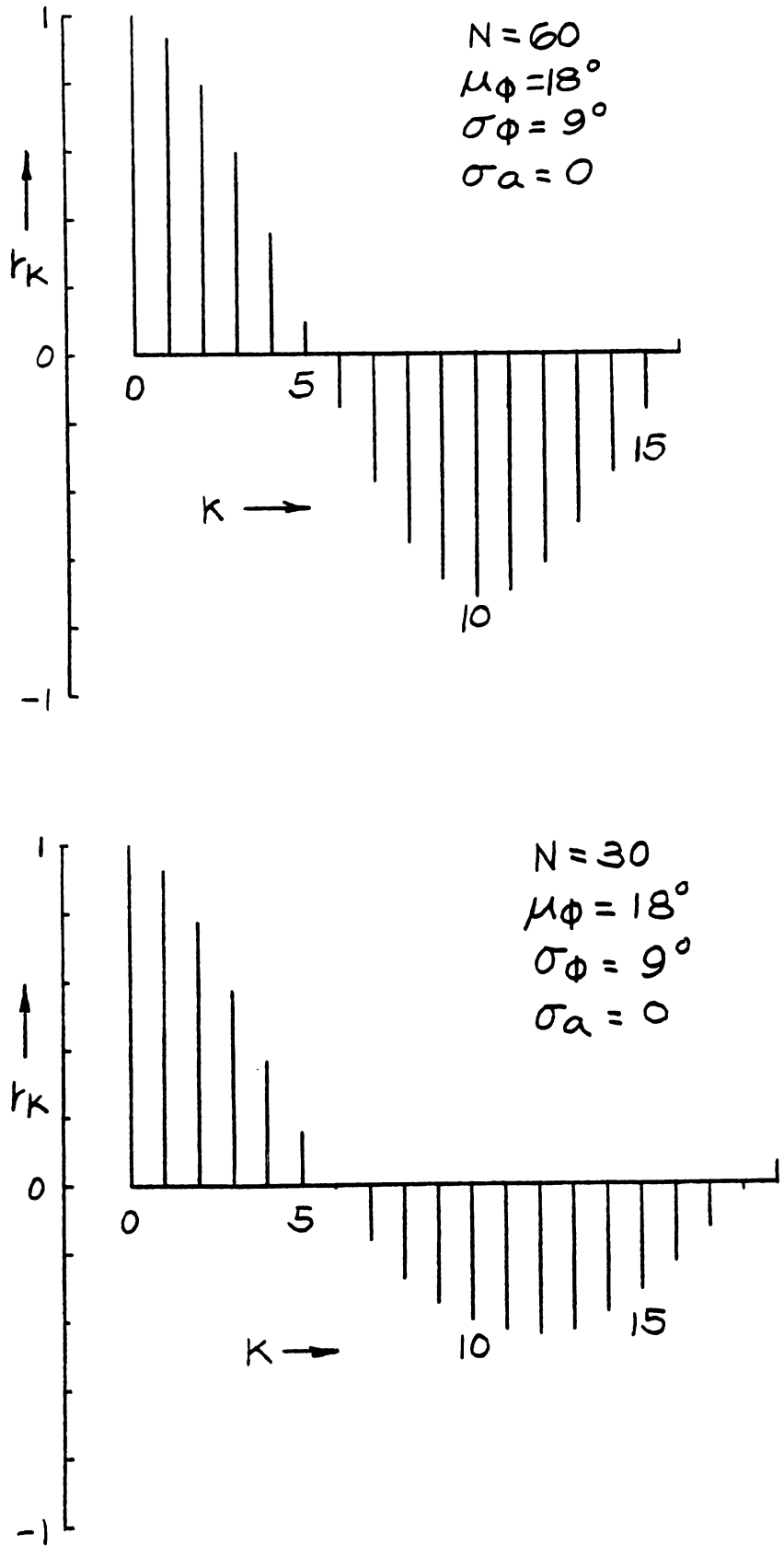


Fig. 10. Autocorrelation functions of periodic data with phase noise, showing shift due to reduction in number of data points (N).

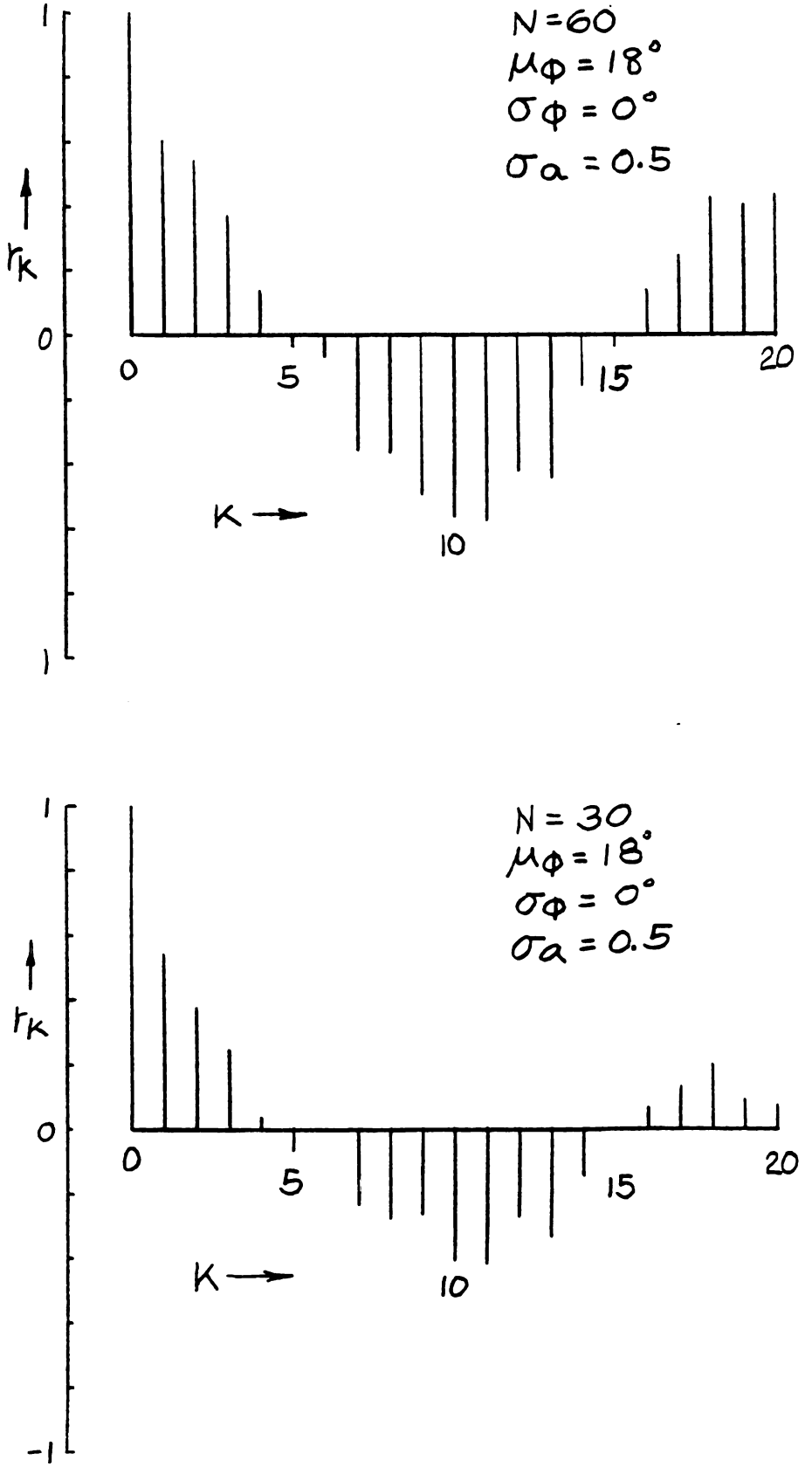
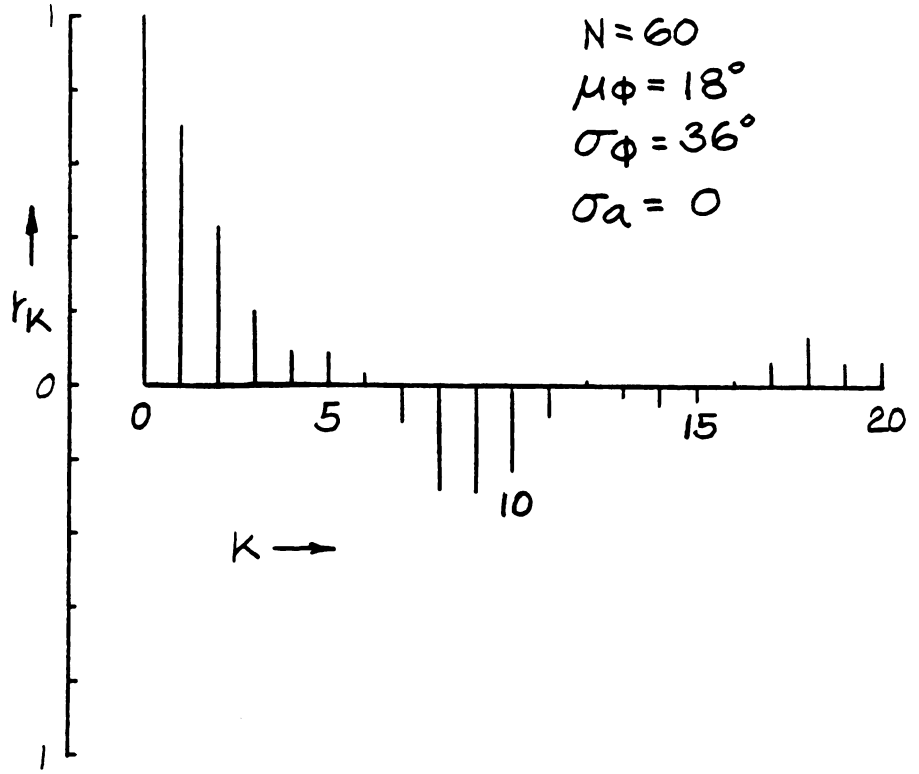


Fig. 11. Comparison of autocorrelation functions, having different N, both with amplitude noise.



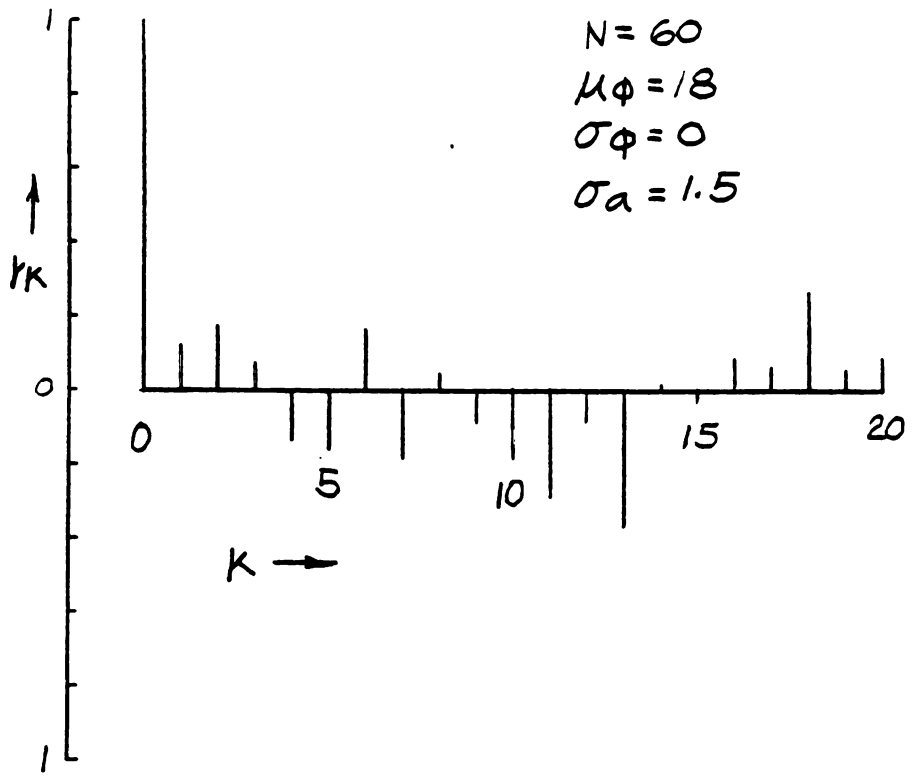


Fig. 12. Autocorrelation functions of periodic data with high phase noise (top), and high amplitude noise (bottom).

actual glucose data, a least squares linear fit was made to the data. The linear estimate of this fit was subtracted pointwise from the data. The a.c.f.s. of glucose baseline data are given in figs. 13 to 22, and summarized in table 9. The limited number of data points making up these samples in the presence of high noise levels in the data make accurate determination of underlying periodic behavior difficult.

Fig. 13 shows the a.c.f.s. of only 30 samples of Beckman baseline data using a 100 mg/dl glucose standard. The estimates of T_1 and T_2 indicate that the analyzer may by random drift be introducing rhythms of a period between 13 to 15 min. Figs. 14 show only random noise. As a matter of curiosity, notice that the direction of the r_k values is the same for the first 12 values of k in the top and bottom parts of fig. 14 (P=0.00024). Fig. 15 (top) shows YSI baseline data taken in an analogous manner to that described for the Beckman. While there is some tendency for the values of r_k to group, no satisfactory estimate of a period can be deduced. The first crossing in fig. 15 (bottom) is difficult to assess. The crossing at k=6 is probably false because thereafter the r_k values continue positive. A similar problem of false or indeterminate crossing occurs in the bottom part of fig. 16. To conclude that the crossing at k=9, represents periodicity in fig. 16 (top) is hazardous, for the limited amount of data used. What is shown is a gradually declining r_k with only one crossing. To draw any conclusion from fig. 17 (top) is difficult, because of the low values of r_k after the first crossing at around 9.5. The functions in fig. 18 (top) and figs. 19 are based upon too small of sample (N). Fig. 18 (bottom) shows some evidence of periodicity (T_1), but the absence of a second crossing eliminates the possibility of calculating T_2. A good

example of periodic behavior is seen in fig. 20 bottom (ex. 15, table 9). The values of r_k are well grouped and of reasonable size. The estimated periods are the same (61 minutes). Because the data for the functions shown in figs. 22 were taken during a feedback regulation session, the results are not useful for evidence of periodicity.

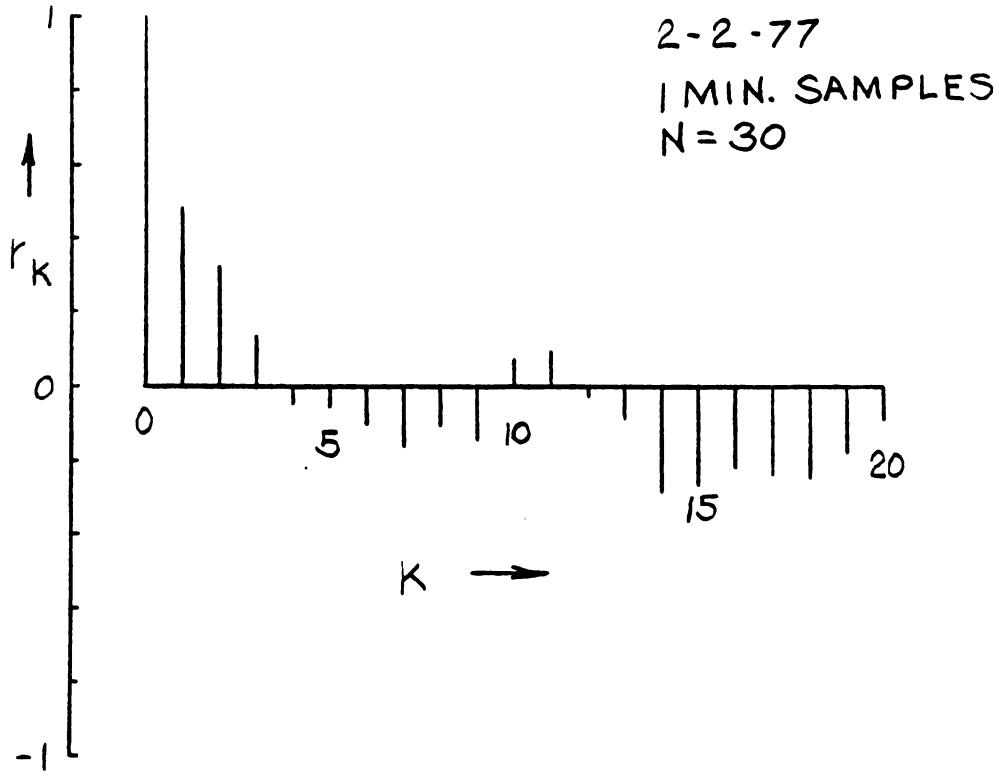


Fig. 13. Autocorrelation function of Beckman glucose analyzer baseline data.

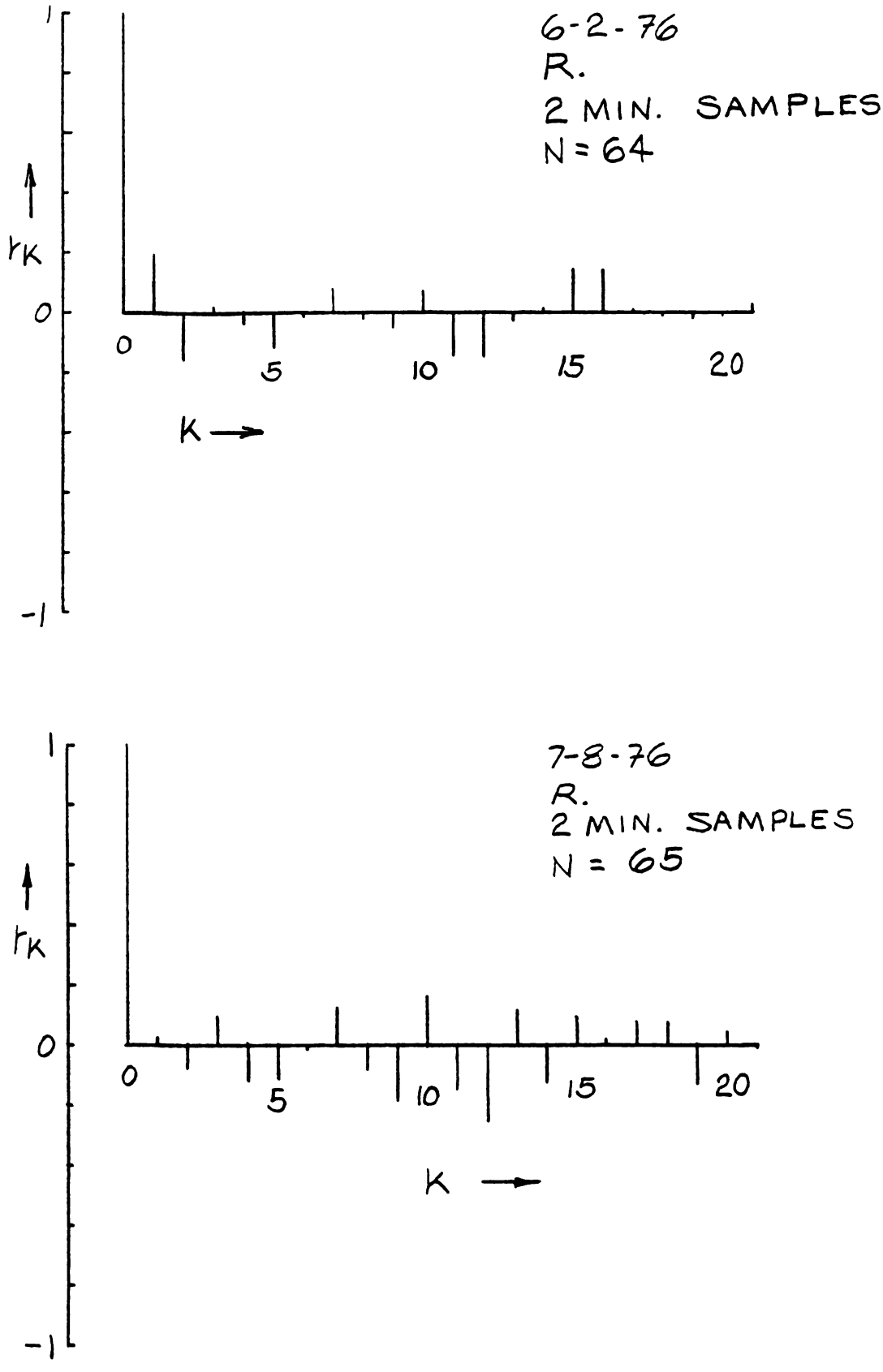


Fig. 14. Autocorrelation functions of subject baseline data using the Beckman analyzer.

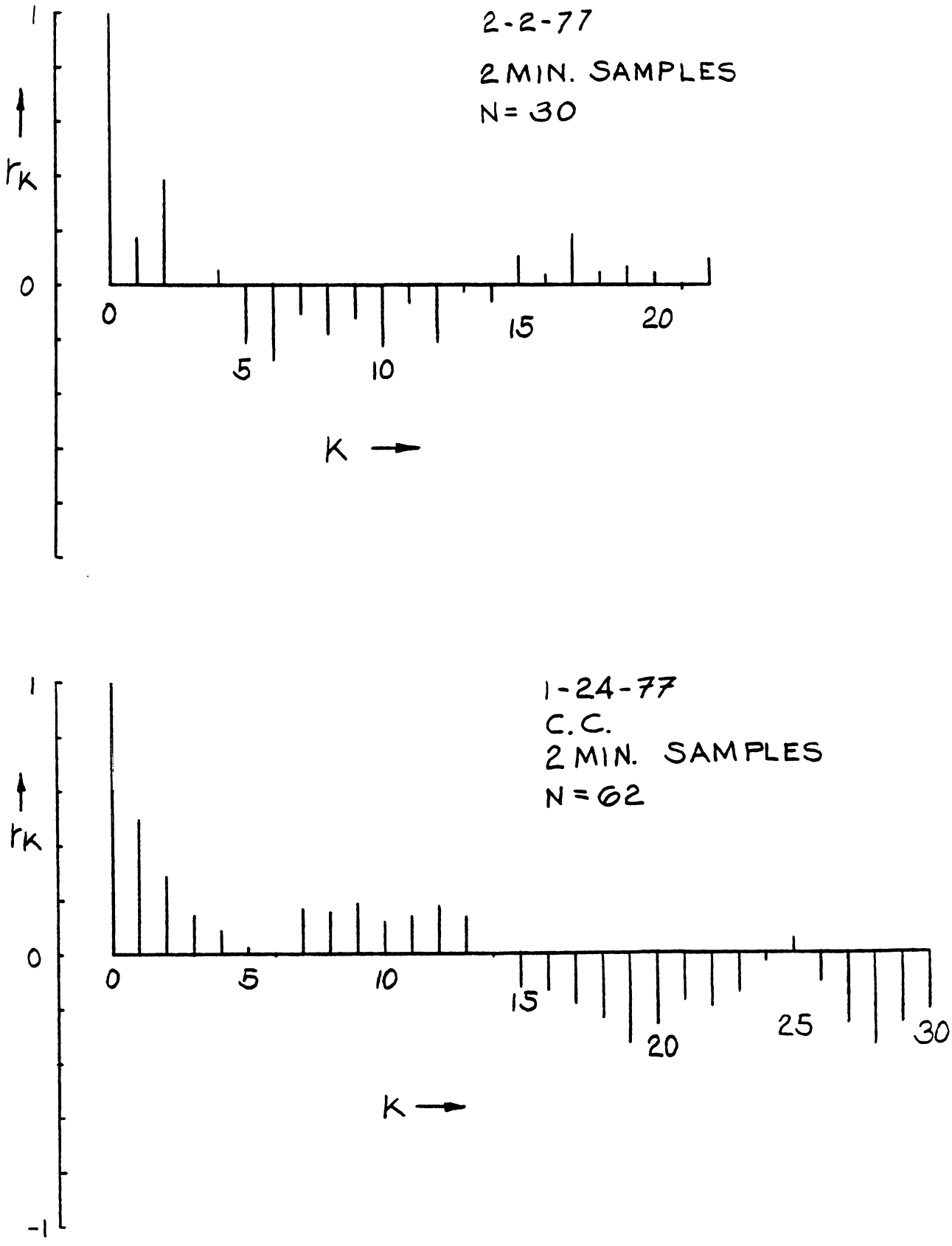


Fig. 15. Autocorrelation functions of YSI analyzer baseline data (top), and subject baseline data (bottom).

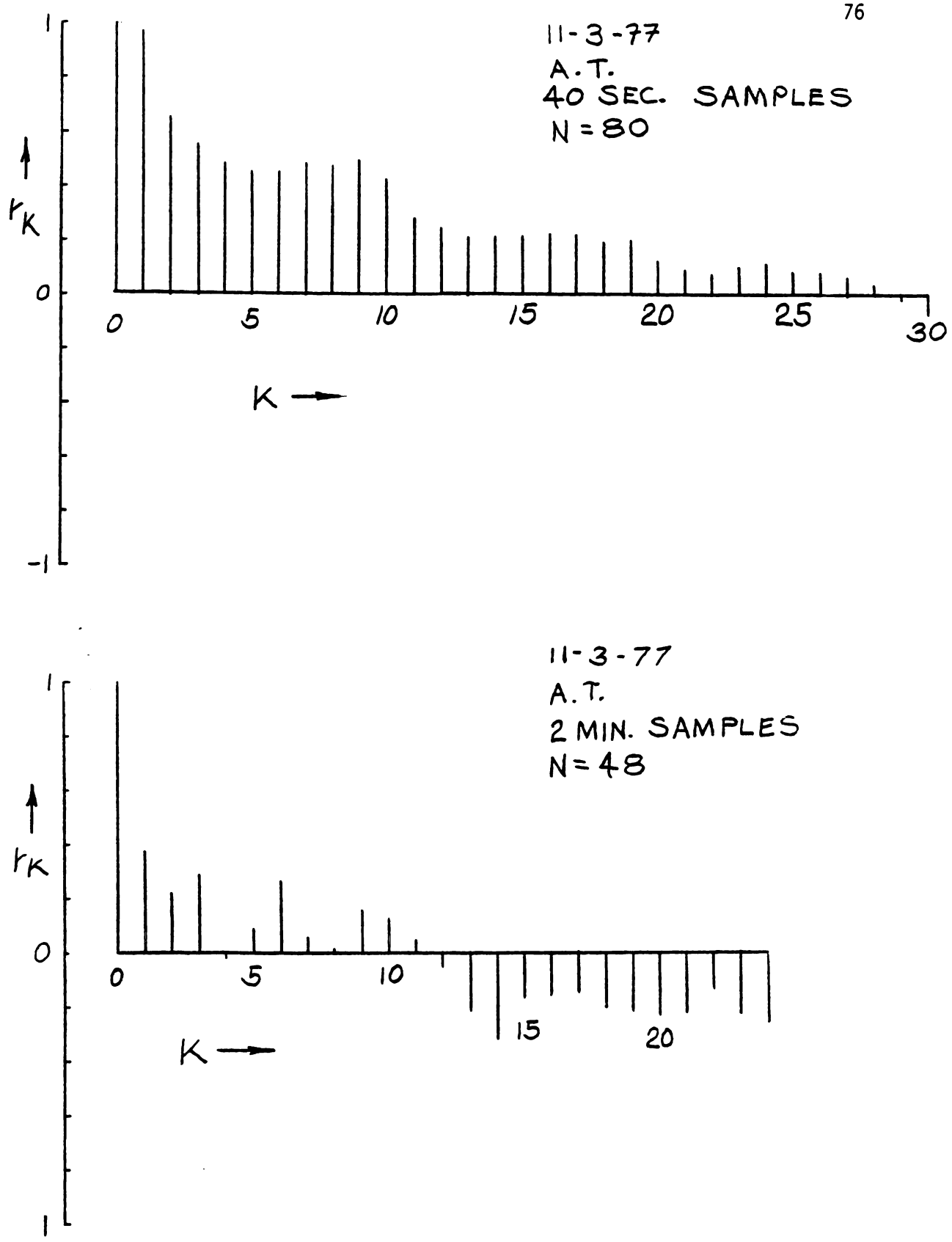


Fig. 16. Autocorrelation functions of Biostator subject baseline data. The same session was sampled at 40 sec. intervals (top), and 2 min. intervals (bottom).

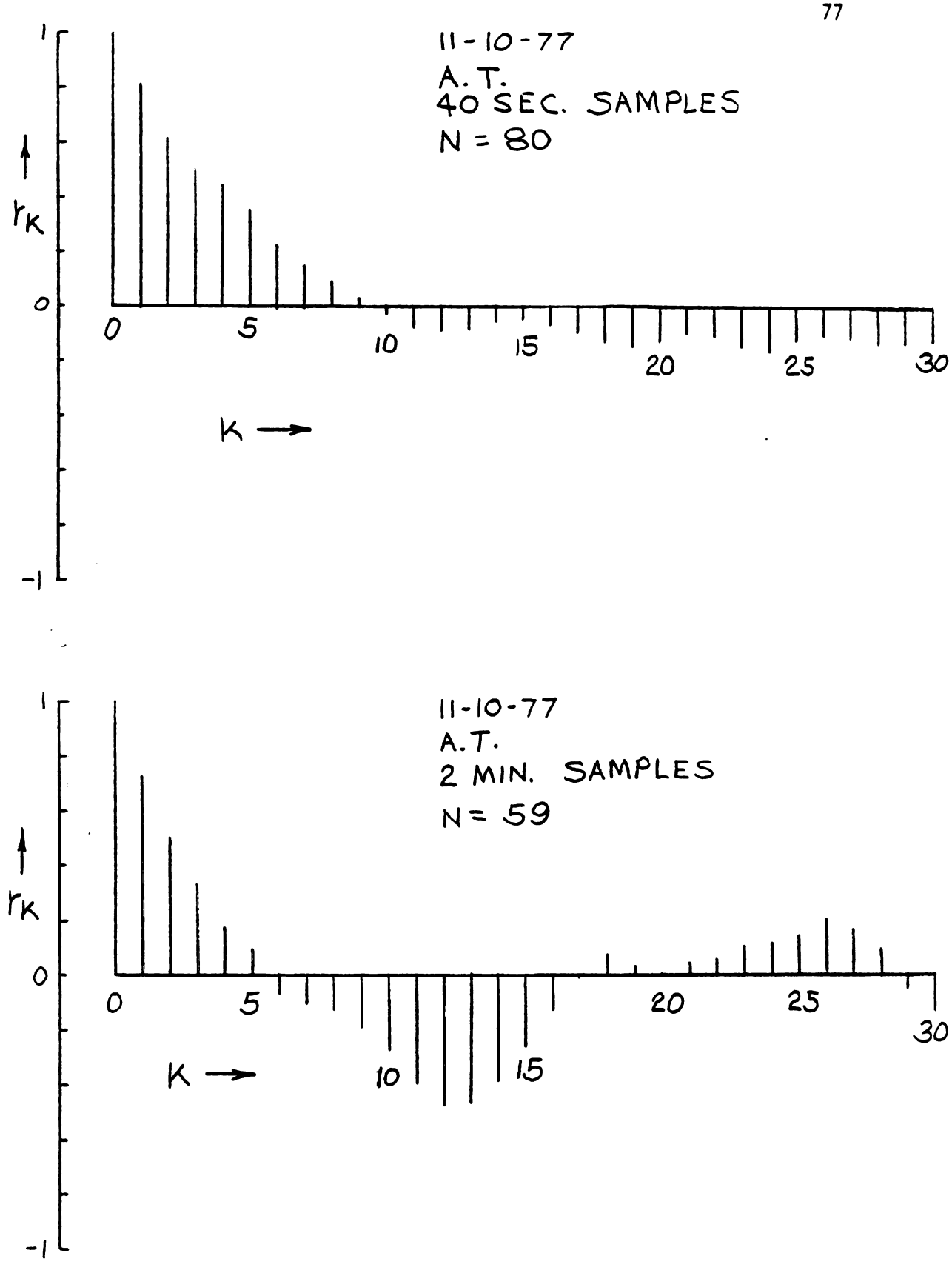


Fig. 17. Autocorrelation functions of Biostator subject baseline data. The same session was sampled at 40 sec. intervals (top), and 2 min. intervals (bottom).

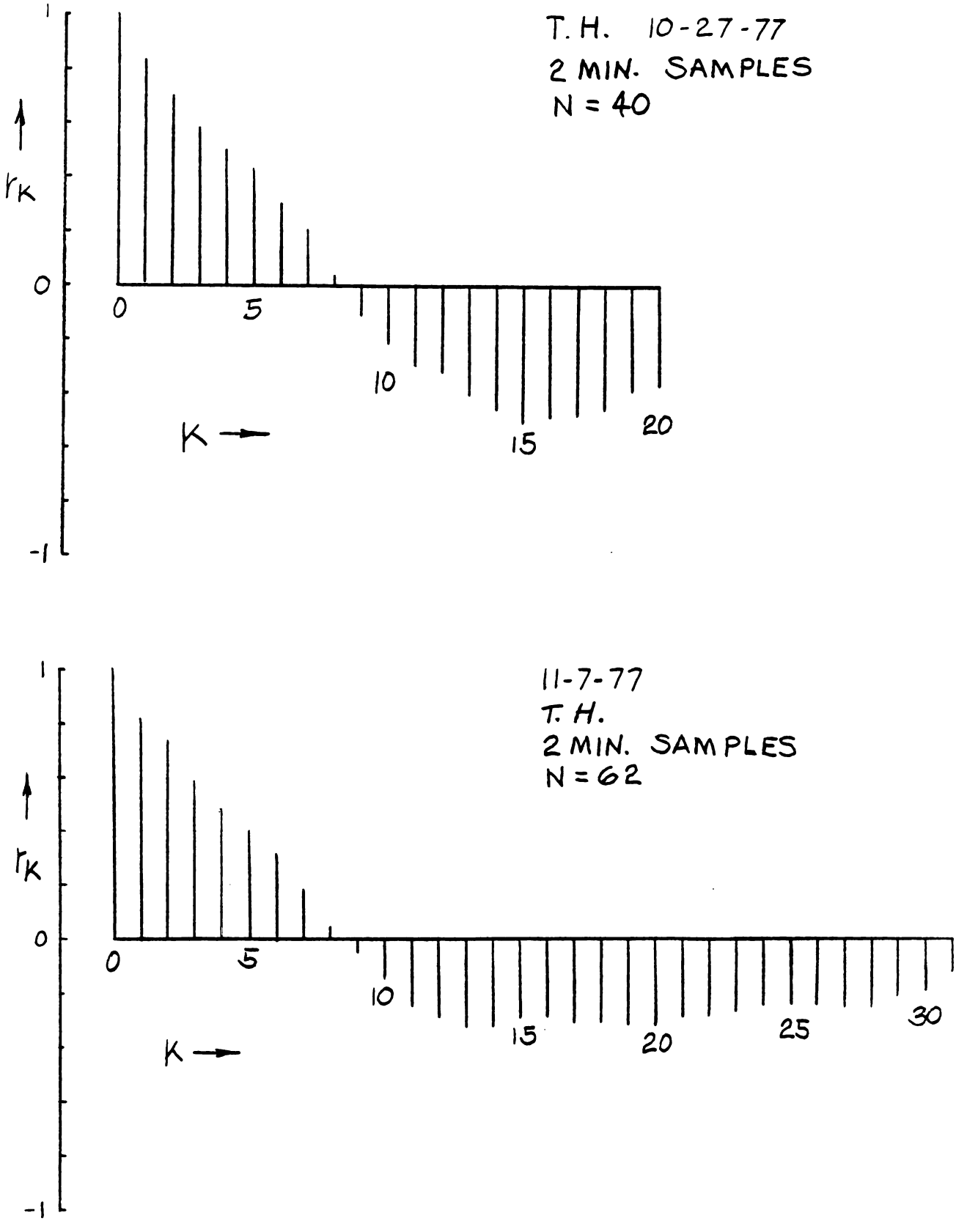
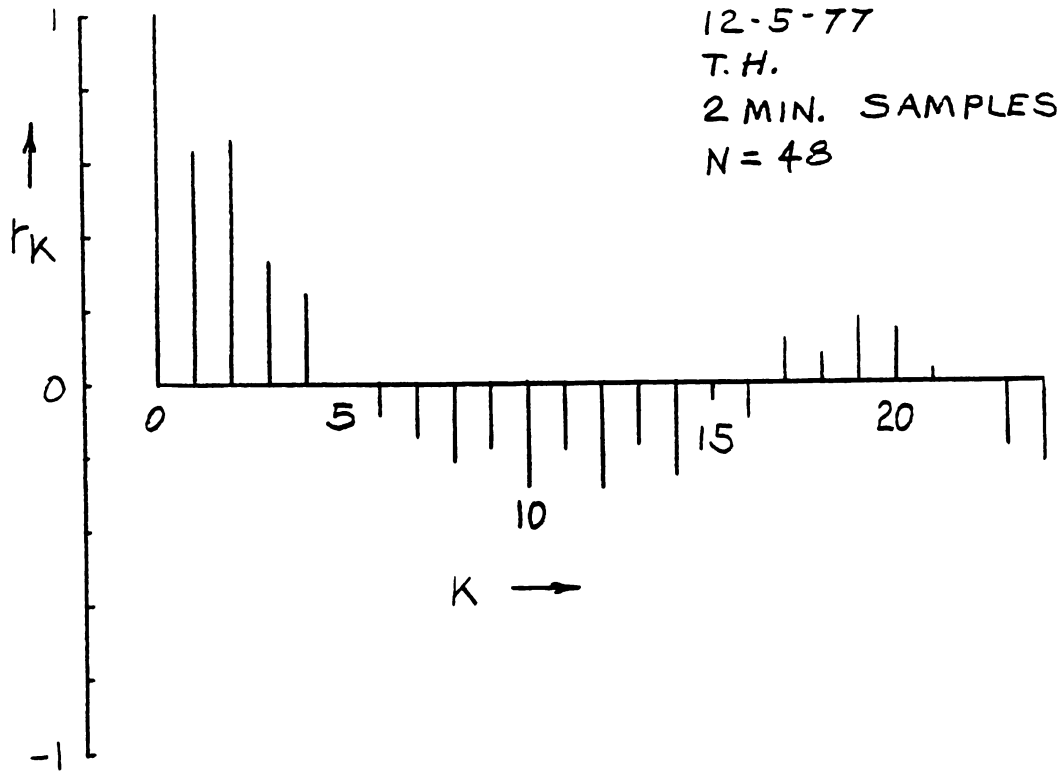


Fig. 18. Autocorrelation functions of Biostator subject baseline data.



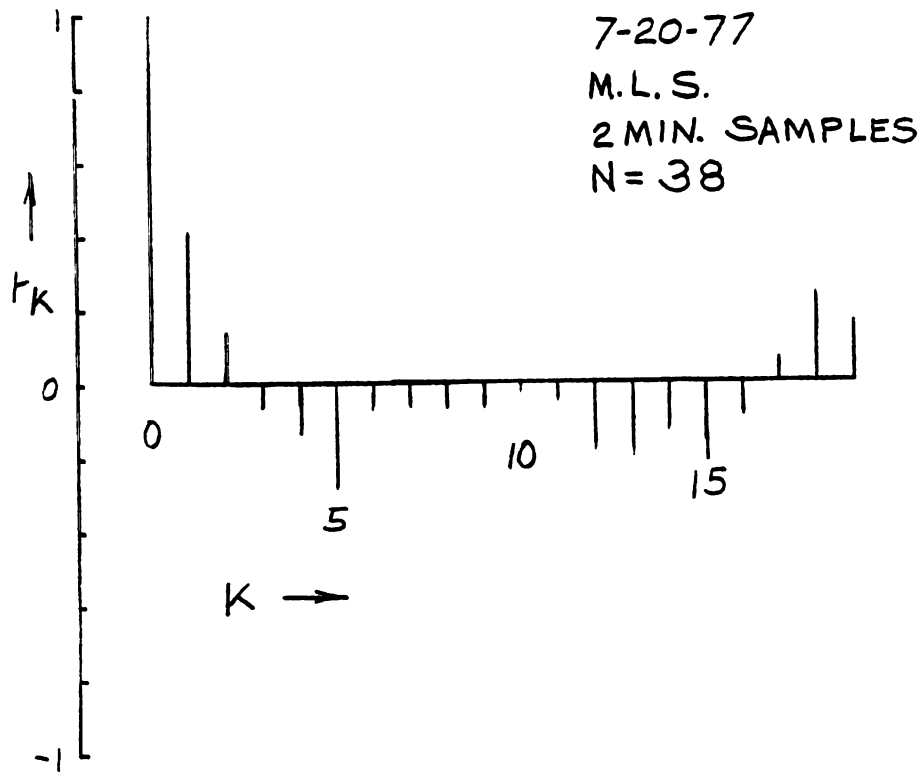
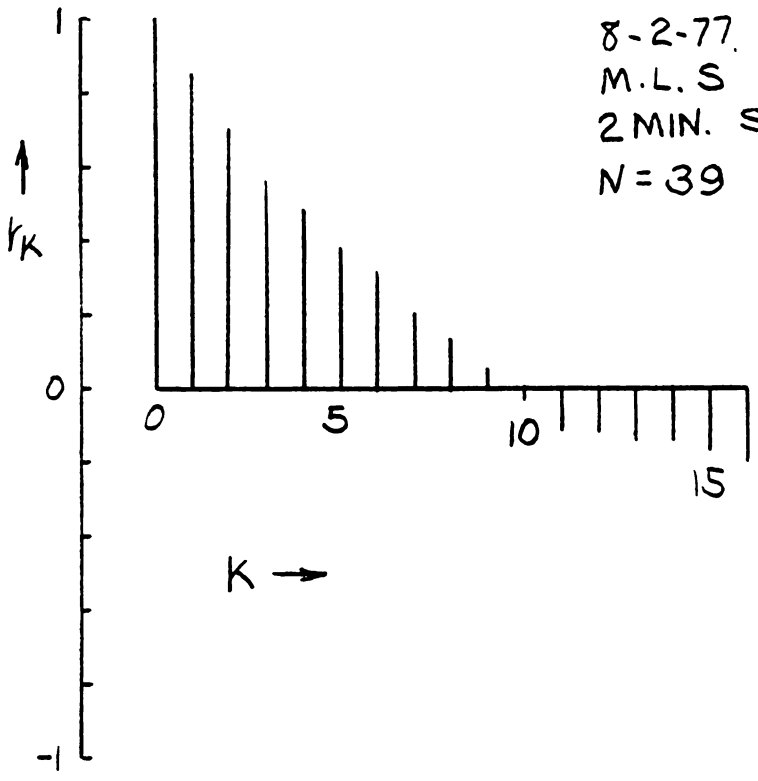


Fig. 19. Autocorrelation functions of Biostator subject baseline data.



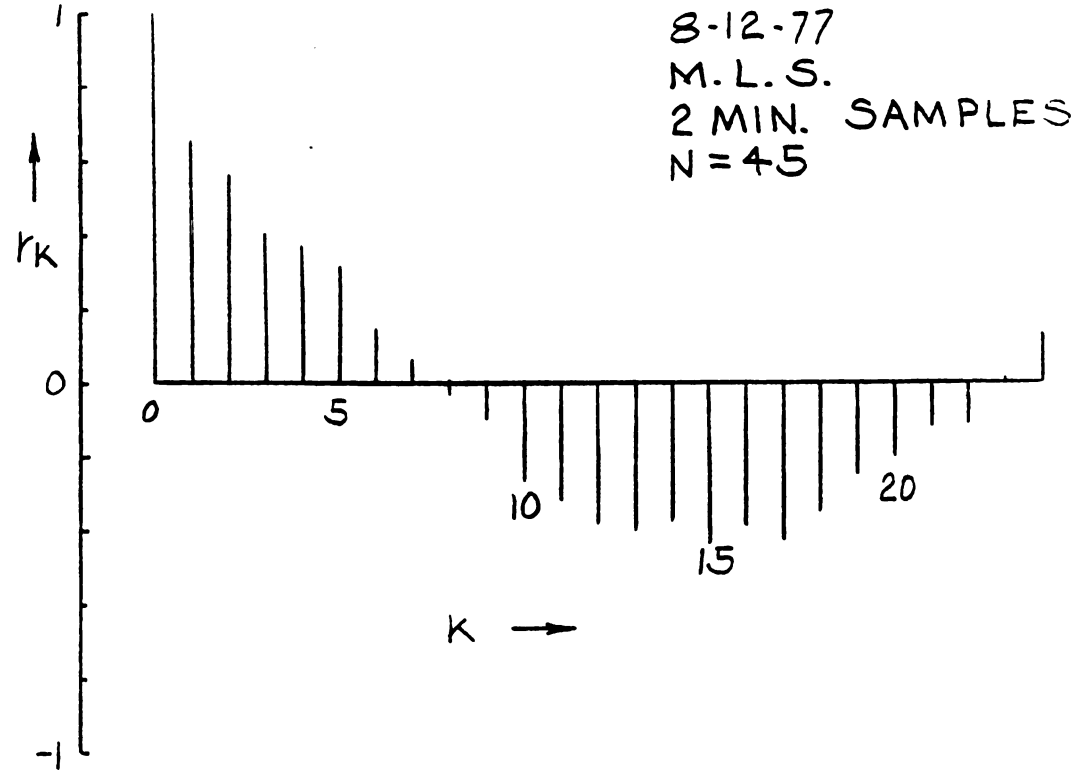


Fig. 20. Autocorrelation functions of Biostator subject baseline data.

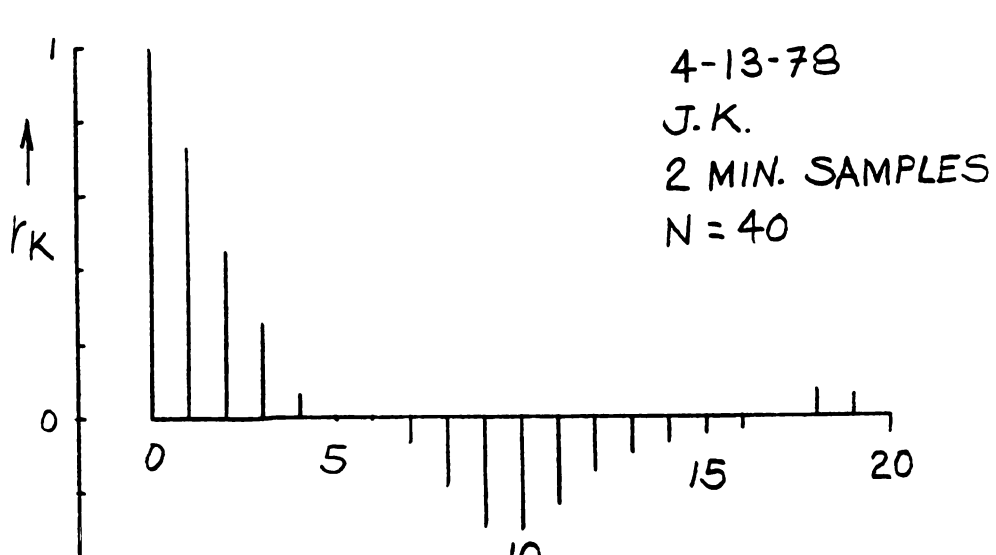


Fig. 21. Autocorrelation function of Biostator subject baseline data.

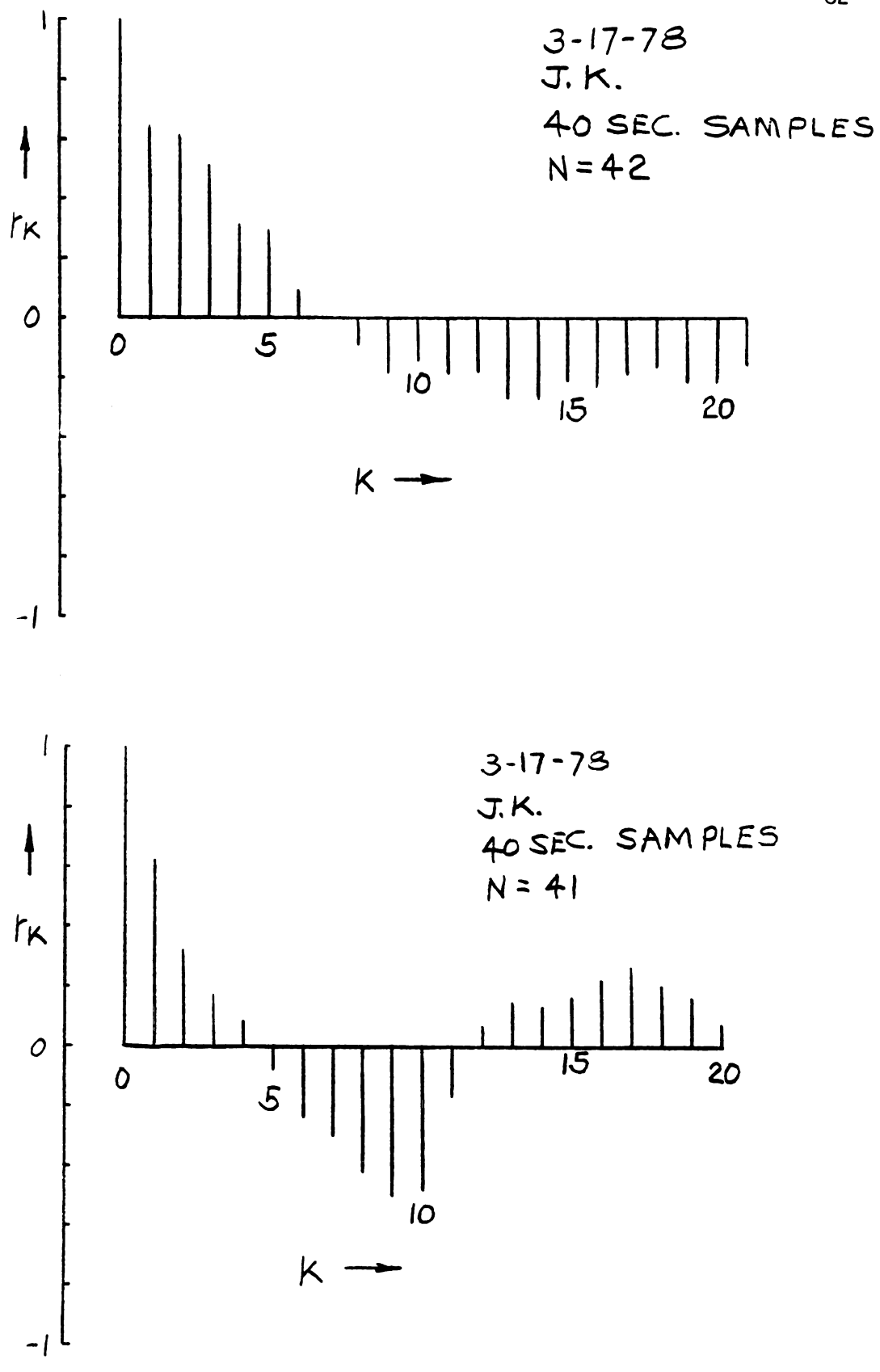


Fig. 22. Autocorrelation functions of a Biostator feedback session showing R_1 (top) and B_3 (bottom).

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