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OPEN-LOOP ANALYSIS OF THE CARBON DIOXIDE RECEPTOR REFLEX.(U)
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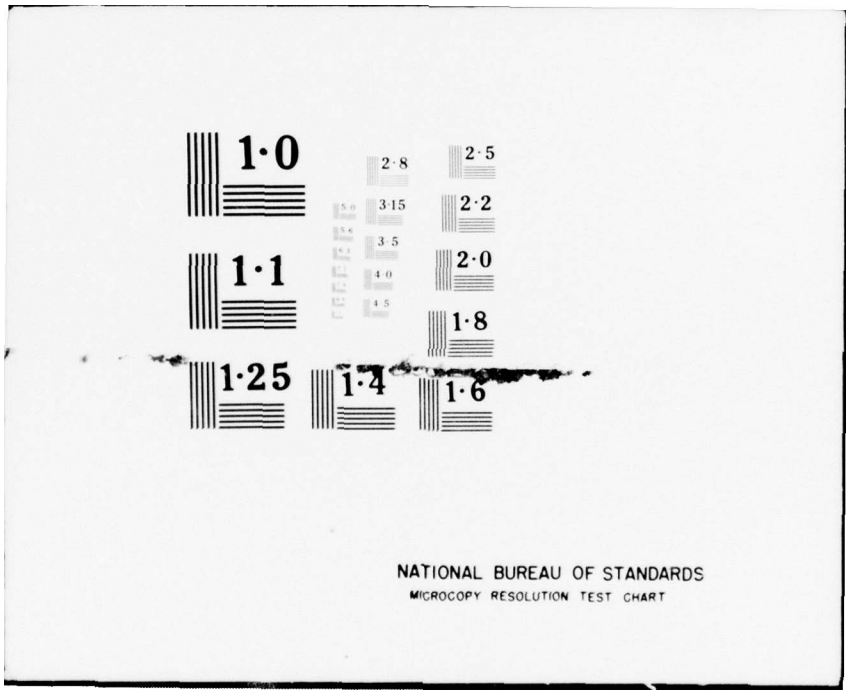
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RF Project 4084
Final Report

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OPEN-LOOP ANALYSIS OF THE CARBON DIOXIDE RECEPTOR REFLEX

10 Albert L. Kunz
Department of Physiology

9 Final rept.
1 May 69 - 31 Jan 77,

For the Period
May 1, 1969 - January 31, 1977

DEPARTMENT OF THE NAVY
Office of Naval Research
Arlington, Virginia 22217

15 Contract No. N00014-75-C-0133

12 77p.

11 May 1977

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267 360 LB

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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) CARBON MONOXIDE STUDIES		5. TYPE OF REPORT & PERIOD COVERED Final 11/1/74 - 10/31/75
		6. PERFORMING ORG. REPORT NUMBER 4084 Final
7. AUTHOR(s) Albert L. Kunz		8. CONTRACT OR GRANT NUMBER(s) N00014-75-C-0133 new
9. PERFORMING ORGANIZATION NAME AND ADDRESS The Ohio State University Research Foundation, 1314 Kinnear Road Columbus, Ohio 43212		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS Dept. of the Navy, Office of Naval Research Arlington, Virginia 22217		12. REPORT DATE June, 1977 13. NUMBER OF PAGES 69
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

"Approved for public release; distribution unlimited."

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

CO_2 regulation, control of ventilation, respiratory pacemaker, unidirectional ventilation, avian respiration, intrapulmonary CO_2 receptors, CO_2 receptors, biological control systems, feedback regulation, block of receptors, Cheyne-Stokes ventilation, vagotomy

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

This is the final report on a study of the biological control mechanism governing the regulation of CO_2 concentration in the blood and the air of the lung. The chicken is used as a model since, unlike mammals, it can be unidirectionally ventilated and the CO_2 concentration in the lung forced to follow a time pattern controlled by the experimenter. The report consists of a list of the phenomena found, figures illustrating these phenomena and references where each phenomenon is described in detail.

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PREFACE

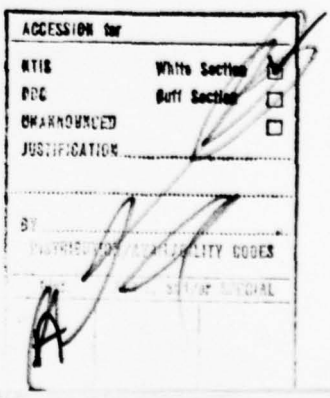
Since the development of the science of servomechanisms in World War II, biologists have been challenged to see the analogies between servomechanisms and homeostasis and to reduce their descriptive analysis of hoeostasis to a set of explicit numerical expressions (a model). This laboratory has been dedicated to understanding the respiratory regulation of carbon dioxide and oxygen on an informational basis; that is, we seek to avoid getting lost in the intrigues of anatomy and membrane biophysics until we understand more precisely how decisions are made by the various control loops (reflexes).

In seeking this goal we have developed specific powerful techniques which allow us to study the deterministic responses of the respiratory system to subtle changes. From open-loop studies, in which we control the concentration of CO_2 in the lung independent of the birds ventilatory movements, we have learned that the respiratory system is sensitive to small oscillations in CO_2 concentration and that breathing will lock onto the period of artificially induced CO_2 oscillations. Closed-loop studies, in which we use the bird's ventilation as feedback to control the carbon dioxide concentration in the lung, strongly suggest that the oscillations of CO_2 produced by ventilation are the major determinant of the respiratory period.

The existence of intrapulmonary CO_2 sensitive receptors (IPC) in the avian lungs is particularly fortuitous because the messages we code in the dynamic changes in CO_2 concentration are quickly sensed and acted upon by the bird. Distortion of the message by transmission through the blood is thereby avoided. We have developed a technique for selectively blocking these intrapulmonary CO_2 sensitive receptors with a small pulse of SO_2, an action which is rapid and reversible. We have learned that intrapulmonary CO_2 sensitive receptors: (1) contribute to the ventilatory drive, (2) mediate the CO_2 pacing phenomenon, and (3) are important to the stability of the regulation of CO_2 concentration.

This laboratory has developed methods by which ventilatory control can be studied by subtly manipulating parameters which are normally altered by the act of ventilation. The control systems are therefore left intact and the techniques provide information about how the systems operate under normal conditions. This would appear to be the best way to set about understanding a control system.

We are deeply indebted to the Office of Naval Research for its early continuous support and considerate administration of this project.



ACCOMPLISHMENTS

The following is a list of the major achievements of this laboratory group during this granting period. Rather than describing each in detail, we have (when applicable) shown a figure illustrating the phenomenon and sited references where more information can be obtained.

1. A surgical procedure[3] has been developed for producing an awake, upright, intact, unidirectionally ventilated preparation in which alveolar gas concentrations can be rapidly changed. The essence of the unidirectionally ventilated chicken preparation is that using a high flow rate of the gas in the lung, the pulmonary gas is forced to follow the CO_2 concentration of the insufflated gas. (See Fig. 1.)

2. An electro-pneumatic transducer[6] was developed to produce a time-prescribed CO_2 concentration signal in the inspiratory gas. This CO_2 signal is modulated by an electrical information signal, like from a signal generator.

Many revisions have made this system capable of producing independent concentration signals for CO_2 and O_2 in a gas stream of constant volume flow and pressure. (See Fig. 2.)

3. Improvements have been made in methods for control of humidity[14] of the insufflated gas. The bird is very sensitive to the drying of airways because the air flow in this preparation is ten times resting minute ventilation. The humidification technique eliminates the need for additional dead space by atomizing water into the air stream.

4. A simple technique for regulating the temperature of inspiratory gas was devised. The bird is extremely dependent upon ventilation as an avenue for heat loss since its feathers are a very effective insulator. Heat was added to the gas stream by running a low voltage current through a twelve ohm twenty-five watt electrical resistor. The temperature of the gas at the trachea's entrance was monitored by a thermister. Since the gas flow was kept constant, the current through the resistor could be easily adjusted to produce the gas temperature desired. The addition of heat also prevented condensation of water in the tubing.

5. A plethysmographic technique has been developed which uses a calibrated leak to allow measurement of rate and volume of respiratory movements while eliminating the troublesome effects of temperature and pressure changes or inboard gas leaks from the preparation.

6. Open-loop transients[1] of the ventilatory response to a step change in CO_2 concentration show an initial proportional crescendo with a time constant of 12 seconds. (See Figs. 3 and 4.)

a. The fact that there is no overshoot in the transient response speaks against the presence of a strong derivative component in the respiratory cycle.

b. The response of ventilation to ramp functions indicates the absence of a strong derivative component.

7. Open-loop steady state analysis[1] show the following:

a. The response of an awake, upright preparation differs from the anesthetized, open-chested, supine chicken preparation reported by Fedde. The awake chickens do not tolerate CO_2 concentrations above 7% while anesthetized ones tolerated up to 20% CO_2. Likewise, the sensitivity of awake chickens to CO_2 is greater than that of anesthetized ones.

b. Bode plots of responses to sinusoidal CO_2 oscillations of varying frequency at constant amplitude and mean CO_2 level show progressive diminution of respiratory envelope oscillations at higher frequencies in constrast to the predictions of rate control. (See Figs. 5 and 6.)

c. Phase plots done on several chickens agree well with the time constant prediction from the step responses.

8. An externally closed-loop preparation[3,4] was developed. The respiratory control loop was externally closed through an analog computer. (See Fig. 7.) The chicken's respiratory movements effect the alveolar CO_2 via the algorithm:

$$\% CO_2 = C \int (\dot{Q} - K \dot{V}_I)\, dt$$

where $\dot{Q}$ = analog of the CO_2 production,

C & K = proportionality constants,

$\dot{V}_I$ = inspiratory flow.

a. The closed-loop preparation is important because:

(1) It helps preserve homeostatic mechanisms, such as those for CO_2 and acid-base balance.

(2) It allows manipulation of an analog of the venous CO_2 load which otherwise would be difficult.

(3) It allows comparison of the transfer function of the biological component in and out of the loop.

(4) It can provide a method of investigating whether the respiratory controller can learn or adapt.

b. The closed-loop preparations showed[4]:

(1) The system seeks a stable equilibrium in which the alveolar CO_2 fluctuates about a constant mean value.

(2) Temporarily elevating the alveolar CO_2 above this normal mean value caused the chicken to breathe faster and deeper, returning his alveolar CO_2 to its previous level. (See Fig. 8.)

(3) If the alveolar CO_2 was temporarily lowered, the chicken would breathe slower and less deeply, returning the alveolar CO_2 to the equilibrium level.

(4) The regulated equilibrium level of alveolar CO_2 was dependent on the CO_2 load. (See Fig. 9.) (The CO_2 load in this preparation represents metabolically-produced CO_2 that must be equal to the CO_2 exhaled for the steady state CO_2 level to be maintained. The CO_2 load was simulated by the analog computer.) The possibility of integral control is refuted by the presence of offset error.

9. It was found that oscillations of alveolar CO_2 would be used to pace breathing.[3]

a. Pacing can be accomplished in open-loop preparation via an input CO_2 ripple about a mean value. (See Fig. 10.)

b. The range of frequencies for which entrainment is possible is two octaves for any given mean CO_2 value.

c. The amplitude of the oscillations was unimportant as long as it was above threshold. (See Fig. 11.)

d. Entrainment of breathing continued on a one-to-one oscillation-to-breath correspondence through frequency modulations of the CO_2 oscillations. (See Fig. 10.)

e. Pacing was also possible in the closed-loop preparation by adding an oscillatory disturbance of CO_2. (See Fig. 12.)

f. Phasing of respiratory movements with the CO_2 oscillations in the closed-loop case was such that the combined effect was to maximize alveolar oscillations. (See Fig. 12.)

10. Delays in the externally closed-loop preparation[4] of number 8 have the following effects:

a. A six-second delay causes periodic sinusoidal oscillations in mean CO_2 and respiratory movements. (See Fig. 13.)

b. An eight-second delay causes frank Cheyne-Stokes respiration. (See Fig. 14.)

11. The chicken's respiratory system appears to be sensitive to two frequency bands of CO_2 oscillations, very slow changes (the mean CO_2) and the frequency of breathing. AC coupling allows the higher frequency oscillation information to be fed back into the system while filtering out the low frequency changes in mean CO_2. (See Fig. 15.) Thus the $CO_2(t)$ has a ripple with each breath but the mean CO_2 over a 5-10 second interval remains constant. This technique with a delay in the feedback loop has led to the following discoveries. (See Fig. 16.)

a. Delays less than the initial period of respiration (with no delay) lengthens the respiratory period a corresponding amount; i.e., a one-second delay lengthens the respiratory period one second.

b. A delay slightly greater than the initial period reverts the period to its original duration.

c. Increasing the delay further lengthens the respiratory period by only one-half the length of the delay; i.e., a two-second increase in the delay time only increases the period one second.

d. This continues until the period becomes slowed to twice the initial period when the period again reverts to the duration of the initial period.

e. A further increase in the delay increases the period by an amount only one-third the amount of the delay; i.e., a three-second increase in the delay yields only a one-second increase in the period.

12. Modelling of the effect of delay on respiratory period suggests[1]:

a. The phenomenon is essentially the interplay of two events, the beginning of the inspiratory movement, and the beginning of lowering the % CO_2. (Respectively B (or 5) and C (or 2). $B \rightarrow C \rightarrow B \rightarrow C \ldots$

b. The interval B-C is the external interval composed of a mechanical delay of 0.4 seconds and a computer delay we can change from 0 to 10 seconds.

c. The interval C-B is the intrinsic delay within the chicken. It is equal to the respiratory period with zero delay.

d. Increasing the B-C interval directly increases period. When the B-C interval becomes longer than the C-B interval a spontaneous B causes a second sequence which is interlocked with the

first. This accounts for the sudden halving of the respiratory period. (See Fig. 17.)

e. We conclude that this mechanism results from the action of a respiratory oscillator which functions during normal breathing in the chicken. This oscillator consists of an information loop running from the brain to the respiratory musculature. Lowered CO_2 (resulting from inspiration) is detected by the CO_2 receptors in the lung; this retriggers the brain to cause another breath. (See Fig. 18.)

13. A second stable feedback algorithm[12] was invented which made the effect of the depth of breathing an all-or-none phenomenon. The algorithm was:

$$\% CO_2 = c \int (\dot{Q} - K f_e) dt$$

$\% CO_2$ = CO_2 in the insufflated gas

C & K = proportionality constants

$\dot{Q}$ = the analog of CO_2 produced

f_e = the frequency of effective (super threshold) breaths (i.e., each breath greater than a certain threshold volume). This threshold volume triggers a lowering of CO_2 a fixed amount K.

This study revealed the following:

a. There was a range of $\dot{Q}_V$ CO_2's in which the bird could frequency modulate to obtain a stable steady state CO_2. (See Fig. 19.)

b. A stable CO_2 could not be maintained above this range.

c. A second mechanism was utilized below this range, that of taking ineffective, subthreshold breaths.

d. Stability is dependent upon a short reaction time between CO_2 sensing and adjustment of tidal volume and frequency. This is almost certainly due to the peripheral CO_2 receptors in the lung rather than central receptors in the brain or spinal fluid.

14. R. M. Weissberg[12] investigated the effects of dynamic changes of pulmonary CO_2 on tidal volume in the unidirectionally ventilated avian preparation. Using a-c coupling, he produced feedback control of CO_2 concentration while producing fast CO_2 concentration changes at different phases in the respiratory cycle.

a. Comparisons between an oscillatory and non-oscillatory CO_2 signal (at the same mean CO_2) showed both tidal volume and

period decreased as a result of the CO_2 oscillations. (See Fig. 20.)

b. When a 2 percent (decreasing) CO_2 step was moved through a respiratory cycle, the bird's tidal volume decreased and its respiratory period increased. The respiratory pattern varied so much with step changes, that careful and systematic moving of the downstep into the cycle did not appear to be practical.

c. When a 2 percent increasing step was moved through a respiratory cycle, tidal volume varied with where in the cycle the upstep occurred. The maximum effect on tidal volume resulted when the upstep came in mid-expiration. Three different models were presented to possibly reconcile this phenomenon:

(1) Derivative sampling of CO_2 during a fixed part of the respiratory cycle.

(2) Sampling of mean CO_2 during a fixed part of the respiratory cycle.

(3) The clipping effect due to a nonlinear property of the CO_2 receptor.

These results support the hypothesis that dynamic behavior of pulmonary CO_2 effect tidal volume.

15. D. A. Miller[11] investigated the avian respiratory control system for regulation of CO_2 by changing the algorithm of the computer component in the feedback loop.

a. A change in the gain of the plant component does not result in a proportional change of the open-loop gain of the system. This suggests that there is a provision for automatic gain control. Automatic gain control might be important in some pulmonary diseases where the effectiveness of ventilation in eliminating Co_2 is decreased.

b. Changing the gain of the plant does not, however, significantly change the intercept of the ventilation vs. mean CO_2 curve (i.e., the apneic level of mean CO_2). This intercept is directly related to the set point of a negative feedback regulator.

c. The biological "controlling system" is surprisingly linear. Data of ventilation vs. forced CO_2 disturbance and of mean CO_2 vs. forced CO_2 disturbance fall in straight lines. The latter plot allows determination of the respiratory system open-loop gain. This measure describes the effectiveness of CO_2 regulation in the presence of metabolic disturbances. The relatively decreased noise on the ventilation vs. mean CO_2 response curve compared to the noise on the rate and tidal volume vs. mean CO_2 response curves infers that ventilation is the central output variable rather than independently generated values of rate and tidal volume.

d. The sensitivity of the respiratory controlling system is a function of the CO_2 oscillation amplitude, at the same mean CO_2 larger CO_2 oscillations have an inhibitory effect upon ventilation. The results for very small CO_2 oscillations approaching the static case demonstrate that the dynamic and the static characteristics of the respiratory controlling system are quite different. (See Fig. 21.)

16. In the closed-loop preparation with % CO_2 held constant, the feedback algorithm controls the O_2 concentration. Without breathing the % O_2 drifts down at a rate $\dot{Q}$ (the computer analog of rate of O_2 consumption). With each inspiration % O_2 is raised an increment proportional to the tidal volume of the breath. It was found that:

a. At low $\dot{Q}$ values this was a stable closed-loop system, which regulated pulmonary % O_2 at about 20 volumes per cent. (See Fig. 22.) If momentarily O_2 was increased to 30% the animal would breathe a little slower and the O_2 would be returned to 20%. Conversely if O_2 were momentarily decreased to 12% faster and deeper respiratory movements would return the O_2 to about 20%. (See Fig. 23.)

b. At a medium $\dot{Q}$ value a slow oscillation in mean O_2 of a frequency of about 0.01 Hz developed. (See Fig. 24.) A further increase in the $\dot{Q}$ value produced large amplitude O_2 oscillation of about the same 0.01 Hz frequency with characteristic Cheyne-Stokes breathing. (See Fig. 25.)

c. No such instability exists in our CO_2 regulating chicken preparations. The difference may be explained by the delay between the time of increased breathing movements and the time the receptor detects the effect. CO_2 receptors are present in the lungs and O_2 receptors are about 5 seconds down the line in arteries or the brain.

17. Cyclic Instability as a Function of Feedback Delay: Using the standard closed-loop preparation, an absolute time delay was added to the feedback loop. We found (see Fig. 26):

a. The system responded to a pulse disturbance similar to a alightly under-damped second order system.

b. Adding a 2-second absolute time delay to the system decreases the apparent damping coefficient of the system slightly. Adding a 4- or 6-second delay produces more under-damping.

c. An 8-second delay produces an apparently undamped second order system which oscillates without decrement.

d. Adding further delay produces a system in which the oscillation crescendos until saturation.

e. The shape and symmetry of these oscillations may be indicative of a surprisingly linear system.

f. Since the total system is second order and the external feedback element is first order, the biological respiratory controller is behaving as a linear first order element.

g. We have worked out the mathematical approximation of how a time delay effects the apparent damping coefficient and natural frequency of a second order system.

h. Measurements of the apparent damping coefficient from the amplitudes of the oscillations agree well with theoretical predictions.

18. Since our experiments suggest the avian respiratory pacemaker involves a monostable delay element in the brain, we were intrigued by the work of Davies and Yamamoto in which they paced the respiration of a rat with slow sinusoidal currents applied to small areas in the medulla. In R. P. Morgan's investigation[13], he:

a. Repeated the open-looped pacing of Davies.

b. Demonstrated two-to-one block (i.e., stimulus rate double the response rate).

c. Observed effect of light, non-pacing sinusoidal stimulus falling at different times in the respiratory cycle.

d. Used feedback signal from electro-spirometer to autostimulate these pacing areas of the rat medulla.

e. He discovered addition of delay to the feedback loop generated a pattern of ramps in the period vs. delay graph like those of the unidirectionally ventilated chicken.

f. He found there was a systemic deviation of each ramp from the predicted slope. The deviation is caused by a slight slippage in in phase relationship between stimulus and response through each ramp (i.e., the period was a function of phase).

19. Open-Loop Pacing of Respiration with Different Shaped Wave Forms[7]: Sine waves, square waves, triangular waves and saw tooth waves were used. The range of pacing was the same for each--just under two octabes. We looked for an event in the CO_2 waveform which might be triggering the next breath. Such an event should happen a constant time period before the next breath. We had postulated this event to be the time of CO_2 lowering since it has been shown that a great volley of impulses pass up the vagus nerve with CO_2 lowering. But the time between

CO_2 lowering and the next inspiration varied from waveform to waveform. The time between when CO_2 first starts up (after having passed through a minimum) until the next inspiration remained constant at about 0.8 seconds. So it is presumably the triggering event. We have plans of further experiments with more exotic and aperiodic waveforms to test this finding.

20. Developed a technique for selectively blocking a set of intropulmonary CO_2 receptors (IPCs) in the awake bird.

a. This technique involved adding a measured pulse (approximately one minute in duration) of sulfur dioxide, SO_2 to the insufflating air stream in a unidirectionally ventilated chicken.

b. Single fiber recordings of the vagal afferent fibers from these IPCs showed after a latency of about 30 seconds the IPCs would stop firing for 5 to 10 minutes and then would return. (See Fig. 27.)

c. Administration of the SO_2 block of IPCs during pacing experiments showed pacing would break after a similar latency of approximately 30 seconds (see Fig. 28) and returns after 5 to 10 minutes (see Fig. 29).

d. When SO_2 is given by insuflation it could be acting at two sites: (1) directly on IPCs, or (2) systemically through the blood to arterial or brain receptors, or both. The second possibility was ruled out when the intravenous injection of the same dose SO_2 did not break pacing. (See Fig. 30.)

In Fig. 30, apparently the acidity of the injection causes a speeding of respiratory rate and a loss of synchrony due to the range of pacing being raised. But when the frequency rate of the CO_2 oscillation is increased, synchrony again appears.

e. Administration of SO_2 block of IPCs during closed-loop regulation of CO_2 showed the regulated level rose from 4% to 6% and fell back down to 4% after eleven minutes (see Fig. 31) in at least one experiment.

f. Administration of SO_2 block during closed-loop regulation at another time showed decreased stability of CO_2 regulation, a periodic oscillation of CO_2 level similar to the oscillation produced by feedback delay. (See Fig. 32.)

g. This instability of the CO_2 regulation system after SO_2 blocked the IPCs was modeled. Figure 33 shows the three known sets of receptors with feedback regulation of CO_2. The artery represents a transmission line delay. Figure 34 expresses this relationship in block diagram form and lumps the receptor in the carotid body and medulla as systemic chemoreceptors with a delay

component (blood transit time) in the beedback loop. Figure 35 shows the analog simulation of Fig. 34. Figure 36 demonstrates two sets of parameters which give reasonable approximations of the patterns of response to pulse changes seen in Fig. 32.

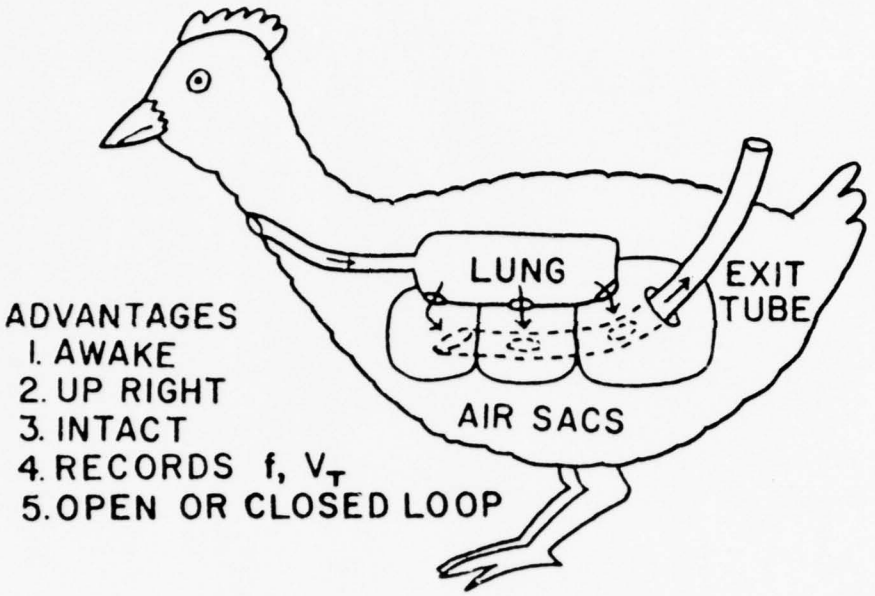
h. Large doses of SO_2 produced a slow deep inspiration similar to the pattern caused by bilateral vagatomy. Compare Fig. 37 with Fig. 38 as a control.

21. One drawback with the unidirectionally ventilated bird preparation is that air flows at a much faster rate and not through the same routes as in normal ventilation. Carbon dioxide (or conversely, fresh air) pulses into the air stream tend to reach all areas of the lung at once and not in the sequence of normal breathing. The following preparation eliminates these objections, yet still shows that ventilatory movements are triggered by changes in CO_2. Figure 39 shows the experimental setup. The bird breaths through a tracheostomy from a gas stream in which the CO_2 concentration can be quickly changed from 5% CO_2 (about the value of end expiratory CO_2) to 0% CO_2 (fresh air) and then back. This is called a pulse of "fresh air." Ventilation is monitored by a whole body plethysmograph and the time of beginning of inspiration, t_i, used to trigger the pulse of "fresh air." Therefore, when the animal breathes, the first air to reach his lungs is the air from the dead space in his trachea (Ca 5% CO_2). This air is followed by the 5% CO_2 in gas stream preceding the pulse. Fresh air comes next and lastly 5% CO_2.

a. Figure 40 shows how changing the delay, τ, between inspiration and the pulse of fresh air effects respiratory period.

As τ is increased respiratory period, T, and the period of inspiration, T_i, are both increased. This dependency holds true on a breath-by-breath basis when τ is changed dynamically. In Fig. 5, τ has been varied in a sinusoidal pattern; T_i and T follow. Note that K, the time between the rise in CO_2 and expiration begins, t_i, stays relatively constant. We believe this shows a rise in CO_2 triggers the next expiration.

b. To test whether the event triggering expiration was the down-stroke or the up-stroke of the pulse, the width of the pulse was changed. The value of K stayed constant while the time between the down-stroke of CO_2 and the beginning of expiration increased the same amount the pulse was increased. Therefore, the down-stroke was not triggering event. (See Fig. 41.)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3. INTACT
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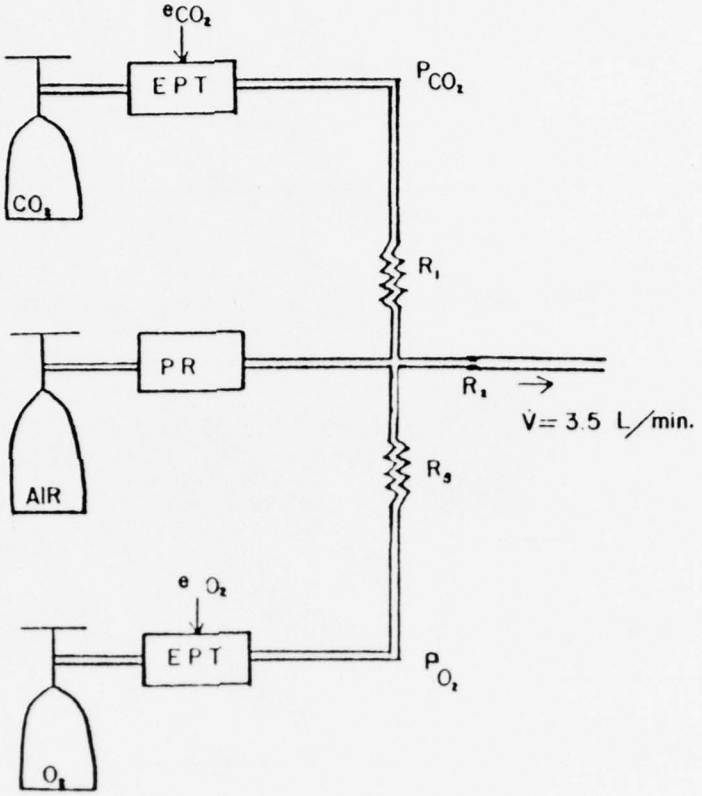
5. OPEN OR CLOSED LOOP

Figure 1



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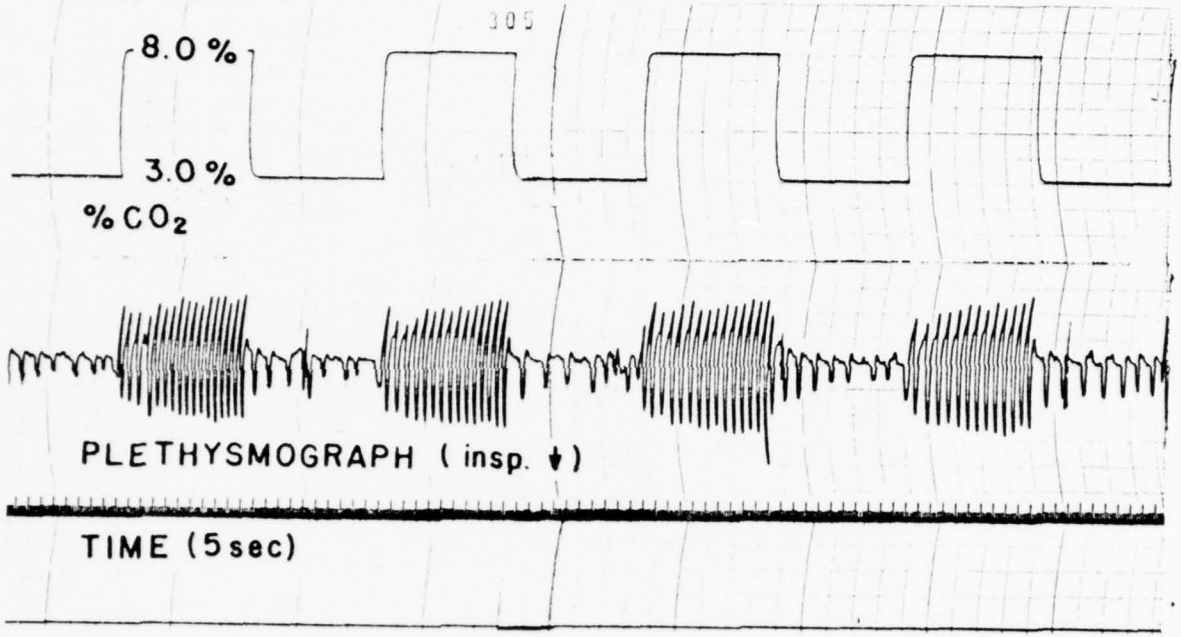

Figure 3

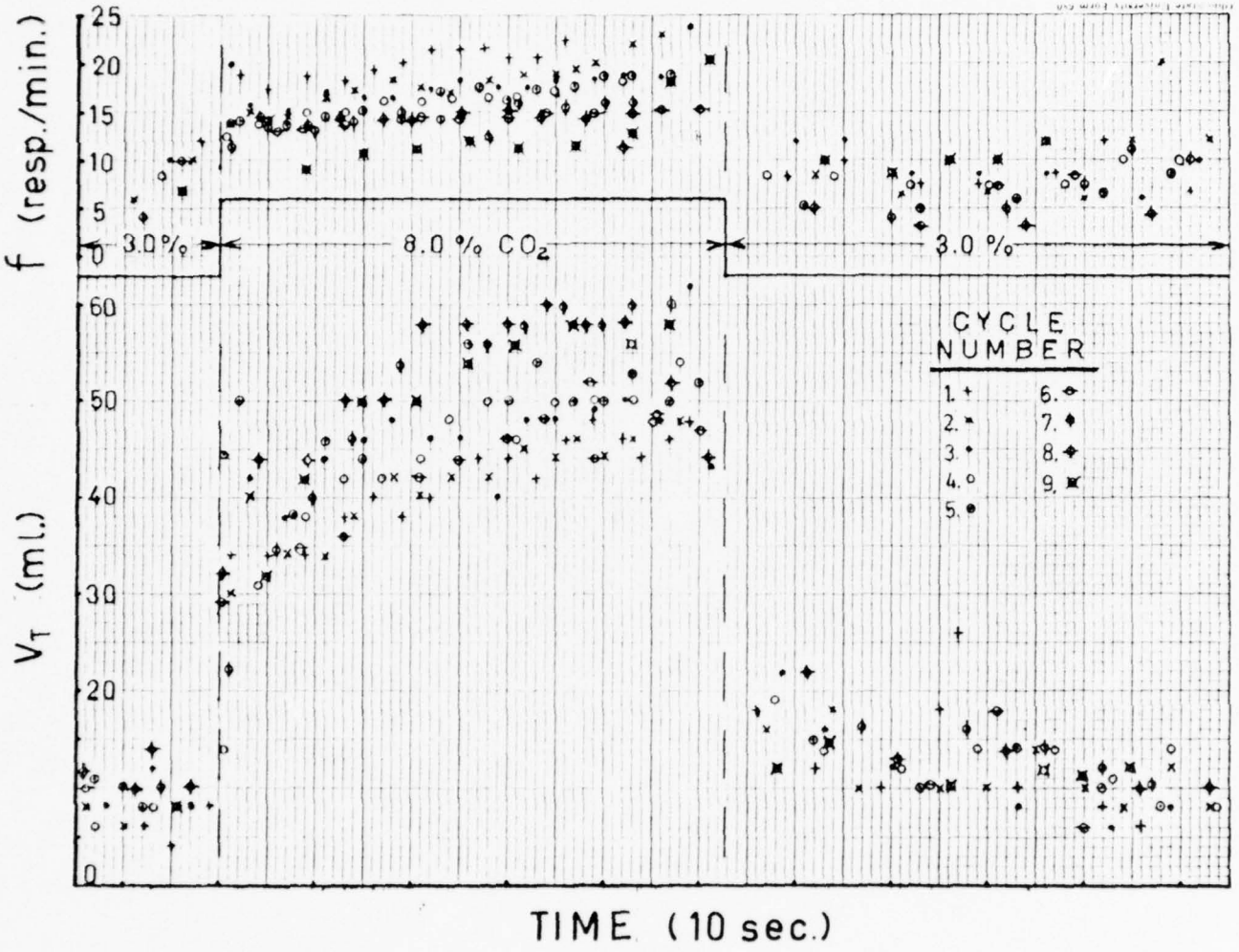
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Figure 4

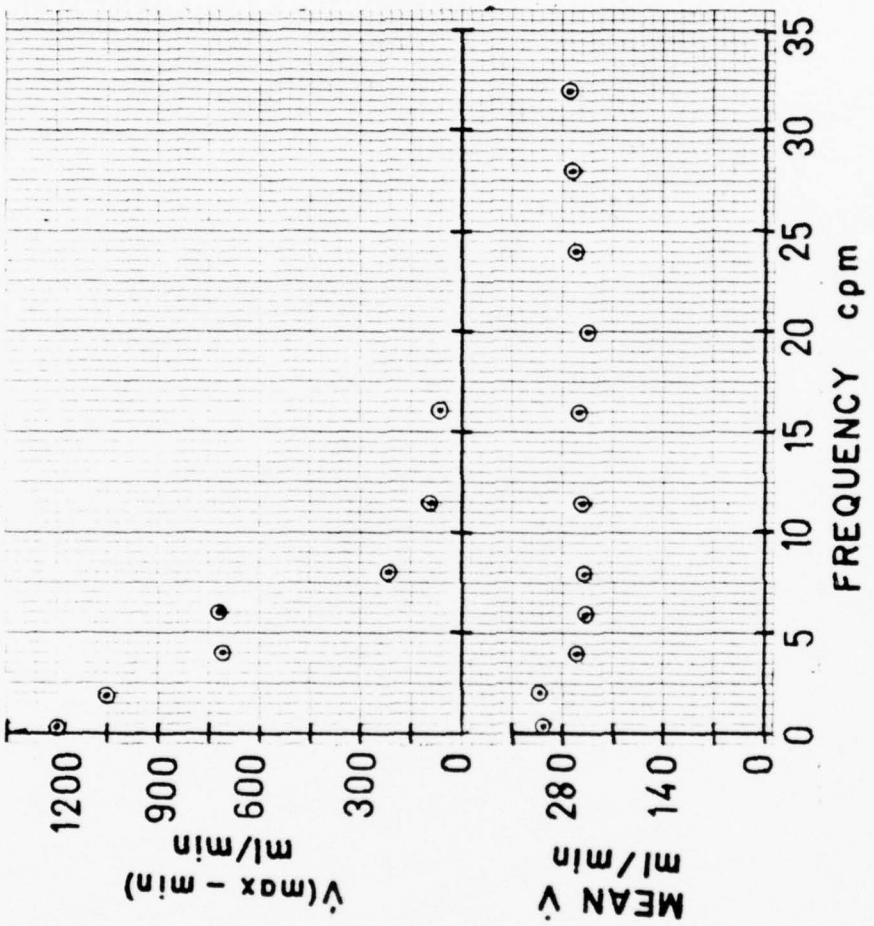
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Figure 5

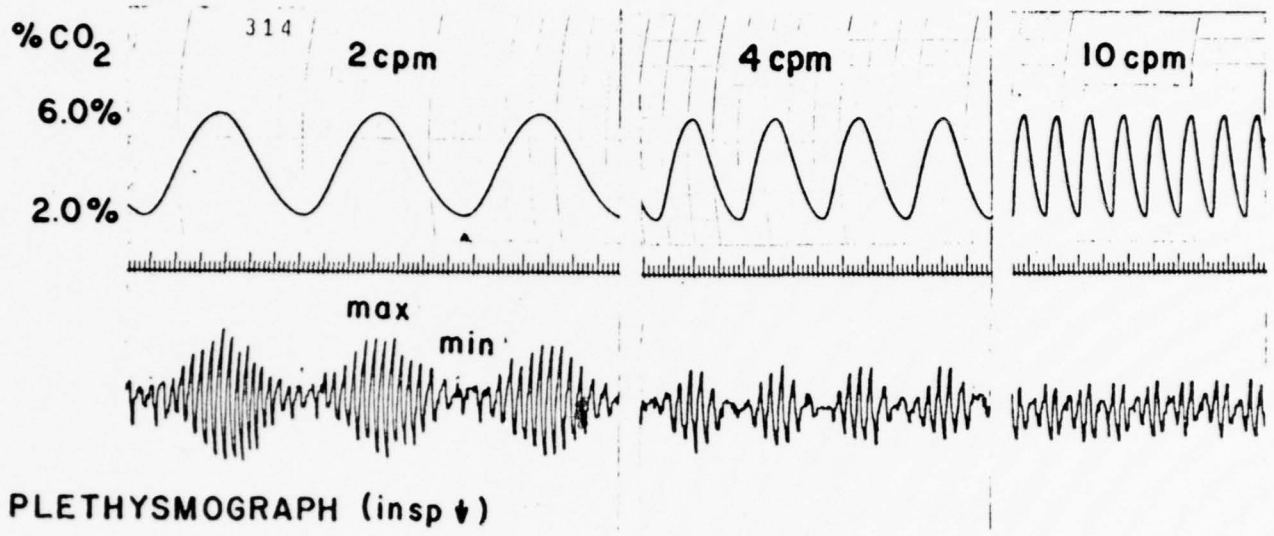


Figure 6

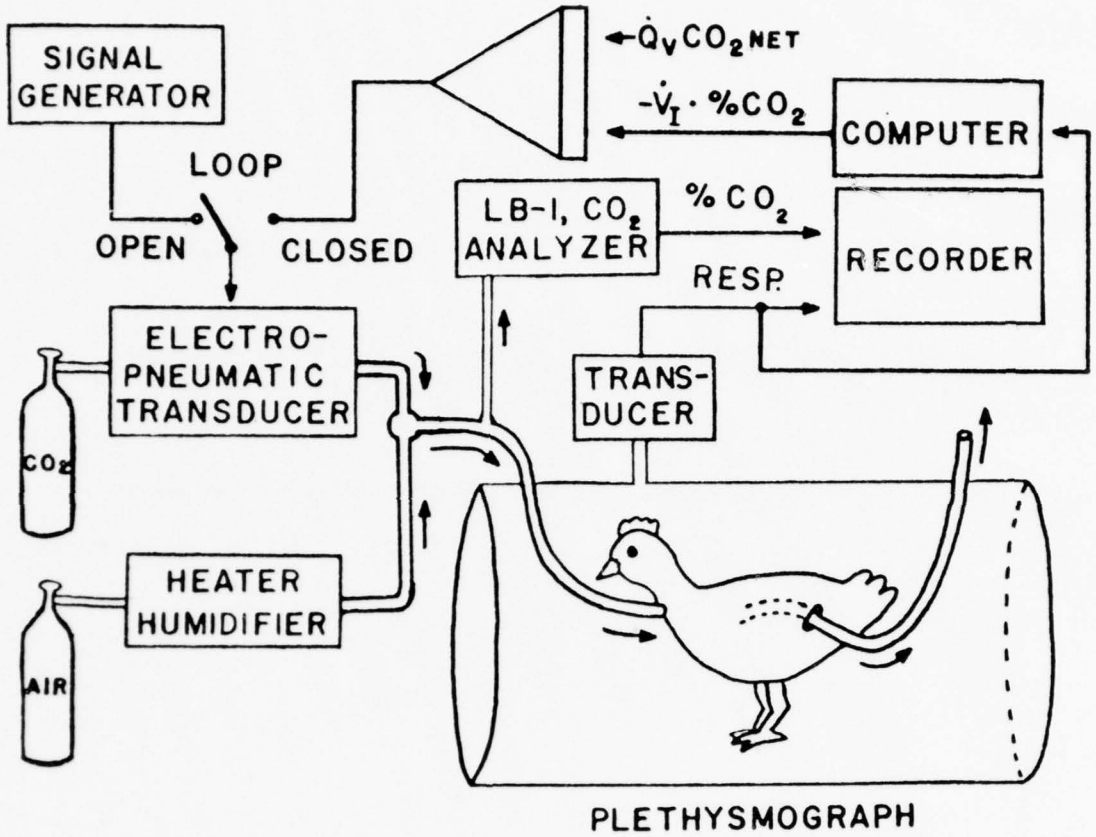

SIGNAL GENERATOR
LOOP
OPEN
CLOSED
$\dot{Q}_V CO_{2\,NET}$
$-\dot{V}_I \cdot \%CO_2$
COMPUTER
LB-I, CO_2 ANALYZER
$\%\,CO_2$
RECORDER
RESP.
ELECTRO-PNEUMATIC TRANSDUCER
TRANS-DUCER
CO_2
HEATER HUMIDIFIER
AIR
PLETHYSMOGRAPH

Figure 7

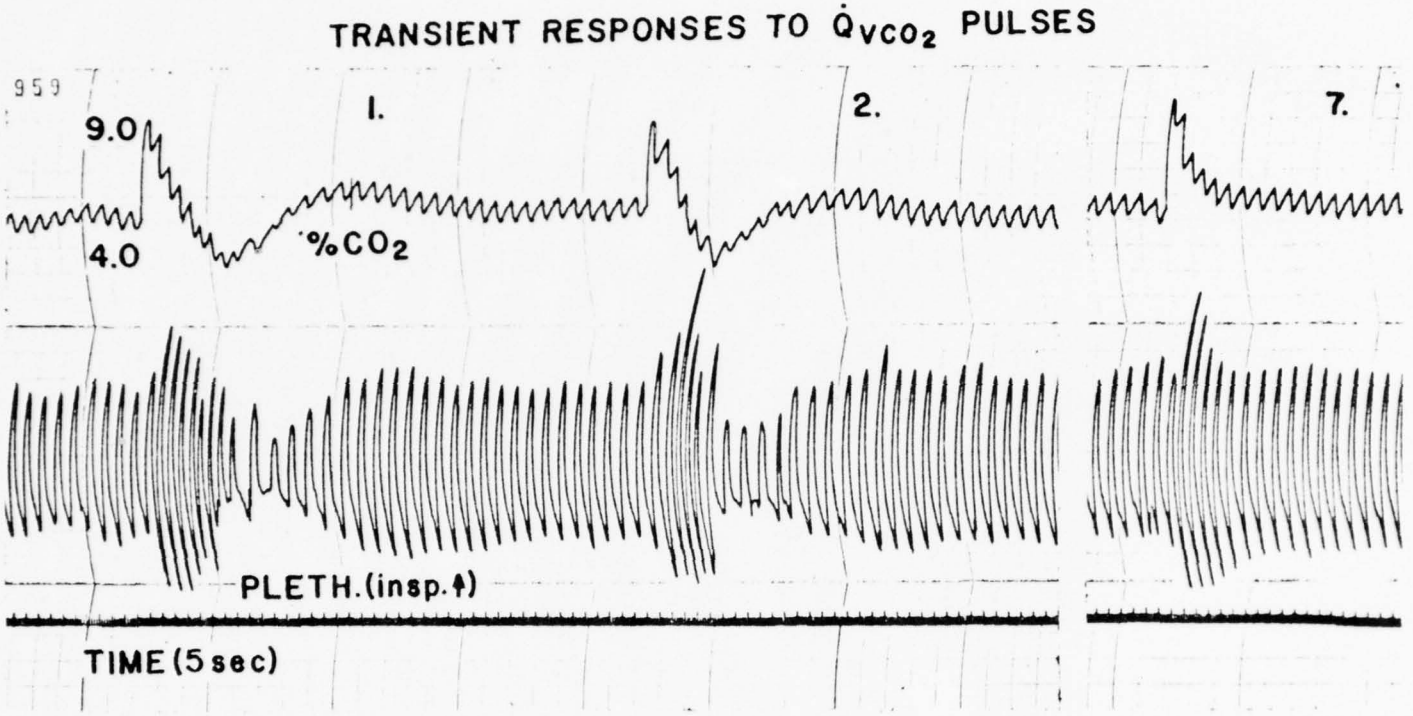

TRANSIENT RESPONSES TO $\dot{Q}_{VCO_2}$ PULSES
959
9.0
4.0
%CO2
1.
2.
7.
PLETH. (insp. ↑)
TIME (5 sec)

Figure 8

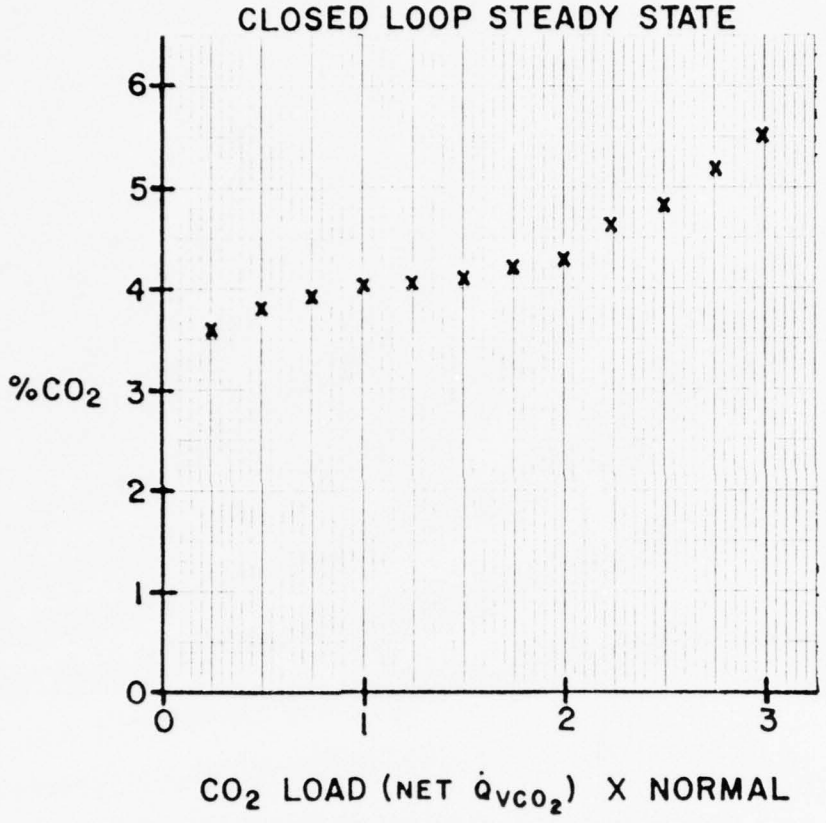

CLOSED LOOP STEADY STATE
%CO2
0
1
2
3
4
5
6
0
1
2
3
CO2 LOAD (NET V̇CO2) X NORMAL

Figure 9

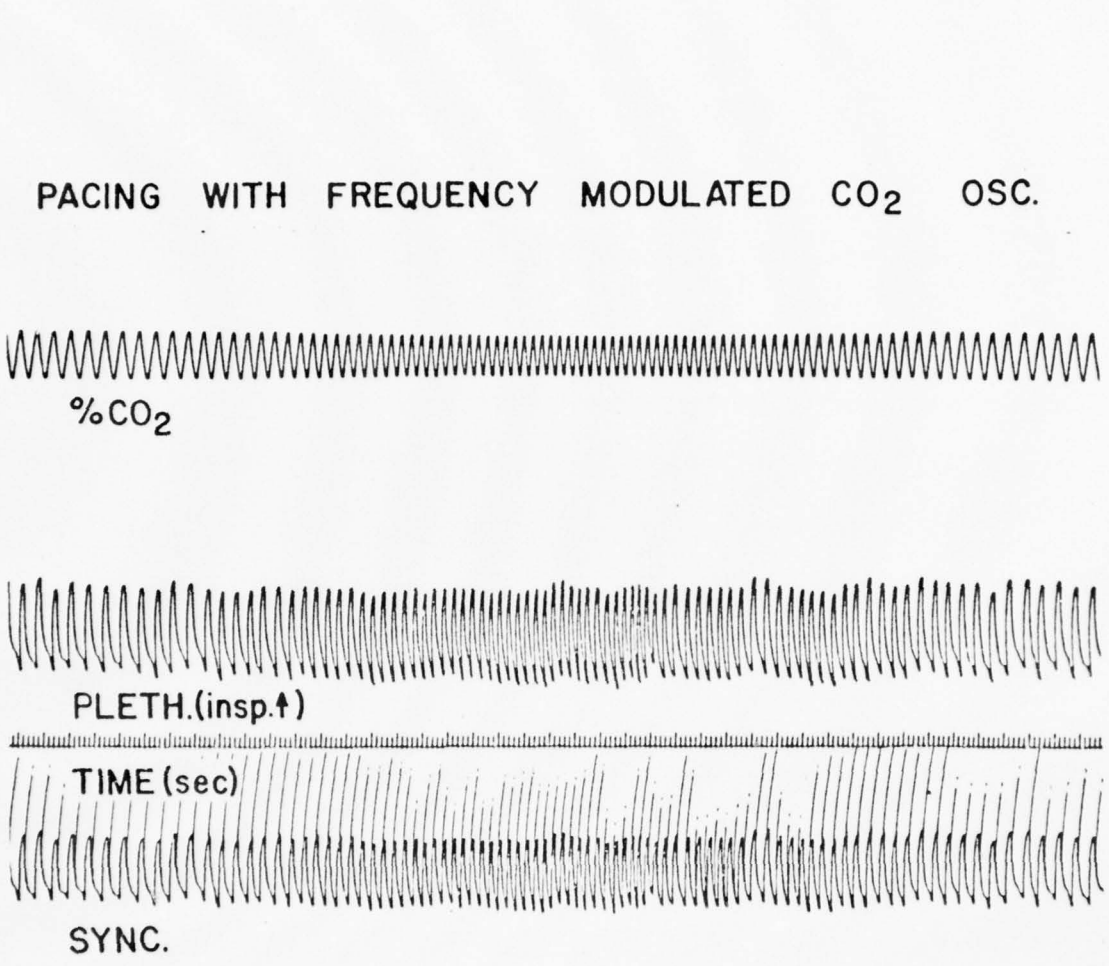

PACING WITH FREQUENCY MODULATED CO_2 OSC.
$\%CO_2$
PLETH.(insp.↑)
TIME (sec)
SYNC.

Figure 10

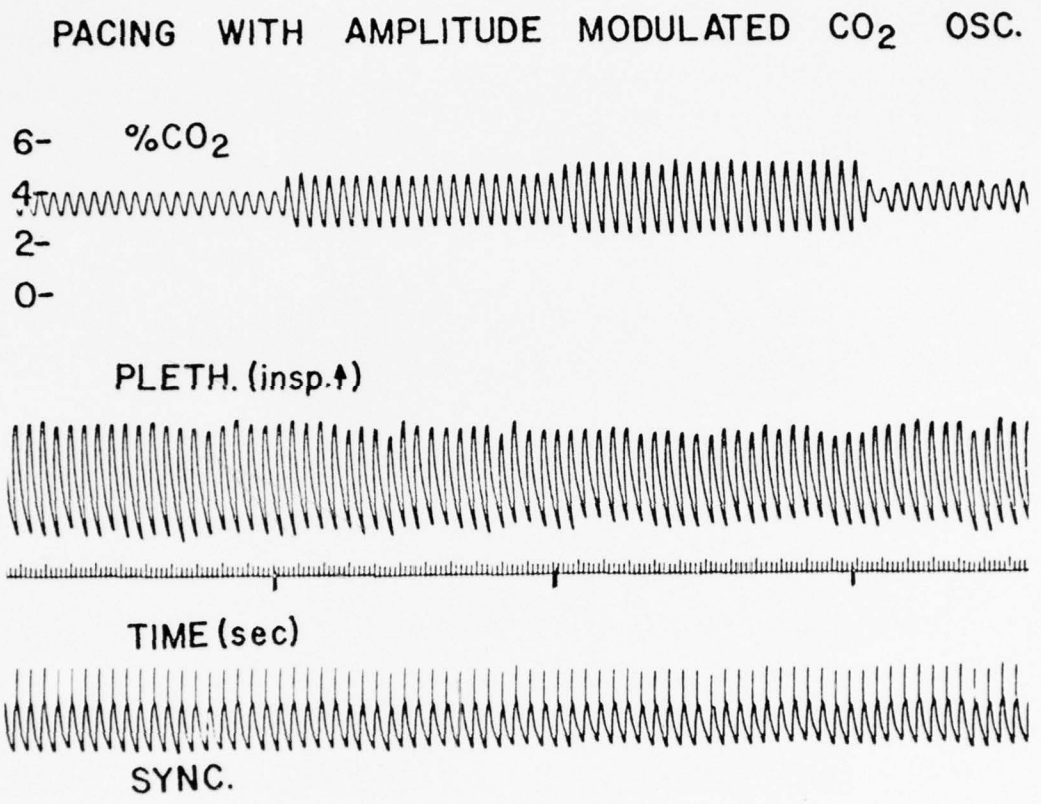

PACING WITH AMPLITUDE MODULATED CO_2 OSC.
6-
%CO_2
4-
2-
0-
PLETH. (insp.↑)
TIME (sec)
SYNC.

Figure 11

PHASE RELATIONSHIP BETWEEN OSC. DISTURBANCE AND INTRINSIC CO_2 OSC.

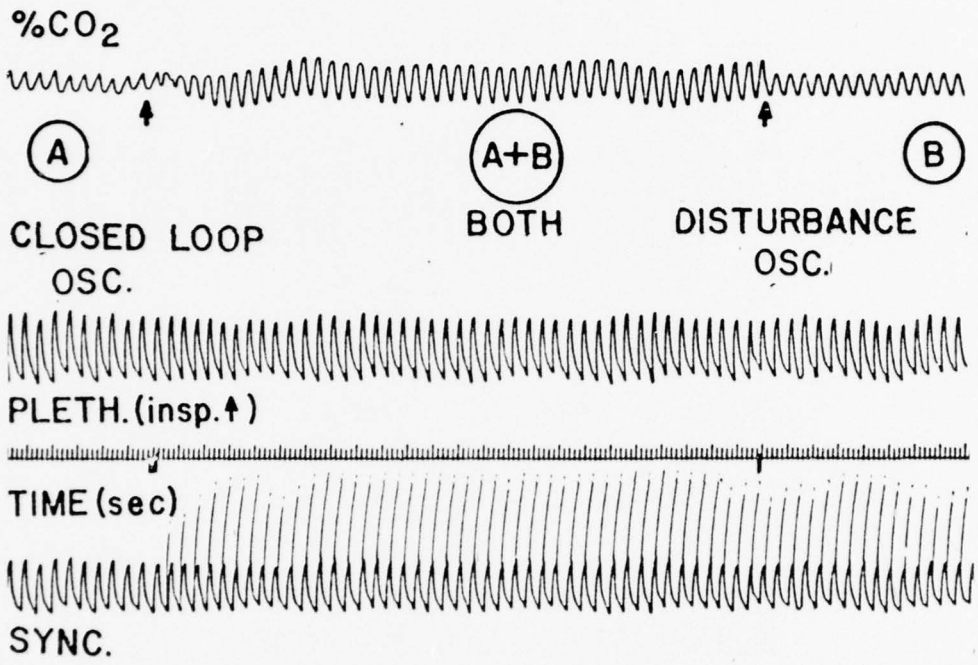


Figure 12

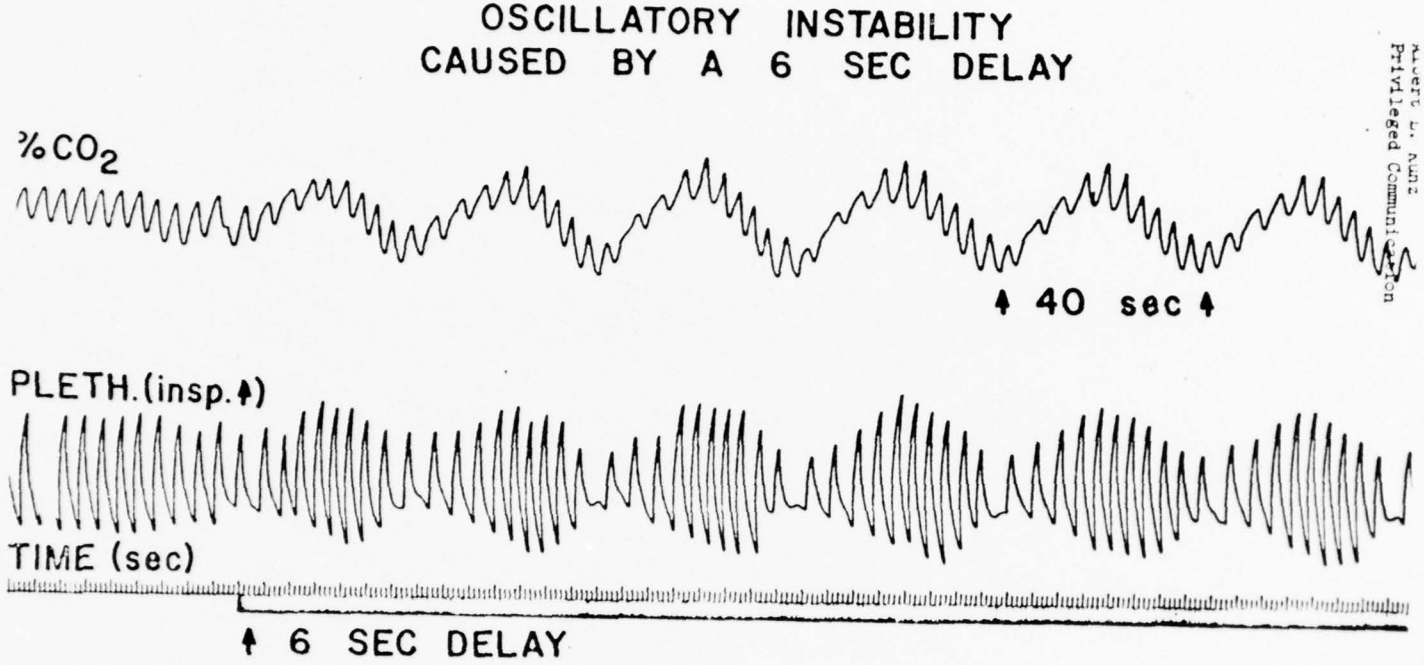
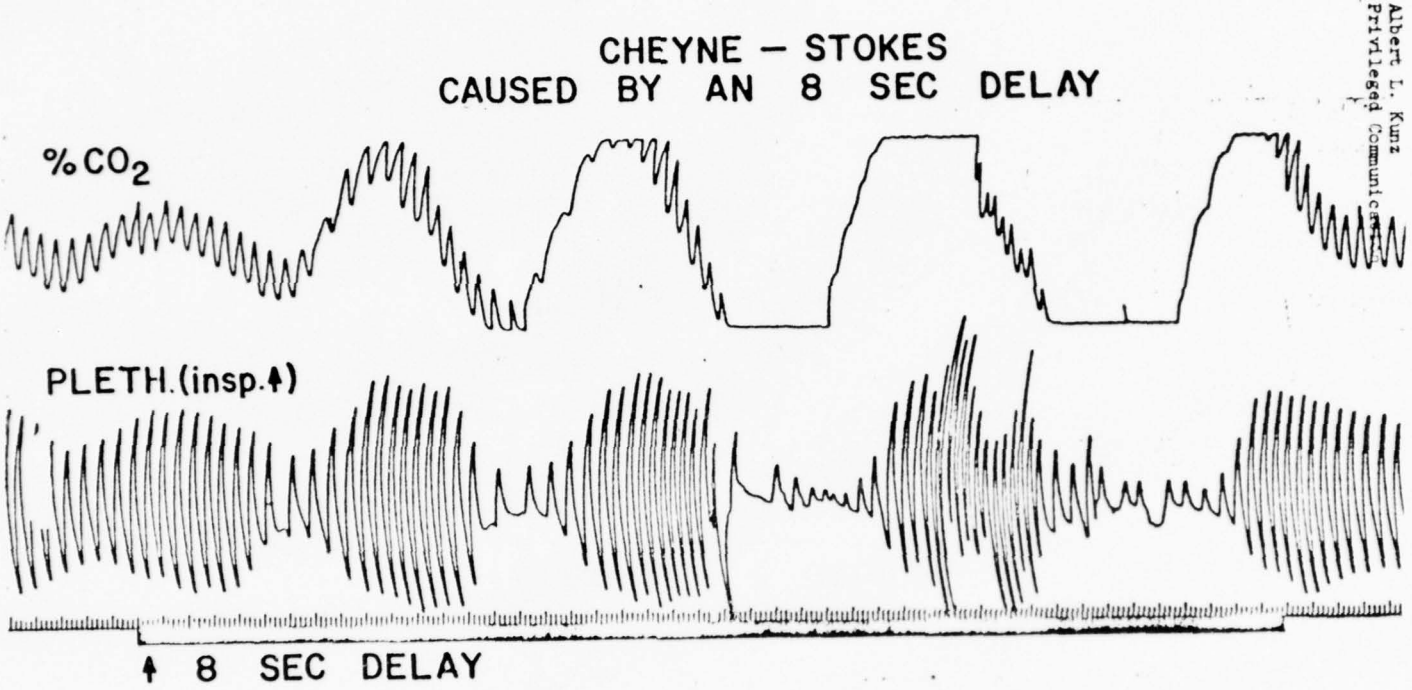


Figure 13



Albert L. Kunz
Privileged Communication

Figure 14

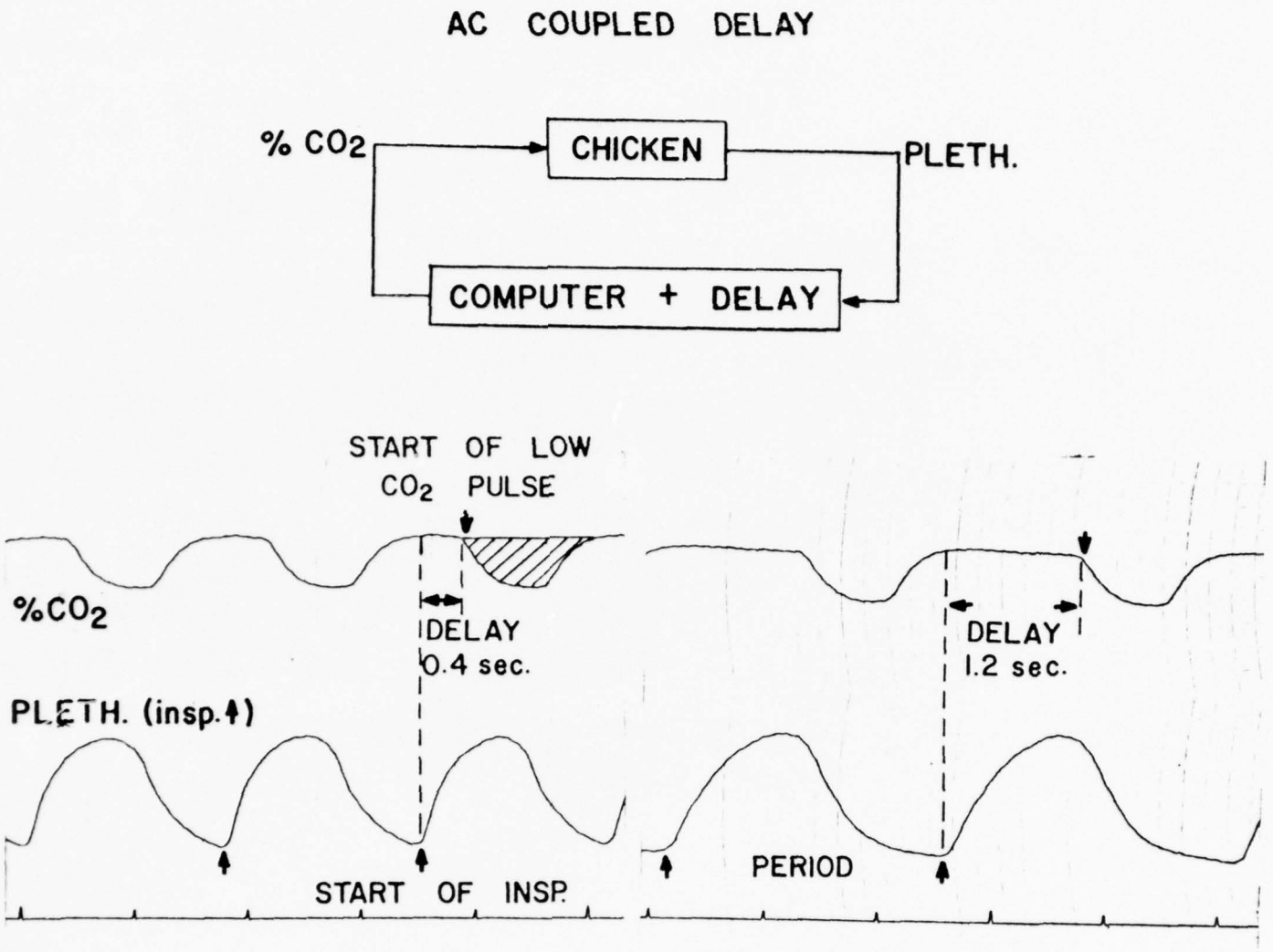

AC COUPLED DELAY
% CO2
CHICKEN
PLETH.
COMPUTER + DELAY
START OF LOW
CO2 PULSE
%CO2
DELAY
0.4 sec.
PLETH. (insp.↑)
START OF INSP.
DELAY
1.2 sec.
PERIOD

Figure 15

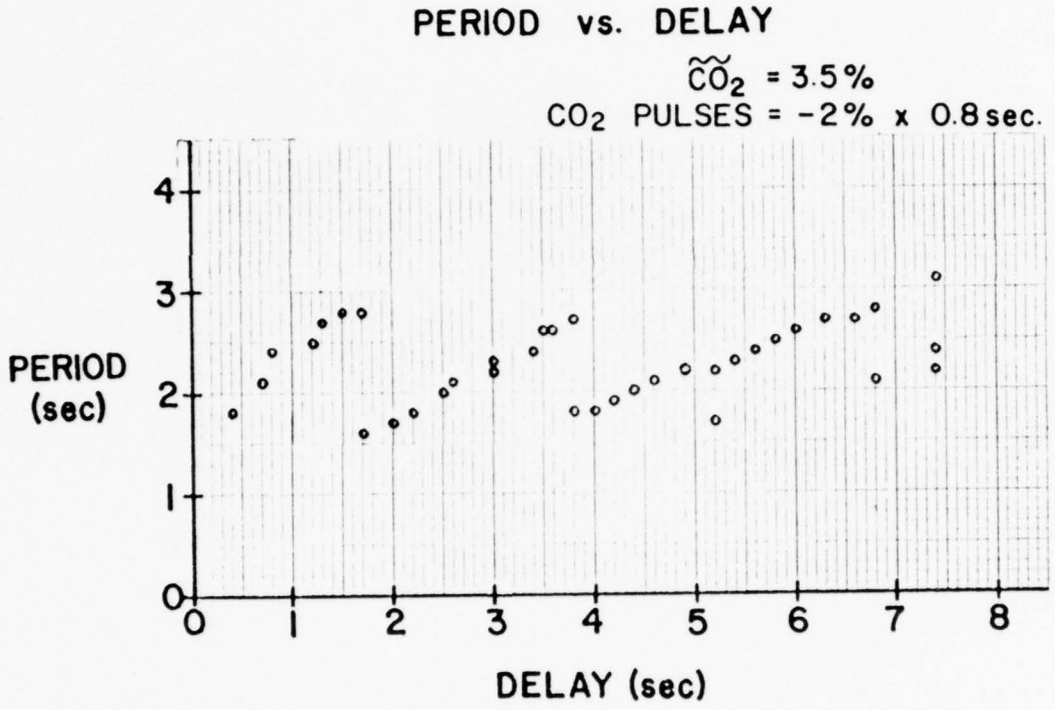

PERIOD vs. DELAY
$\widetilde{CO_2}$ = 3.5%
CO_2 PULSES = -2% x 0.8 sec.
PERIOD (sec)
0
1
2
3
4
0
1
2
3
4
5
6
7
8
DELAY (sec)

Figure 16

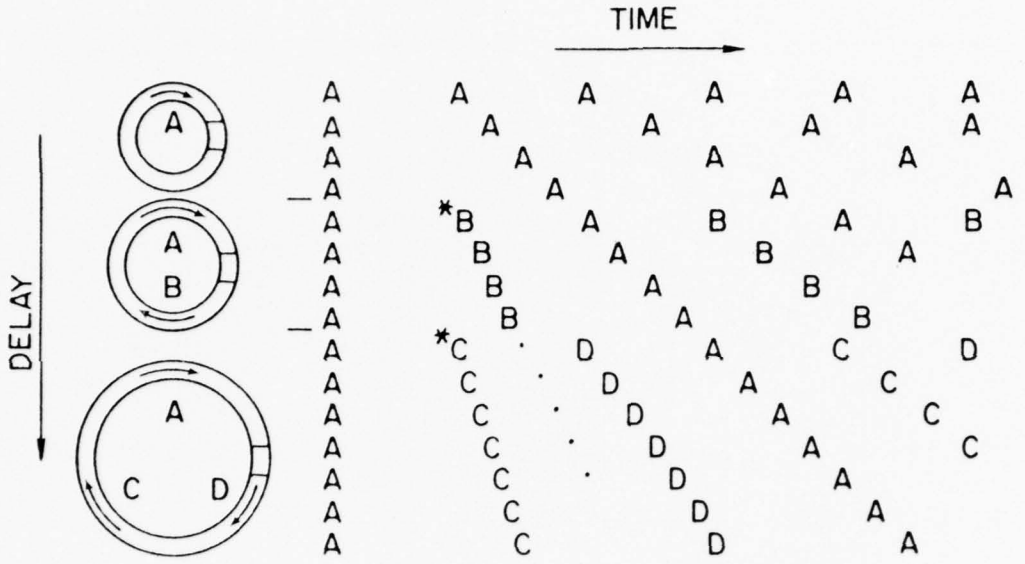


Figure 17

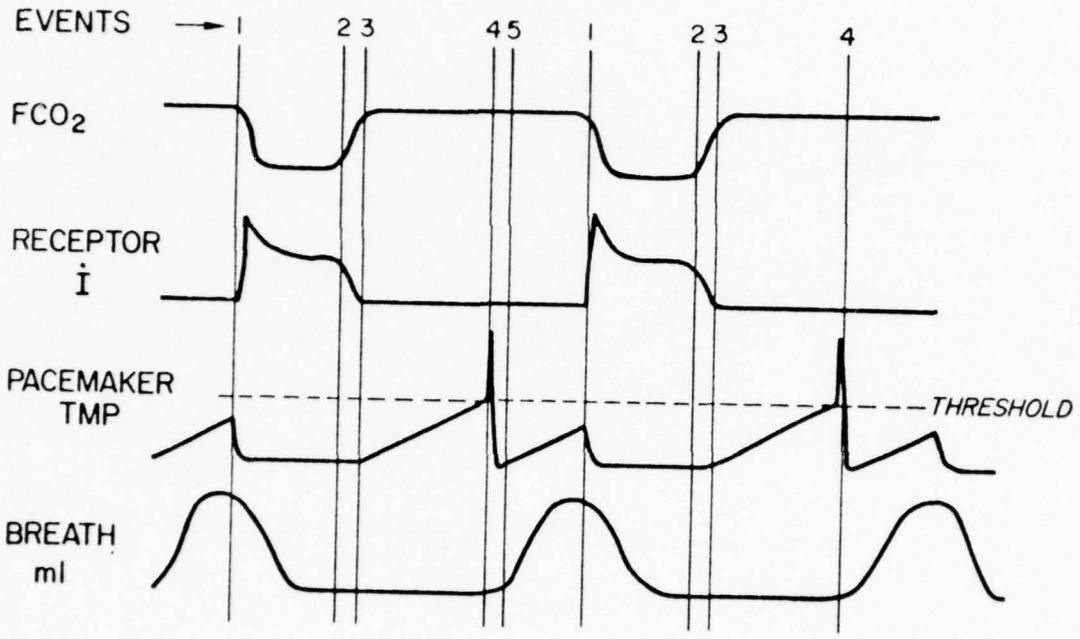
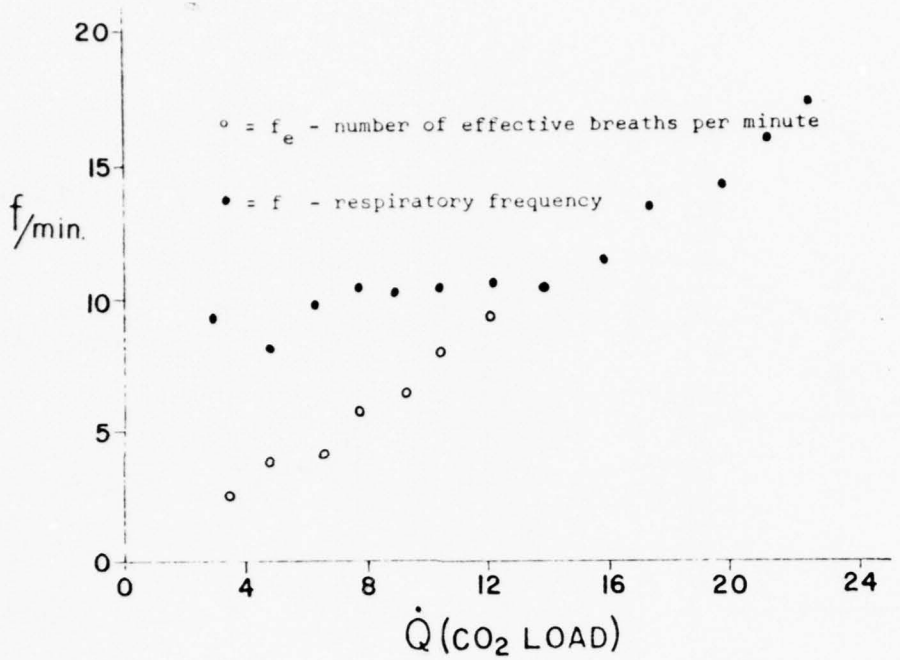
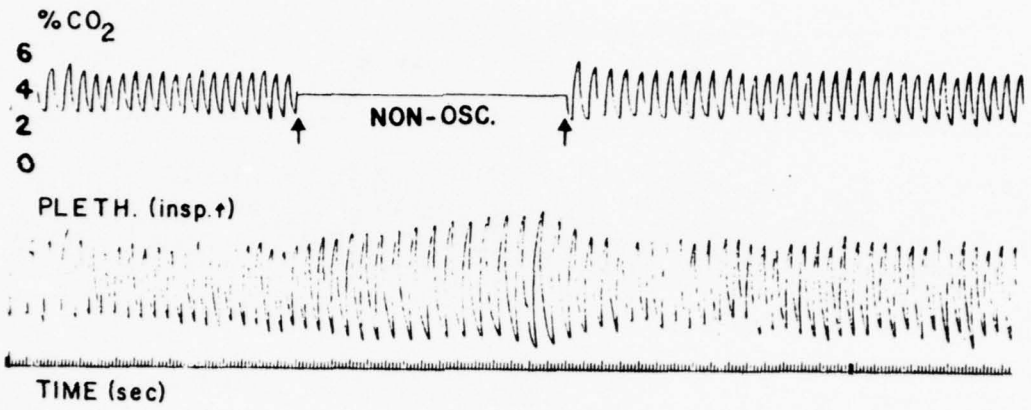

EVENTS
1
2 3
4 5
1
2 3
4
FCO2
RECEPTOR
İ
PACEMAKER
TMP
THRESHOLD
BREATH
ml

Figure 18



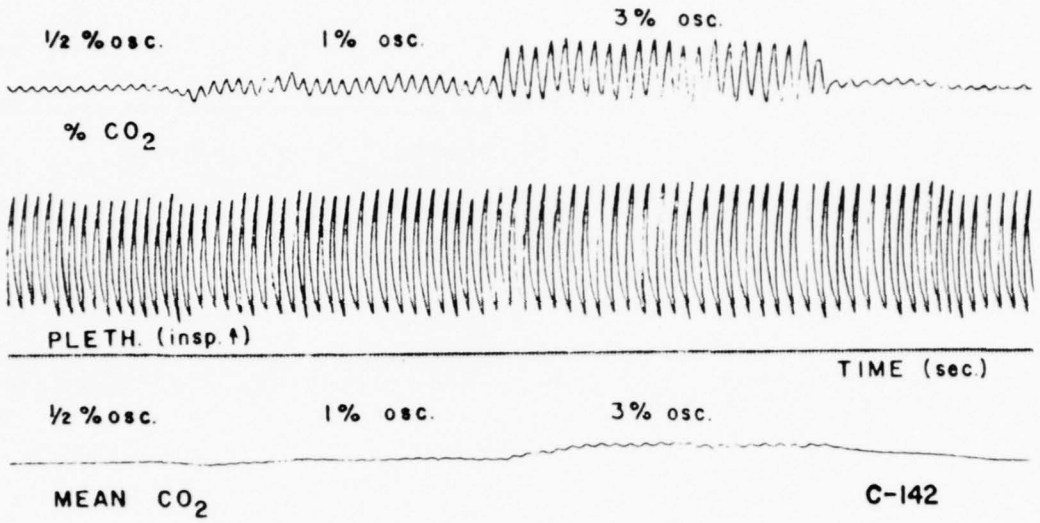
Frequency Range vs. CO_2 Disturbances

Figure 19



AC Coupling via Tidal Volume

Figure 20



Effect of Amplitude of CO_2 Oscillation

Figure 21

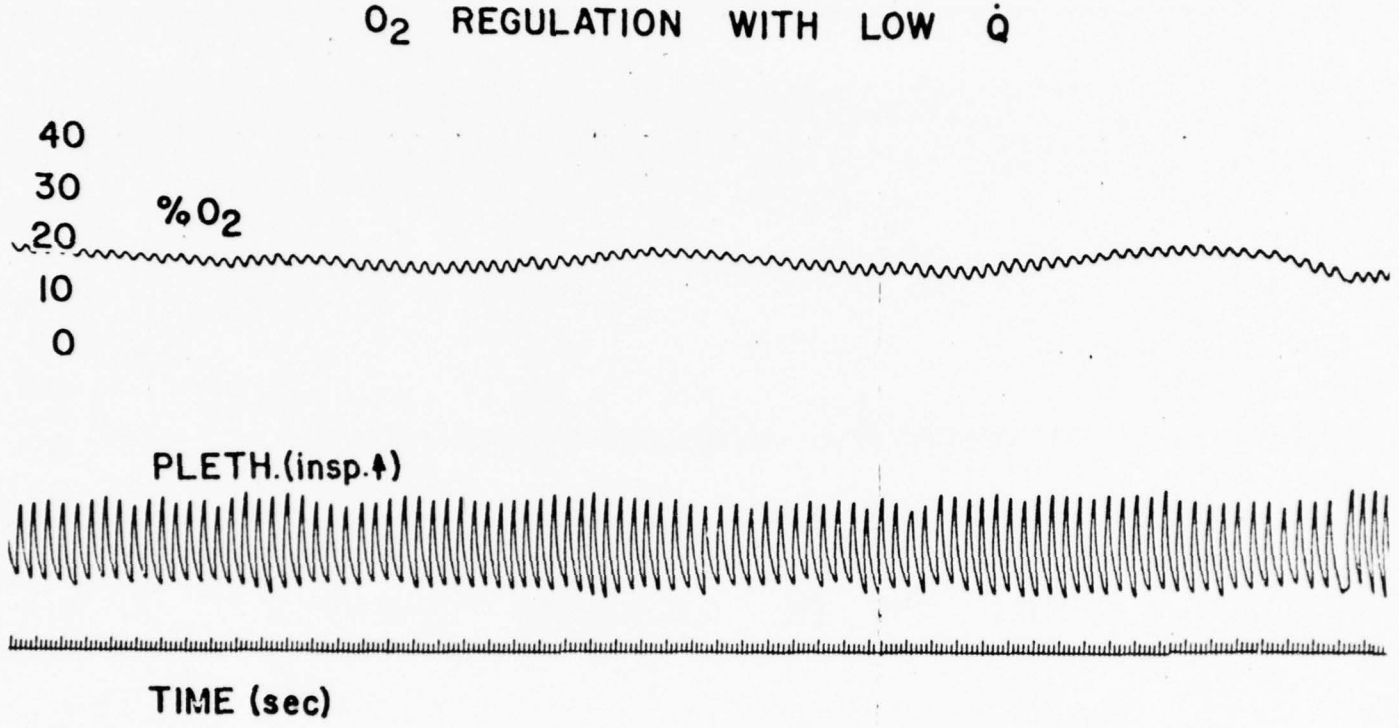

O_2 REGULATION WITH LOW $\dot{Q}$
40
30
20
10
0
%O_2
PLETH.(insp.↑)
TIME (sec)

Figure 22

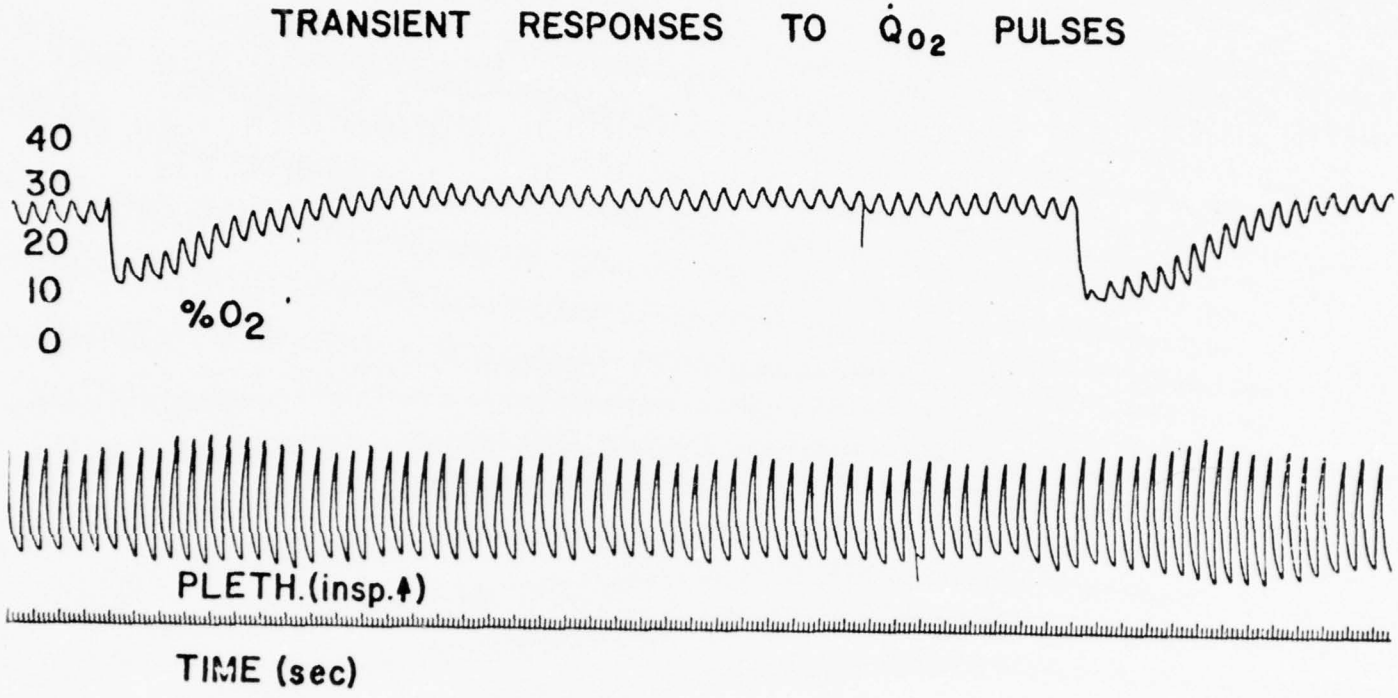

TRANSIENT RESPONSES TO $\dot{Q}_{O_2}$ PULSES
40
30
20
10
0
$\%O_2$
PLETH. (insp.↑)
TIME (sec)

Figure 23

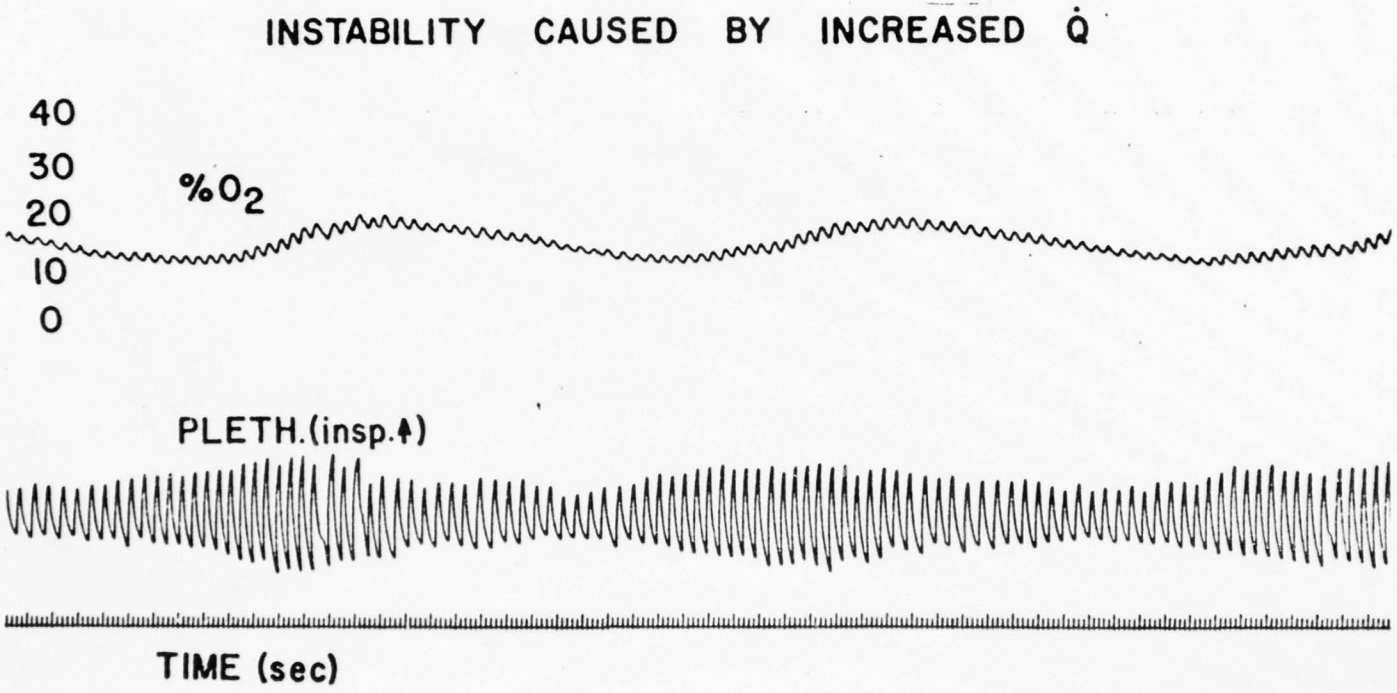

INSTABILITY CAUSED BY INCREASED Q̇
40
30
20
10
0
%O2
PLETH.(insp.↑)
TIME (sec)

Figure 24

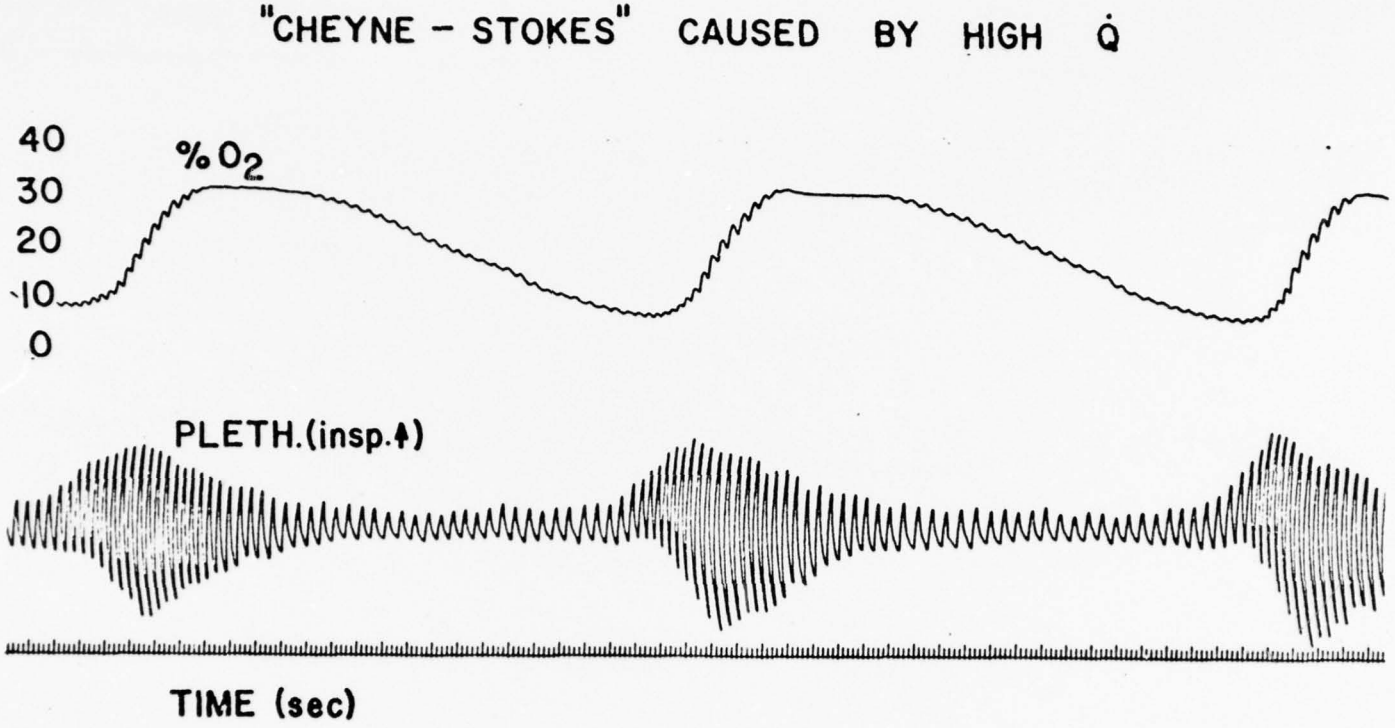

"CHEYNE - STOKES" CAUSED BY HIGH Q̇
40
30
20
10
0
%O2
PLETH.(insp.↑)
TIME (sec)

Figure 25

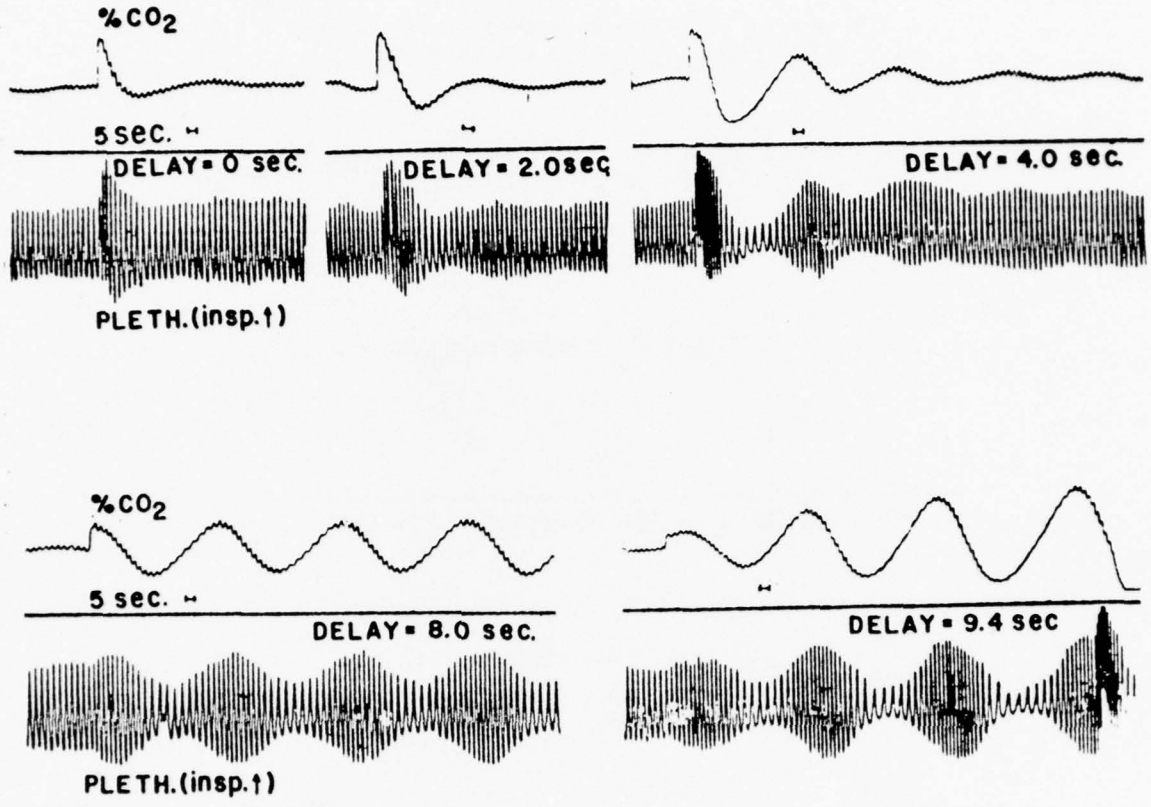
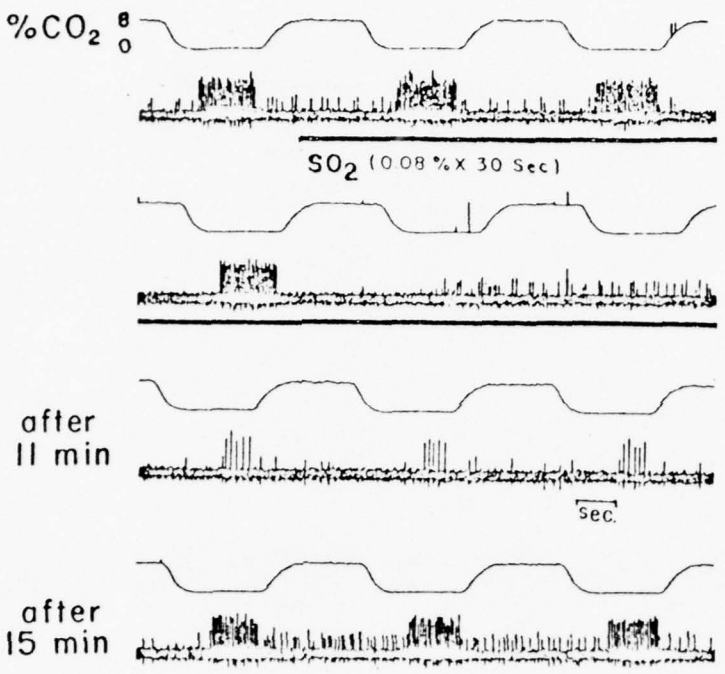

%CO2
5 sec.
DELAY = 0 sec.
DELAY = 2.0sec
DELAY = 4.0 sec.
PLETH.(insp.↑)
%CO2
5 sec.
DELAY = 8.0 sec.
DELAY = 9.4 sec
PLETH.(insp.↑)

Figure 26



Single Unit Recording of SO_2 Blocking IPC and its Spontaneous Recovery (From Kunz et al)

Figure 27

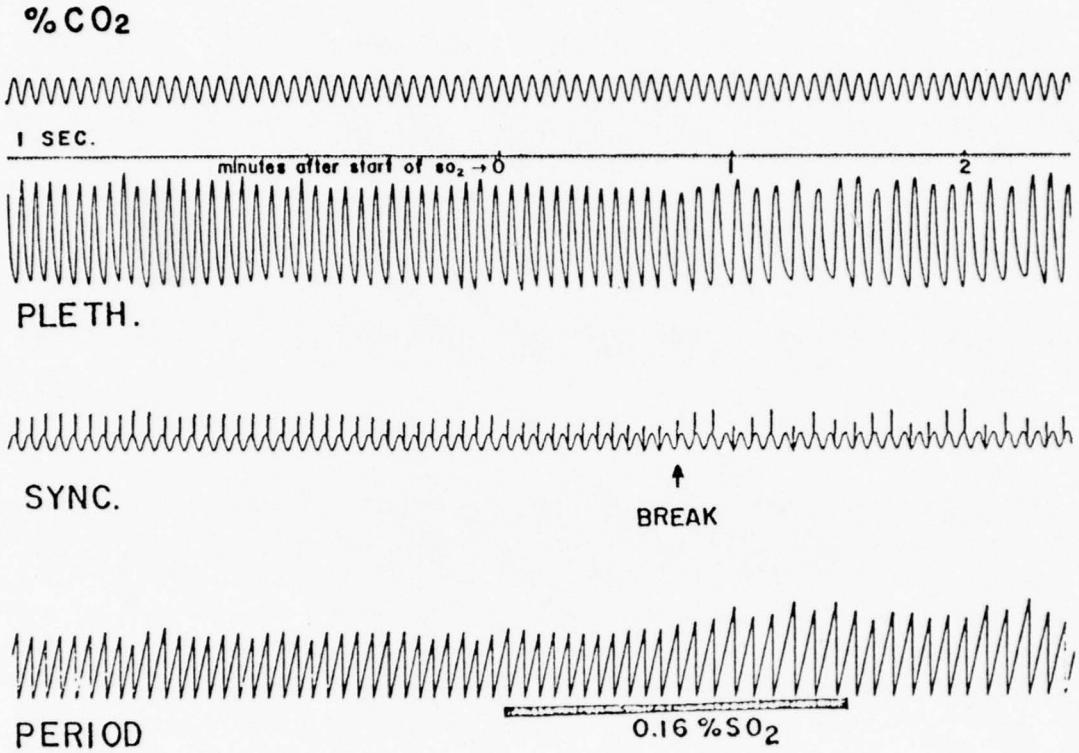

%CO2
1 SEC.
minutes after start of SO_2 → 0
1
2
PLETH.
SYNC.
BREAK
PERIOD
0.16 %SO_2

Figure 28

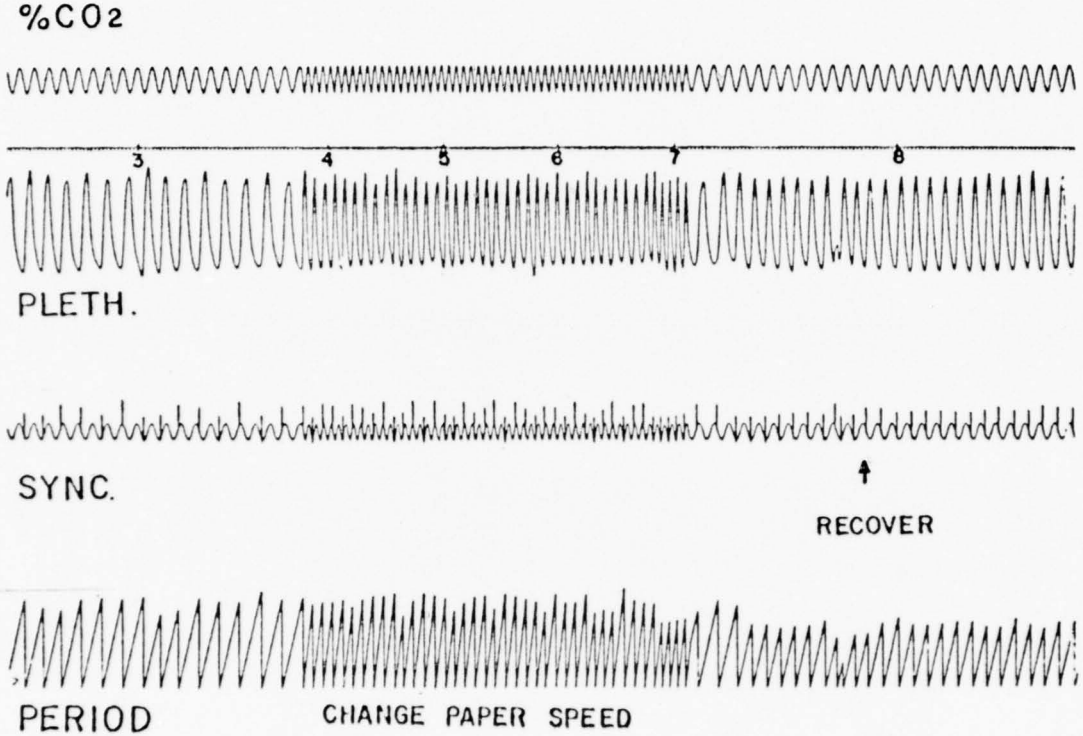
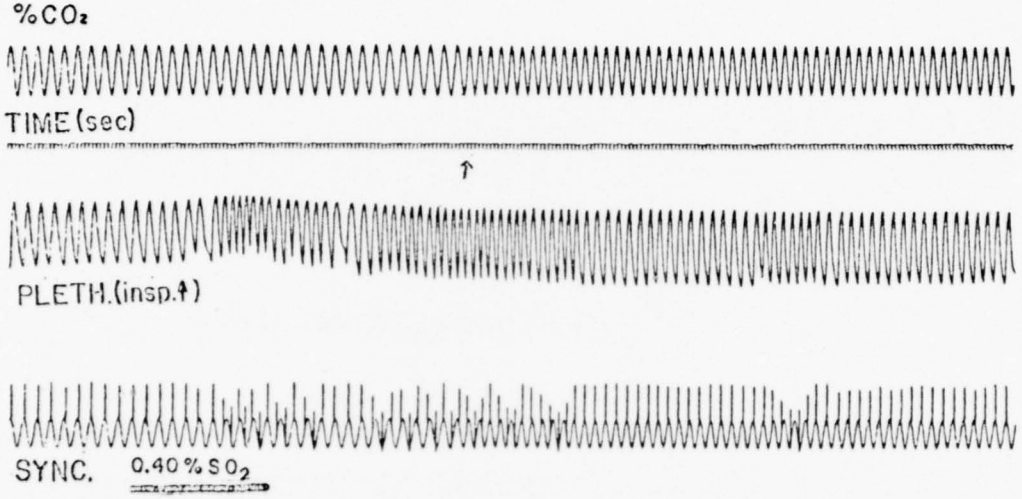
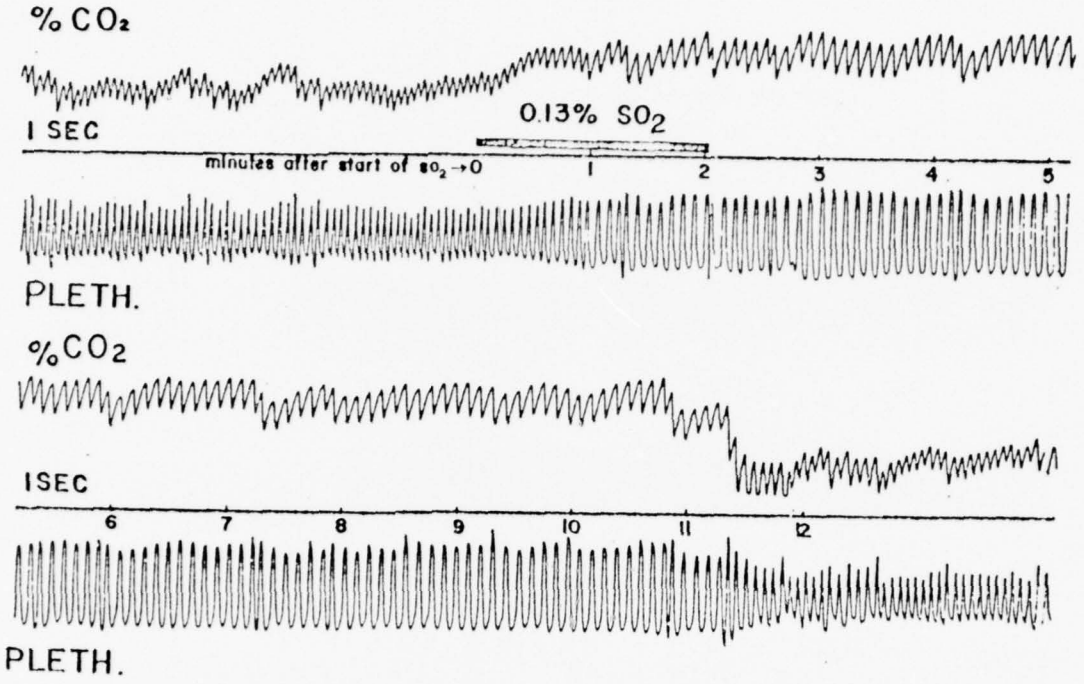


Figure 29



I.V. Infusion of SO_2-Aerated Saline in CO_2 Pacing

Figure 30



Closed-Loop CO_2 Regulation after Small Doses of SO_2 in the Steady-State

Figure 31

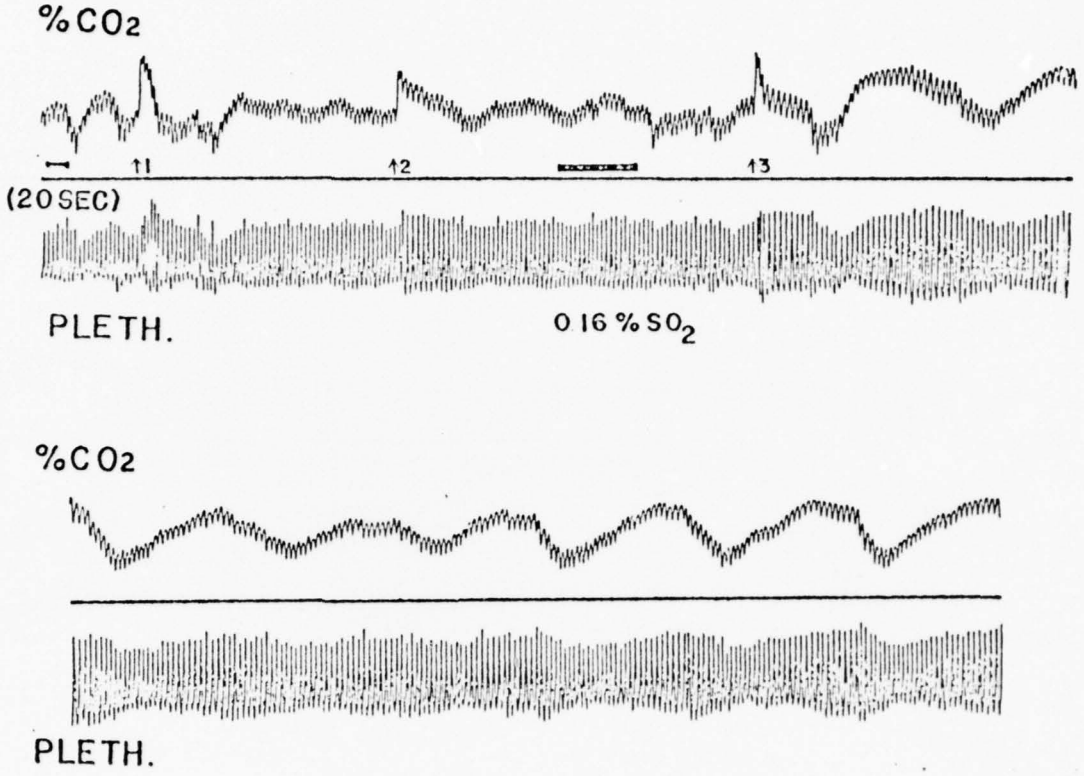
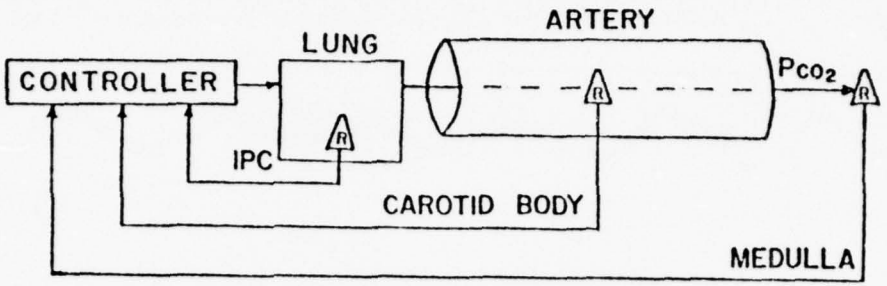
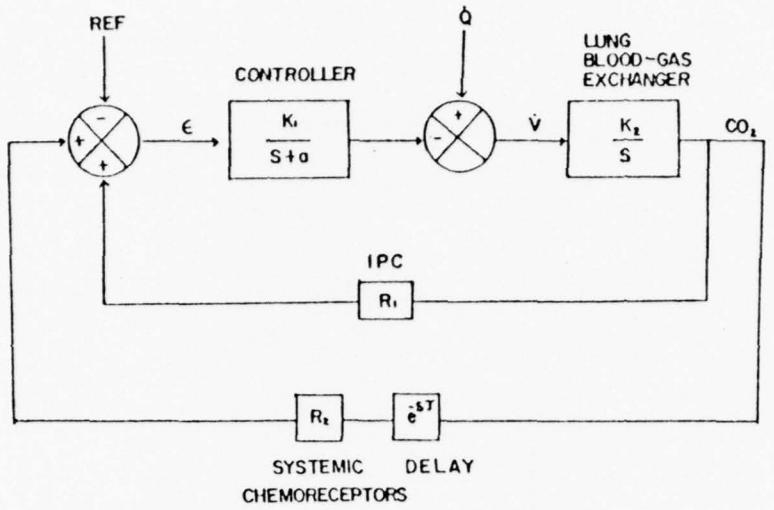


Figure 32



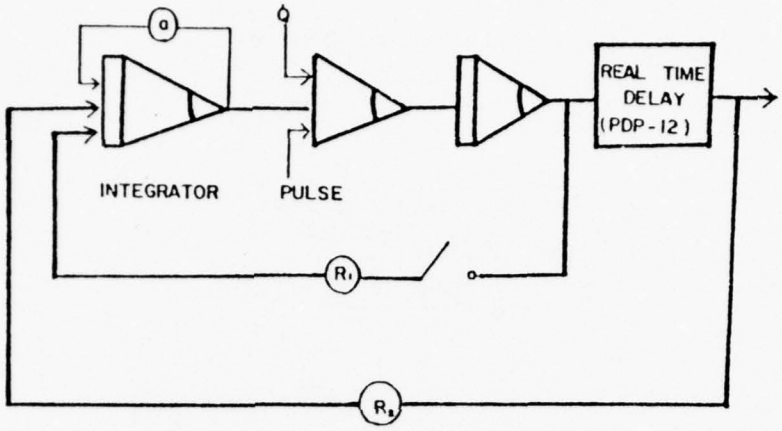
Three CO_2 Receptors with Their Inherent Delays

Figure 33



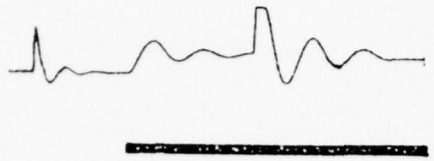
Possible Respiratory Drive of Multiple Feedback Diagram

Figure 34



Analog Simulation Model

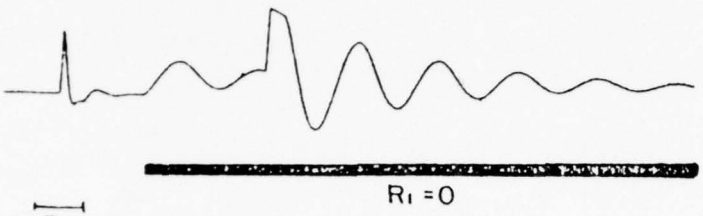
Figure 35



a = 5.0
R_1=1.0
R_2=0.5
DELAY
=1.0 sec.

5 sec.

R_1 = 0

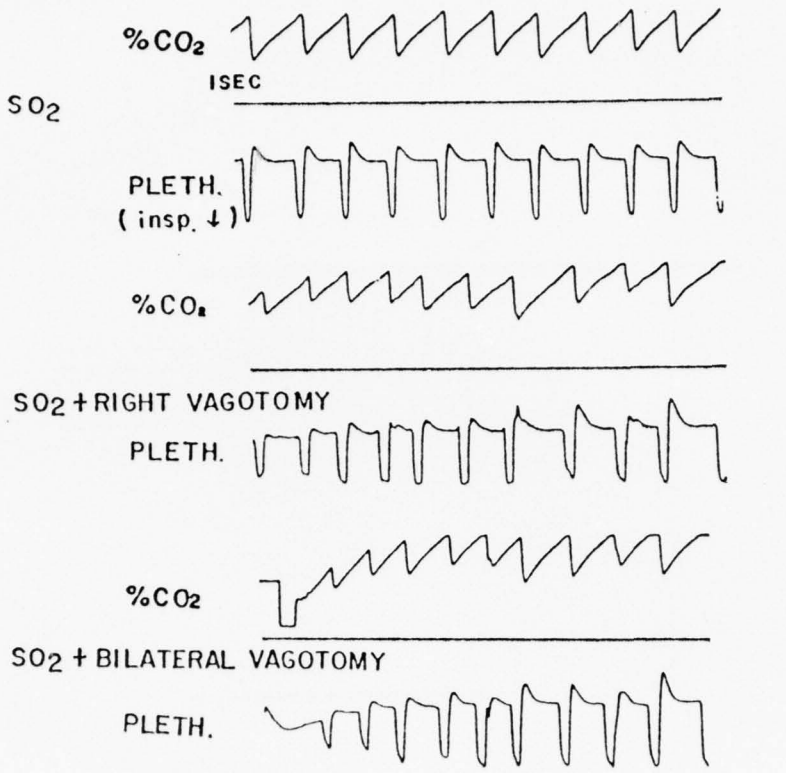


a =5.0
R_1=1.5
R_2=0.7
DELAY
= 4.0 sec.

5 sec.

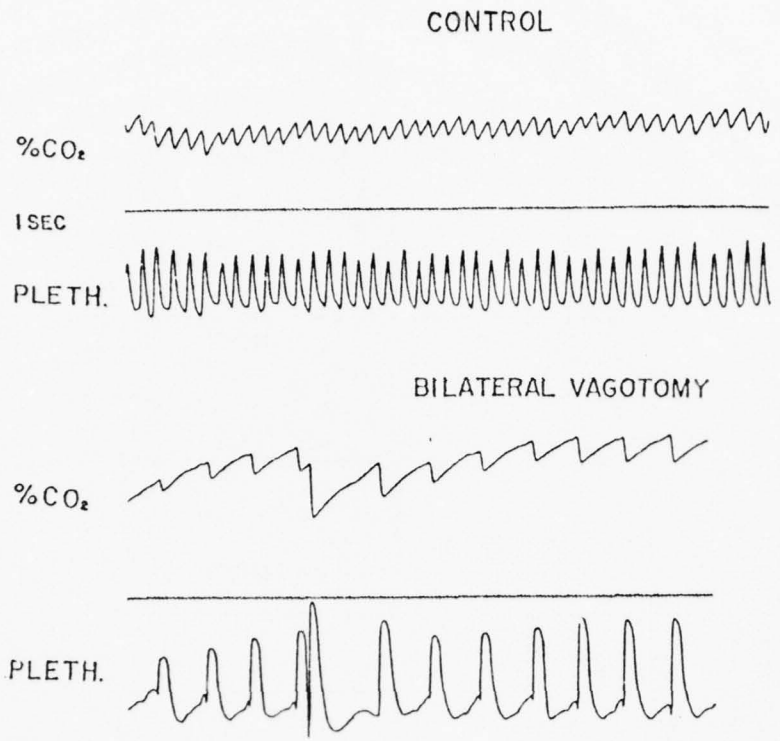
R_1 = 0

Figure 36



PVLB and Subsequent Unilateral and Bilateral Vagotomy

Figure 37



Controlled Closed-Loop Steady-State CO_2 Regulation and Subsequent Surgical Vagotomy

Figure 38

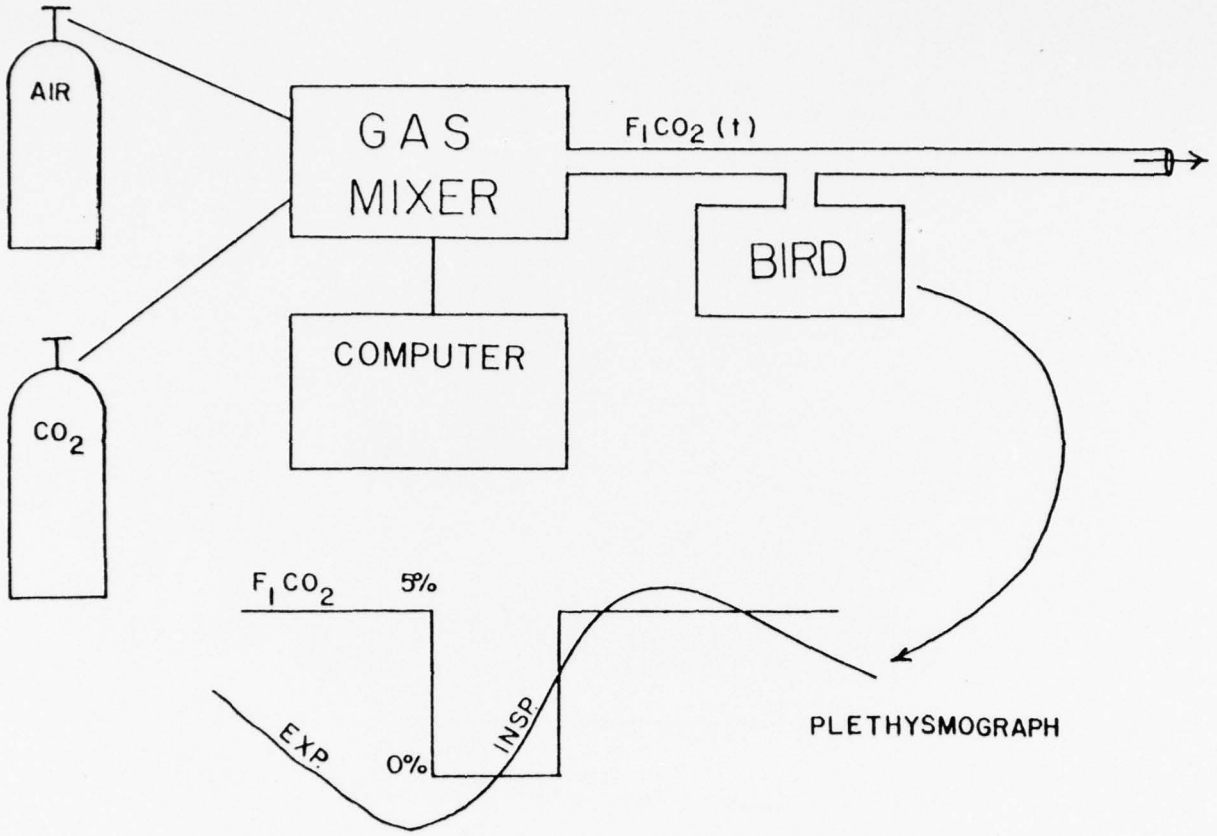

AIR
GAS
MIXER
F_ICO_2 (t)
BIRD
COMPUTER
CO_2
F_ICO_2
5%
0%
EXP.
INSP.
PLETHYSMOGRAPH

Figure 39

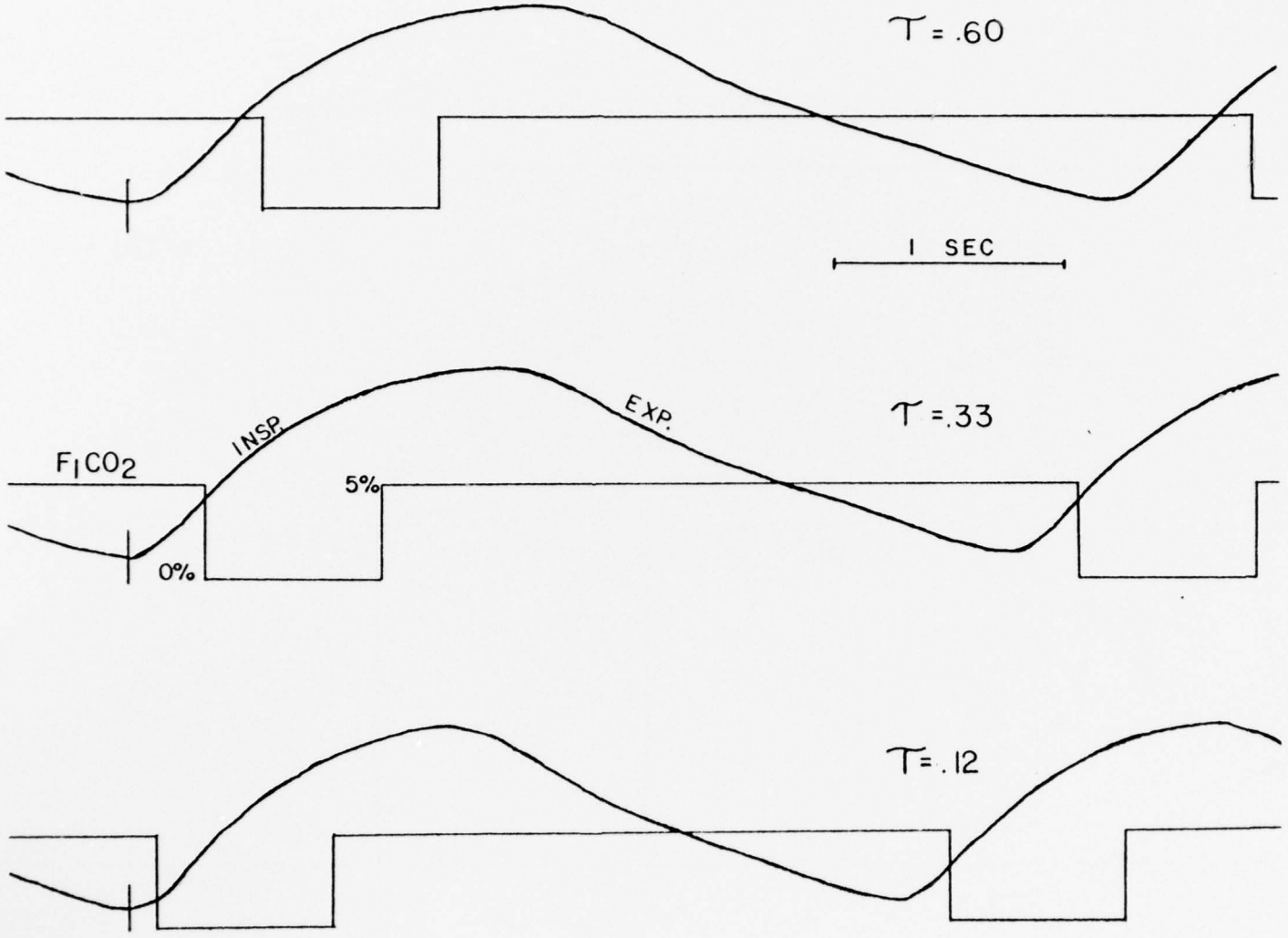


Figure 40

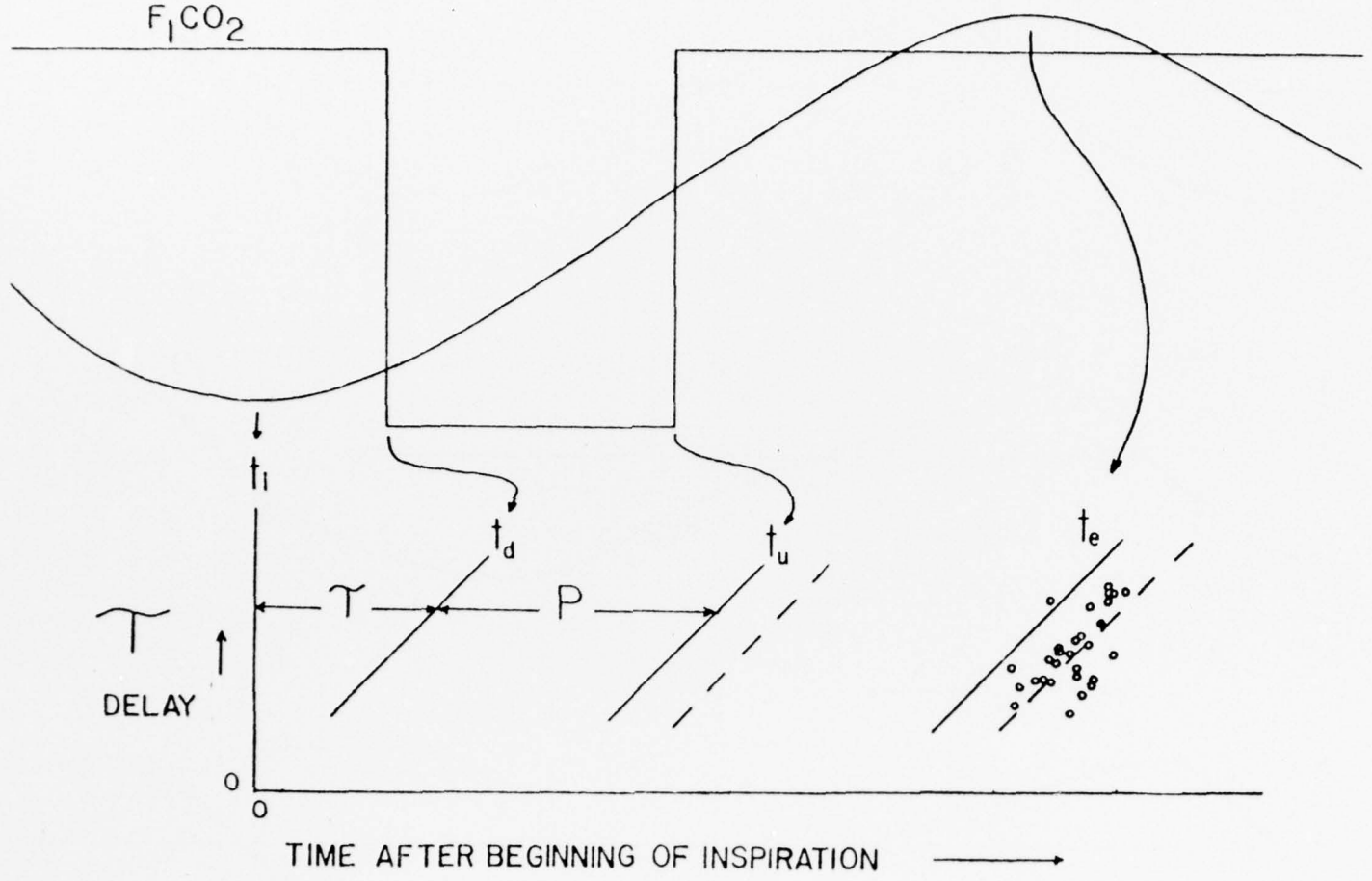

F_ICO_2
t_i
t_d
t_u
t_e
τ
P
DELAY
0
0
TIME AFTER BEGINNING OF INSPIRATION

Figure 41

PROFESSIONAL PERSONNEL

Albert Kunz, M.D.
David A. Miller, Ph.D., 1972
Robert M. Weisberg, Ph.D., 1972
Robert P. Morgan, Ph.D., 1972
Ming-Jen Chiang, Ph.D., 1976
Philip Berger, Post Doctoral Fellow
Richard D. Tallman, Jr. (Ph.D. Candidate)
Dana N. Stone (Ph.D. Candidate)
Keith Michal, Ph.D. (WOC)
Dr. Harold S. Weiss, W.D.C.

TECHNICAL PERSONNEL

Margret Perry
Joan Zipf
David Rittinger
John F. King
Katherine Satter
Gloria McClain
Richard Jackson
Larry Lily
William Dinan
Jane Carman
Dianne Dietrich
Heide Fishpaw
Alan Levinstone
Mike Berman

ARTICLES

1. Kunz, A.K., D.A. Miller and R.M. Weissberg. "The Avian Respiratory Pacemaker: An Analysis of the Effect of CO_2 Dynamics." In: Iberdel, A.S. and A.C. Guyton (eds.), Regulation and Control in Physiological Systems, International Federation of Automatic Control, Rochester, New York (1973), pp. 300-303.

2. Kunz, A.L. and D.A. Miller. "Cyclic Instability of the Avian CO_2 Regulatory System as a Function of Feedback Delay." Proceedings VII International Congress on Cybernetics, pp. 149-158, Association Internationale de Cybernetique, Namur, 1974.

3. Kunz, A.L. and D.A. Miller. "Pacing of Avian Respiration with CO_2 Oscillation." Respir. Physiol. 22: 167-177, 1974.

4. Kunz, A.L. and D.A. Miller. "Effects of Feedback Delay Upon the Apparent Damping Ratio of Avian Respiratory Control System." Respir. Physiol. 22: 179-189, 1974.

5. Miller, D.A. and A.L. Kunz. "Avian Ventilatory Responses to Dynamic CO_2 Signals." J. Appl. Physiol. 39: 129-134, 1975.

6. Kunz, A.L. and Takeo Kawashiro and Peter Scheid. "Study of CO_2 Sensitive Vagal Afferents in the Cat Lung." Respir. Physiol. 27: 347-355, 1976.

7. Miller, D.A. and A.L. Kunz. "Evidence that a Cyclic Rise in Pulmonary CO_2 Triggers Inspiration in Birds." Respir. Physiol. In Press.

8. Kunz, A.L., P.J. Berger, and M.J. Chiang. "Abolition of the Discharge of Intrapulmonary Chemoreceptors of Sulfur Dioxide." Submitted for publication.

9. Tallman, R.D., A.L. Kunz and D.A. Miller. "The Effect of Changing the Temporal Pattern of FCO_2 in the Inspiratory Gas Flow of Birds." In Prep. for Resp. Physiol.

10. Chiang, M.J., P.J. Berger and A.L. Kunz (1977) "The Involvement of Intrapulmonary Chemoreceptors in Pacing in the Domestic Fowl (Gallus domesticus)." Submitted for publication.

The Following Ph.D. Dissertations:

11. Miller, D.A. "Closed-loop Analysis of the Avian Respiratory Controlling System by Varying the Parameters of the Plant." Ph.D. Dissertation, The Ohio State University, Columbus, Ohio (1972).

12. Weissberg, R.M. "The Dynamic Effects of Pulmonary CO_2 on Tidal Volume in a Unidirectional Ventilated Avian Preparation." Ph.D. Dissertation, The Ohio State University, Columbus, Ohio (1972).

13. Morgan, R.P. "Self-paced Respiration in Rats: The Effect of Feedback Delay." Ph.D. Dissertation, The Ohio State University, Columbus, Ohio (1972).

14. Chiang, Ming-Jen. "The Effects of Sulfur Dioxide Block of Avian Intrapulmonary Chemoreceptors on the Ventilatory Regulation of CO_2." Ph.D. Dissertation, The Ohio State University, Columbus, Ohio (1976).

ABSTRACTS

1. Kunz, A.L., R.P. Morgan and D.A. Miller. "Respiratory Responses to Step and Sinusoidal Changes of Alveolar CO_2 Concentration in Unidirectionally Ventilated Chickens." (Abstract), Fed. Proc., March, 1970.

2. Miller, D.A., A.L. Kunz and R.M. Weissberg. "Respiratory Responses to Increased CO_2 Loads in Externally Closed-Loop Chickens." Physiologist 13: 261, August, 1970.

3. Kunz, A.L. and D.A. Miller. "Pacing Respiratory Movements with Alveolar Carbon Dioxide Oscillations." Fed. Proc. 30: 270, March, 1971.

4. Kunz, A.L., R.M. Weissberg and D.A. Miller. "Effect of Controlled Delays in an External Respiratory Feedback Loop." Proc. Intl. Union Physiol. Sci. IX 329, 1971.

5. Kunz, A.L. "Dynamics of Alveolar CO_2 Control." BUMED-ONR Sponsored Navy-wide Workship in High Pressure Biomedical Research, p. 3, May 18-20, 1971.

6. Weissberg, R.M., A.L. Kunz and M.S. Peery. "Feedback Control of Alveolar CO_2 via Respiratory Frequency." Physiologist 14: 251, 1971.

7. Kunz, A.L., D.A. Miller and R.M. Weissberg. "Control of Alveolar O_2 While CO_2 is Kept Constant in an Externally Closed-Loop Preparation." XIX International Congress of Aviation and Space Medicine, p. 68, Tel-Aviv, October, 1971.

8. Miller, D.A. and A.L. Kunz. "Effect of the Amplitude of Respiratory CO_2 Oscillations on Ventilation." Fed. Proc. 30: 428, 1972.

9. Morgan, R.P. and A.L. Kunz. "Self-paced Respiration in Rats: The Effect of Feedback Delay." Physiologist 15: 221, 1972.

10. Tallman, R.D. and A.L. Kunz. "The Effect of Changing the Temporal Pattern of FCO_2 in the Inspiratory Gas Flow of Birds." Physiologist, 19: 385, August, 1976.

11. Berger, P.J., R.D. Tallman, Jr., and A.L. Kunz. "Effect of Temporal Changes in Inspiratory FCO_2 on Intrapulmonary CO_2 Receptor Discharge in Decerebrate Ducks." In press. Fed. Proc. April, 1977.

12. Tallman, R.D., Jr., and A.L. Kunz. "Changes in Inspiratory Duration as a Function of When FCO_2 is Increased in the Inspiratory Gas Flow of Birds" In press. Proceedings. XXVII International Congress of Physiological Sciences, Paris, 1977.

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