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Percutaneous Pco2; a technique for continuous monitoring

Ward John McFarland Jr.
Yale University

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Date

PERCUTANEOUS Pco_2

A Technique for Continuous Monitoring

Ward J. McFarland, Jr.

Submitted to the Department of Surgery
in partial fulfillment of the
requirements for the degree of
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1972

PREFACE

This paper will describe a possible method for noninvasive monitoring of arterial Pco_2. The technique is based on the permeability of the skin to carbon dioxide and on a presumed relationship between skin Pco_2 and arterial Pco_2. Construction details for a suitable apparatus for measuring skin Pco_2 will be presented with results obtained in preliminary *in vitro* and *in vivo* tests. These results will be discussed. and a theoretical justification for this approach will be given

ACKNOWLEDGEMENTS

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The author also owes a special debt of gratitude to his wife, whose help in the preparation of this manuscript was invaluable.

CONTENTS

To B.J.--

In anticipation

INTRODUCTION

Several techniques are commonly available for continuous monitoring of certain physiologic variables; these include temperature, blood pressure, central venous pressure and the electrocardiogram. Techniques are also being developed for continuous monitoring of blood chemistry values (1) and blood gases (1,2,3,4,5,6).

For patients with disorders of respiratory function, the most pertinent measurements of physiologic status include the arterial pH, Po_2 and Pco_2. These will give a semiquantitative estimate of the degree of functional impairment and the efficacy of treatment. Although the more important variable is usually the Po_2, there are situations where simply knowing the Pco_2 would be adequate. As the level of arterial Pco_2 is directly proportional to alveolar ventilation, disorders characterized by alveolar hypoventilation, such as airway obstruction, drug overdose, neuromuscular abnormalities or decreased chest wall compliance, may all be monitored by the Pco_2 alone. Glenn *et al.* (7), studying the effects of electrical stimulation of the phrenic nerve on patients with central hypoventilation, showed that the improvement in the Pco_2 when alveolar ventilation was increased closely paralleled the improvement in Po_2.

The standard method for monitoring a patient's blood gases involves taking repeated arterial blood samples, either from multiple arterial punctures or from an indwelling arterial catheter.

This gives only a discontinuous picture of the patient's status. Because an acutely ill patient may suffer an insidious deterioration not manifested by clear-cut and immediate physical changes, there may be a considerable delay in detecting such a deterioration if blood gas measurements are not performed frequently enough.

To aid in managing such problems, several methods have been developed to allow continuous monitoring of the blood gases. Such methods permit immediate recognition of any changes, so that appropriate modifications of therapy can be made more quickly and effectively. One straightforward method used by several investigators (2,3,4,6) involves the creation of an external arterio-venous shunt where blood from the artery flows past a cuvette containing Po_2-, Pco_2- and pH-sensitive electrodes. The output of these electrodes can be processed and displayed near the patient. This type of system will respond rapidly to changes in blood gases, being limited only by the response time of the electrodes, which is generally less than two minutes. Folkman *et al.* (8) also used an A-V shunt to measure Po_2 and Pco_2, but pumped the blood through thin-walled silicone rubber tubing, through which carbon dioxide and oxygen could readily diffuse. With an ingenious method for measuring the pressure change as the gases diffuse outward from the blood, they were able to closely monitor the Po_2 and Pco_2. An alternate method, which does not involve extracorporeal blood flow, was used by Wald *et al.* (5). A catheter with a gas-permeable tip is placed in an artery or vein. A vacuum applied to the other end

of the cannula causes a continuous flow of carbon dioxide and oxygen from the blood through the tubing to a mass spectrometer where it is measured.

All of these techniques have hazards associated with arterial entry (9,10,11). Mortenson (10), in an exhaustive study of over 3,000 arterial entries, found an overall complication rate of 13 per cent. Infants and children had an increased risk, as did patients with clinically recognized arteriosclerosis or hypertension. Patients with severe aortic insufficiency and those taking anticoagulants had a 40 to 75 per cent risk of complications. Perhaps surprisingly, transcutaneous puncture and cutdown with repair were found to present about equal risks; the Seldinger technique of transcutaneous needle catheterization was considerably more hazardous. Although Mortenson does not deal with the problems of prolonged arterial catheterization, there undoubtedly is an increased risk of thrombosis and infection with catheters left in place several days, as is found with venous catheterization (12). Thus, care should be taken that the advantages of blood gas monitoring, either continuously or with frequent discrete samples, should not be outweighed by the risks.

In order to overcome the difficulties and hazards of obtaining arterial blood for blood gas studies, "arterialized" capillary blood (13) and mixed venous blood (14) have been proposed as alternative sources of blood for blood gas measurements. There is considerable controversy (13,14,15,16,17,18), however, about the degree to which

these techniques are correlated with arterial measurements, particularly in very ill patients, and they are not universally accepted techniques.

The ideal solution would be a totally noninvasive technique which is accurate and reliable. Since carbon dioxide and oxygen are exchanged through the lungs, techniques which measure alveolar concentrations of these gases, such as described by Farhi and Haab (19), can be used to estimate their tensions in mixed venous blood. However, in the presence of significant ventilation-perfusion abnormalities, the alveolar and arterial gas tensions will not correlate well.

An interesting technique for monitoring Pco_2 was suggested by Johns *et al.* (20). They reasoned that in the presence of adequate blood flow, the Pco_2 of the skin should be closely related to the arterial Pco_2. By means of a Pco_2 electrode mounted against the skin surface, they were able to measure skin Pco_2 in eight patients, and reported a very good correlation with arterial Pco_2. This approach seemed potentially useful as the basis of a clinical monitoring device, and because additional information concerning this technique could not be obtained from the authors, it was decided to conduct a study which would further determine the limitations and capabilities of the technique. This paper will describe a suitable apparatus for measuring skin Pco_2 and will provide some preliminary data on its operation *in vivo*.

EXPERIMENTAL DESIGN

As will be discussed further in a later section, human skin permits the passive diffusion of most gases, including carbon dioxide. Because it is a passive process, the direction and rate of flow of carbon dioxide across the skin depends to a large degree on the difference in partial pressures of the gas present on the two sides of the skin. Under normal conditions, gas is diffused outward from the relatively high internal partial pressure of carbon dioxide to the environment, where its partial pressure is nearly zero. If the carbon dioxide which passes through the skin is prevented from being dissipated into the environment, then a gradual accumulation of carbon dioxide will take place on the outer surface until the concentration there equals that under the skin, at which point no further net flux can occur.

Utilizing this principle, a device for determining the Pco_2 of an area of skin was constructed. As shown in cross-section in Figure 1, the sensitive tip of a Pco_2 electrode is separated from a site on the skin by a thin rubber washer. When the electrode is first placed against the skin, the gas within the chamber formed between the electrode tip and the skin surface will be composed of room air, and the Pco_2 will be almost zero. After the electrode is left in place for a time, diffusion through the skin will cause the Pco_2 within the chamber to approach that of the underlying skin.

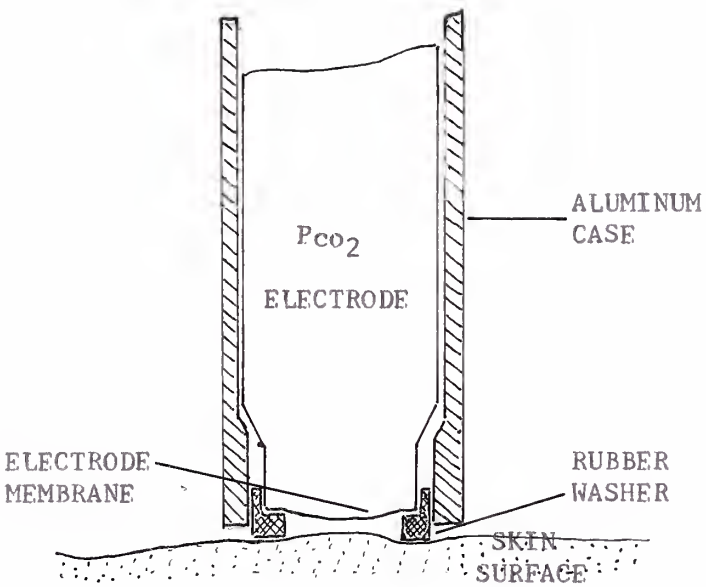

FIGURE 1

Cross-section of
Electrode-Skin Junction

The rate at which equilibrium within the chamber is reached depends on several factors: the diffusion rate of carbon dioxide through the skin, the area of skin covered by the chamber, the volume of the space between the electrode and the skin and the rate at which the diffused carbon dioxide is mixed with the gas already present within the chamber. To minimize the waiting time between application of the electrode and establishment of an equilibrium, several of these factors can be optimized. The diffusion rate of carbon dioxide through the skin can be increased by removing all or most of the stratum corneum by a process described in the next section. The area of the skin site can be increased, but this will simultaneously increase the volume of the chamber and therefore will increase the quantity of carbon dioxide which must pass through the skin in order to reach equilibrium. The volume of the chamber can be reduced by using as thin a washer as possible. The elimination of the washer entirely would result, of course, in minimum volume, but this is not possible, as will be discussed in the next section.

The Pco_2 electrode is described in detail in Appendix II. Briefly, it measures Pco_2 by measuring the change in the acidity of a dilute bicarbonate solution. This change is caused by the presence of dissolved carbon dioxide in the solution. A pH-sensitive glass electrode is separated from a thin, gas-permeable membrane (typically Teflon or silicone rubber) by a porous spacer in which

the bicarbonate solution is trapped. Carbon dioxide diffuses freely through the membrane and dissolves in the bicarbonate solution, and the resulting change in pH is measured by the glass electrode. Since the gas-permeable membrane is composed of a material which is permeable only to gases, the electrode will operate equally well in gases or in liquids containing carbon dioxide. The electrode employed in this study is a commercially available unit* which is approximately 1.5 cm in diameter and 8 cm in length, with a sensitive tip 0.7 cm in diameter. The electrode is furnished with 0.005 M sodium bicarbonate solution, a 12 Teflon sheet for the membrane and Joseph paper (thin lens paper) for the spacer. Twenty-five micron silicone rubber was also tried as a membrane material.

To provide further mechanical strength and to allow electrical shielding, a tightly-fitting aluminum shell has been added, which surrounds the plastic case of the electrode. The entire assembly (electrode and shell) is then surrounded by a coil of thin-walled 1/8 inch plastic tubing through which preheated water can be pumped to maintain a constant electrode temperature of 36°C. (See Appendix III for details of the thermostatting assembly.)

The rubber washer which fits over the tip of the electrode must form an air-tight seal with the skin surface to prevent leakage

*Radiometer type E5036

of carbon dioxide into the air. A lucite plate (10 x 5 x 0.8 cm thick) is used to mount the electrode against the skin. In the center of the plate a hole is made of just sufficient size to provide a firm friction fit with the aluminum shell of the electrode. When the plate is held flat against the skin with an elastic strap, the electrode remains perpendicular to the skin and the tip can make a firm seal. The tension of the strap can be adjusted as can the distance which the electrode protrudes from the plate, so that the rigidity of the mounting can be varied.

The output of the Pco_2 electrode is a voltage which varies as the logarithm of the Pco_2. This signal is led to an amplifier and an antilogarithmic circuit, as described in Appendix II. The output of this circuit, when calibrated, will be a linear function of Pco_2, where one volt is equivalent to ten millimeters of mercury. This output can be displayed by any convenient means--panel meter, digital voltmeter or chart recorder. In this study, readings were taken at minute or half-minute intervals (depending on the rate of change of the output) on a digital voltmeter* for three-digit accuracy.

The testing of this assembly consisted of four parts, described in greater detail in the next section: an extensive check of the performance of the system in vitro and simulated in vivo

*Keithly Instruments model 160

conditions, a study using an anesthetized domestic pig under controlled laboratory conditions, a series of tests on the skin of the investigator under somewhat less well-controlled conditions and a preliminary study of several patients with known arterial Pco_2 under truly clinical conditions.

RESULTS

In Vitro Results. In general, the Pco_2 electrode proved quite reliable in all in vitro studies. However, one problem was encountered with the use of the Joseph paper spacer supplied by the electrode's manufacturer. Despite careful assembly of the electrode, it was noted that after a period of use there were small bubbles trapped within the Joseph paper between the outer membrane and the glass electrode. These bubbles were not present immediately after assembly of the electrode, and the reason for their formation is obscure. Their effect was clear, however,--the electrode's response rate was greatly slowed. When the spacer material was replaced with a very fine nylon mesh, this problem disappeared.

For calibration and testing purposes, gas mixtures containing known concentrations of carbon dioxide were used. To prevent cooling or drying of the electrode tip, these gases were warmed and humidified before being allowed to flow past the electrode tip. As long as the rate of gas flow was kept reasonably slow to allow complete warming and humidification, there was little variation in the output of the electrode for a given gas. A slow drift towards a lower Pco_2 reading was noted particularly when the bicarbonate solution in the electrode had just been replaced; several days of 'aging' reduced this drift

to a minimum. Even with fresh bicarbonate solution, the drift seldom exceeded 1 mm Hg of Pco_2 per hour.

The slope of the electrode response, ΔVelect/Δ log Pco_2, was calculated from the output of the electrode for two gases of known composition. The average value was 54.1 mV/Δ log Pco_2, with a variation of less than 2 per cent in repeated measurements. Because of the relatively constant nature of this value, the linearizing circuitry was adjusted to use the average value of 54.1, allowing the use of a single known gas for routine calibration checks (see Appendix II).

The Pco_2 electrode does not respond instantaneously to an abrupt change in the Pco_2 at its sensitive tip. The gas must diffuse through the electrode's membrane and establish an equilibrium with the bicarbonate solution. The length of time required for this equilibrium to occur depends on the membrane material, the electrode temperature and the bicarbonate concentration. The latter two factors were kept constant throughout all experiments at 36°C and .005 M, respectively. Figure 2 shows representative curves of the time response of the electrode for two different membrane materials: 12μ Teflon and 25μ silicone rubber. After an abrupt change in Pco_2 from nearly 0 (room air) to 50.5mm Hg, the electrode responds in an exponential manner. The output reaches 90 per cent of its final value in 30 to 40 seconds when the silicone rubber membrane is used, and in approximately 90 seconds with the Teflon membrane. The Teflon

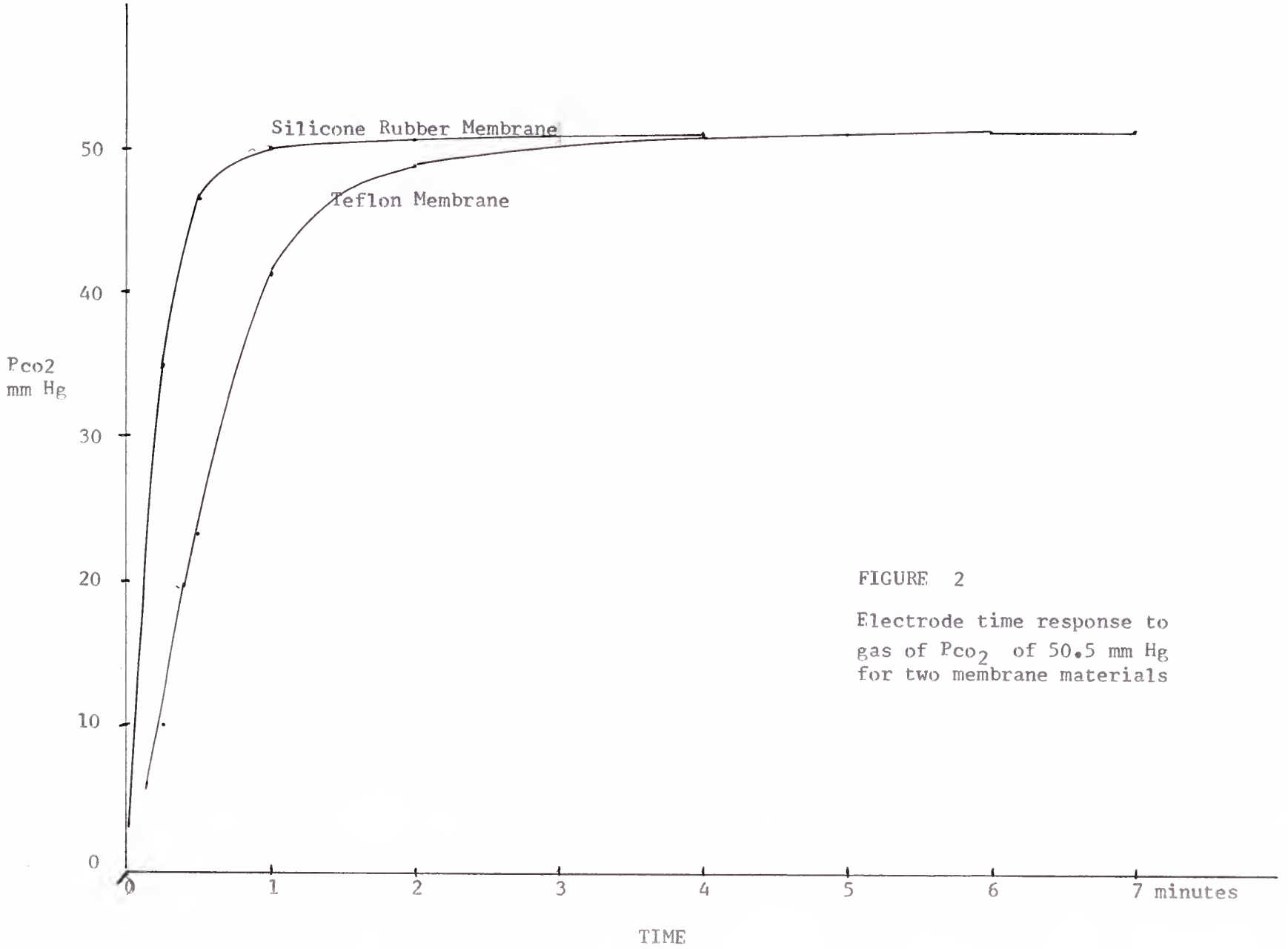

FIGURE 2

Electrode time response to gas of Pco_2 of 50.5 mm Hg for two membrane materials

membrane has certain mechanical advantages as discussed in Appendix I, but due to the more rapid response of the silicone rubber, this was generally the preferred material in this study.

When the electrode is used against the skin, there is no actual movement of gas past its tip, as there is in the *in vitro* studies just described. If there is leakage of gas around the junction between the electrode and the rubber washer, or if the washer actually absorbs gas, the *in vivo* accuracy would be affected. Since neither of these problems can be evaluated while the electrode is being tested with a constant flow of gas, the electrode was placed against a surface of "artificial skin" to test the effects of leakage or absorption. A gas with a Pco_2 of 50.5 mm Hg was allowed to flow through a small open-ended chamber. The open end was covered with a layer of thin silicone rubber, through which the gas could pass by diffusion. The electrode was placed against the rubber and its response was measured. As can be seen in Figure 3, the electrode responded somewhat more slowly, due to the presence of an additional diffusion barrier, requiring about 130 seconds to reach 90 per cent of the final value, as opposed to 30 to 40 seconds for the electrode itself. The final value obtained was identical to that obtained when the electrode was placed directly in the flowing gas, demonstrating that neither leakage nor absorption should affect the accuracy of *in vivo* results.

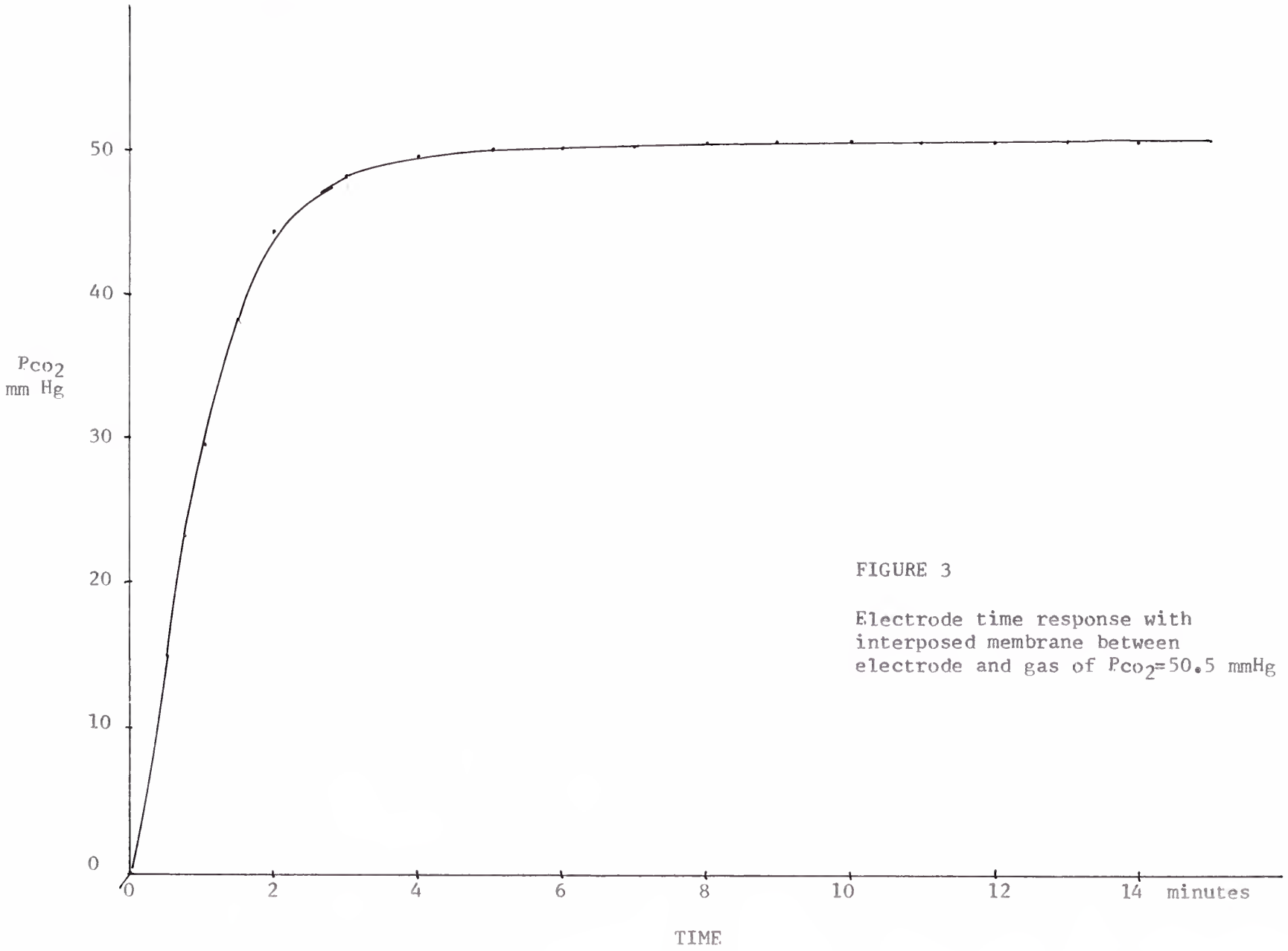

FIGURE 3

Electrode time response with interposed membrane between electrode and gas of P_{CO_2}=50.5 mmHg

In vivo Results. Since all subsequent experiments in this study make use of skin sites from which the stratum corneum has been removed, it is worthwhile to describe the method for accomplishing this and the effects of reducing the thickness of the stratum corneum on the response rate of the electrode. The electrode was first applied to the volar surface of the left forearm of the investigator and its time response determined. For this purpose, the increase in measured Pco_2 occuring in the first two minutes was considered a reasonable measure of the response rate. Then the electrode was removed and successive applications of cellophane adhesive tape (Scotch® tape) were used to remove a portion of the stratum corneum. A piece of tape approximately 2 cm by 3 cm was pressed firmly onto the skin and removed with a rapid peeling motion. This process was repeated 10 times before the electrode was reapplied and the response rate again determined. This entire sequence was repeated, with measurements of the electrode response made after 10, 15, 21, 27, 33, 40 and 50 tape strippings had been made. The results of these measurements are plotted in Figure 4; examination of this figure demonstrates that there is indeed almost a five-fold increase in the response rate after 50 strippings. Most of this increase occurs after the first 25 or 30 strippings. In order to insure a rapid response in subsequent experiments, a minimum of 30 strippings were performed to the skin site chosen for application of the electrode.

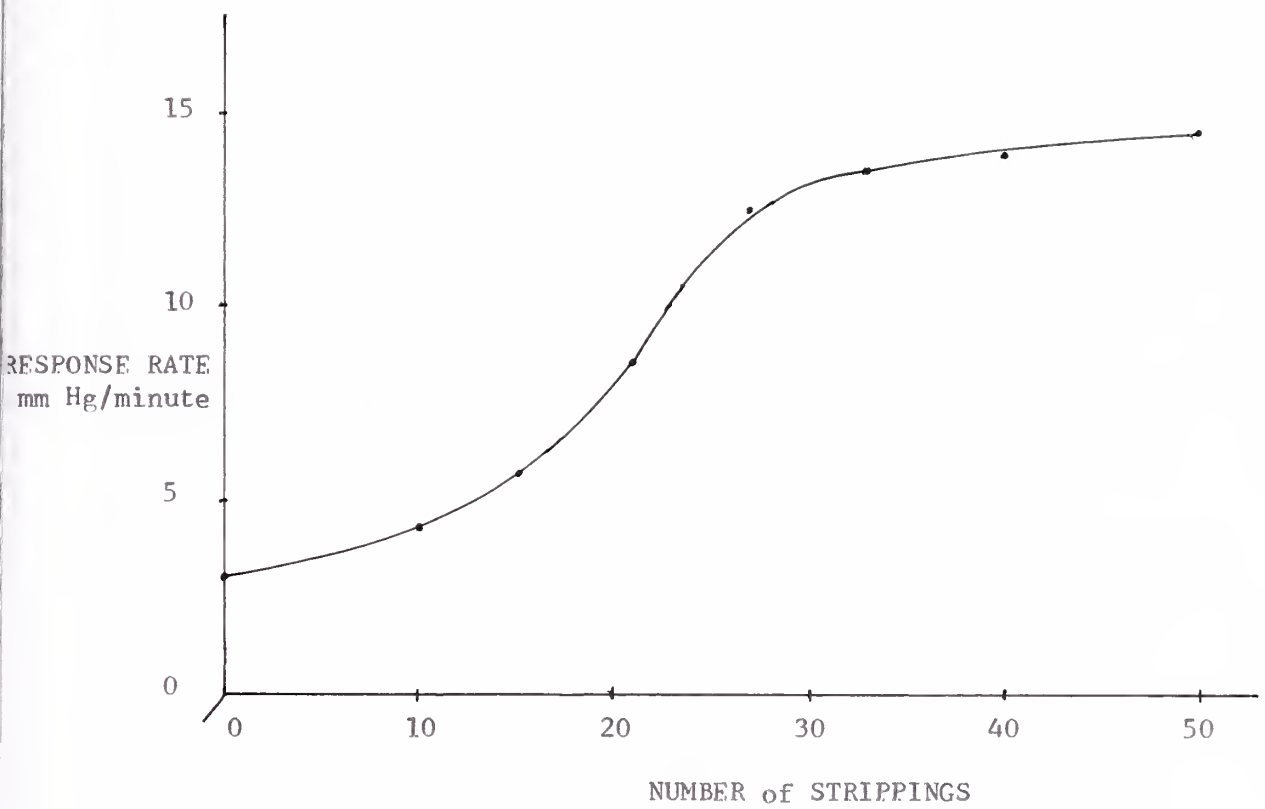

FIGURE 4

Time response of electrode vs. number of skin strippings

After about 30 such strippings, the skin appears somewhat shiny and slightly moist. In addition, the stripping process evokes a mild inflammatory response, particularly if the process is continued well beyond 30 times. The inflammatory response appeared more marked on the investigator's skin than on the skin of others on whom the technique was used. This inflammation disappeared within 12 hours; within several days the skin site appeared slightly hyperkeratotic, a condition which cleared up within two weeks. The stripping process is essentially painless, unless the stripping is continued beyond the point at which inflammation has developed, at which time a mild burning sensation accompanies further applications of tape.

In an attempt to test the electrode under carefully controlled laboratory conditions, a young domestic pig weighing 17 kg was anesthetized with allobarbital and paralyzed with d-tubocurarine. Respiration was artificially maintained via an endotracheal tube, and a femoral artery catheter was in place for obtaining blood samples. A site on the upper abdomen was shaved and the stratum corneum stripped with tape as described. Figure 5 shows the time course of the electrode output after application to the prepared site. Initially, the arterial Pco_2 was constant between 17 and 18 mm Hg with a respiratory minute volume of 6 liters/minute. The corresponding skin Pco_2 was 25.5 mm Hg with a 90 per cent response of 9 minutes for the electrode. When the minute ventilation was varied as shown in the diagram, the skin and arterial Pco_2 closely

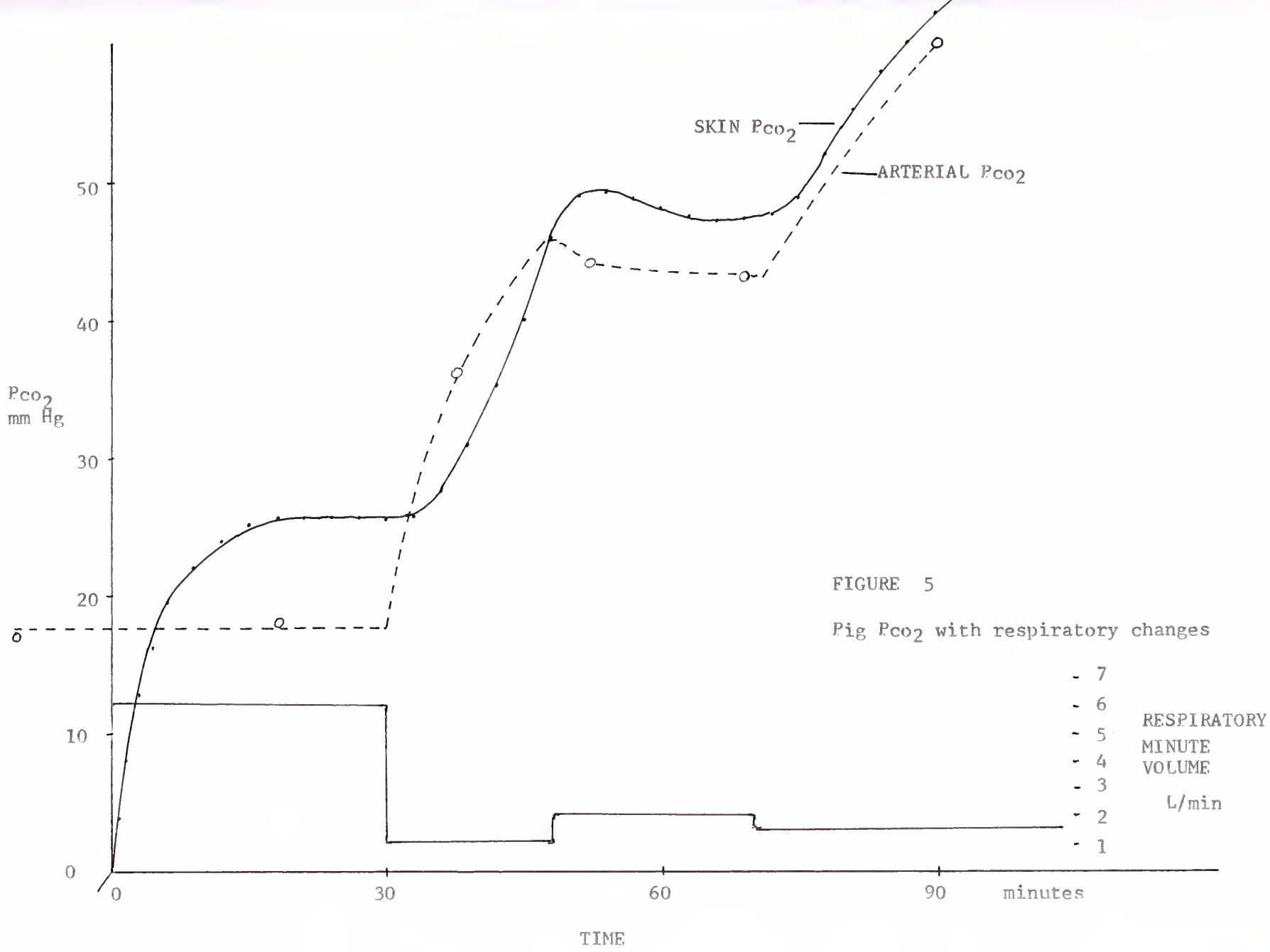

FIGURE 5

Pig P_{CO_2} with respiratory changes

paralleled one another. Although the electrode output for skin Pco_2 tended to lag behind arterial levels during the periods of change, the skin Pco_2 was consistently 5 to 8 mm Hg higher after equilibration was complete.

During early attempts to use the electrode to measure the Pco_2 of human skin, a problem was encountered which at the time appeared quite puzzling. The same Pco_2 electrode which had performed so well *in vitro* frequently developed a significant calibration error after having been used against the skin. In an extreme case the electrode accurately responded to a gas of 49.7 mm Hg Pco_2 before application to the skin and read 61.7 mm Hg for the same gas after 16 minutes against the skin of the investigator's left forearm--a 25 per cent increase. If the electrode was then allowed to remain off the skin, its response gradually returned to normal. Since this problem existed only during *in vivo* use, the most likely cause would be some factor affecting the electrode tip, as this is the only part of the system which is subjected to a different environment *in vivo* than it is *in vitro*.

Several possible factors relating to use against the skin were considered: temperature of the tip, permeability of the electrode to substances other than gases and pressure from skin contact with the electrode tip.

Skin temperature could indeed affect the electrode's response if sufficient coooling of the tip occurred. The body

of the electrode is maintained at a constant temperature as described elsewhere, but the tip temperature can be affected by local conditions. Repeated measurements of the skin temperature at or very near the site of electrode application demonstrated no more than a 1 or 2^{o} C difference between the skin temperature and the electrode temperature of 36^{o} C. In vitro tests of temperature sensitivity to this magnitude of temperature difference showed a small change in the electrode's output, but this was insufficient to account for the amount of error experienced in vivo.

If the membrane surrounding the electrode's sensitive tip were permeable to fixed acids as well as to gases, the response of the electrode could change when the electrode tip were exposed to sweat. However, it can be shown both on theoretical (see Appendix I) and on experimental grounds (by exposing the tip to dilute hydrochloric acid) that the electrode is not responsive to substances other than carbon dioxide.

The possibility of pressure on the electrode tip as the cause of the problem was somewhat more difficult to evaluate. When the electrode is in position against the skin, direct observation of the tip is not possible. However, after the electrode had been in place for several minutes, an imprint left by the rubber washer was visible in the skin surface; in addition a small central depression, undoubtedly due to contact between the electrode and the skin, was frequently noted.

If contact between the electrode and the skin was the cause of the problem, then providing a greater space between electrode and skin should result in eliminating the error. Since the electrode tip is slightly convex, the rubber washer is required to prevent leakage of carbon dioxide from around the tip. However, the thinner this washer can be made, the more rapidly the electrode will respond, as discussed earlier. The contact between electrode and skin results from the pressure which must be exerted by the electrode and mounting plate to maintain a firm, gas-tight seal with the skin and from the elastic properties of the skin which cause it to bulge upwards toward the electrode tip in response to this pressure. A thicker washer should allow this bulging to take place while preventing contact with the tip.

Indeed, increasing the grommet thickness from 0.5 mm to 1.0 mm succeeded in correcting the problem. Except after using an excessive amount of pressure to secure the electrode against the skin, no evidence of tip contact was apparent, nor did any significant calibration error develop after use of the electrode with the thicker grommet. Any increase in response time resulting from the increased volume of dead space between electrode and skin was accepted as necessary for obtaining meaningful data.

Results using the electrode on human skin were generally rather disappointing. Most of these preliminary studies were performed on the volar surface of the investigator's left forearm. The electrode was also applied to several patients with known

arterial blood gases; unfortunately, the aforementioned problems associated with the electrode tip contacting the skin interfered with obtaining meaningful results on all but one of these.

When used on the investigator, a site on the forearm was denuded of stratum corneum with repeated applications of adhesive tape, as described earlier. This removal was generally performed within 30 minutes of the electrode's application. The electrode was applied to this site, protruding from the mounting plate by 1 or 2 mm. The plate was held to the arm with sufficient pressure to insure stability of the electrode with moderate motion of the arm. No evidence of contact between skin and electrode was noted in the results reported here, nor did the electrode's response to a gas of known Pco_2 vary significantly.

Results obtained can be separated into two groups: One group in which the measured skin Pco_2 reached a stable value within 30 minutes or less and another in which this value had reached no apparent end point by this time. The end point is considered stable if there is no significant change in skin Pco_2 over a period of at least five minutes.

In the stable category, there were eight successful trials, lasting for 23 to 50 minutes in length (mean of 32.4 $\pm$ 2.9 minutes). The mean value for the skin Pco_2 in these experiments was 41.5 $\pm$ 0.9 mm Hg with a range of 38.4 to 46.5 mm Hg. The time required for the electrode to reach 90 per cent of its final reading was 7.4 $\pm$ 0.7 minutes, with a range of 5.0 to 10.5 minutes. Figures

6 and 7 are examples of this type of stable performance. In addition, Figure 7 shows the result of one minute of maximal voluntary hyperventilation on the electrode output. The skin Pco_2 begins to fall within 30 seconds of the start of hyperventilation; unfortunately, it was impossible to maintain such a level of hyperventilation for a sufficient period of time to allow the electrode to come to a final equilibrium. Figure 8 demonstrates the effect of inducing maximal inflammation; the skin site had been prepared several hours before application of the electrode and remained moderately erythematous but nontender. The electrode reached a final value of 38.4 mm Hg with a 90 per cent response time of 10 minutes. One drop of histamine phosphate 1:1000 was then applied to the skin site and allowed to remain there for fifteen minutes. An intense pruritis and marked erythema developed. The electrode was then reapplied with all efforts made to use the identical amount of protrusion through the mounting plate and the same tension in the elastic strap. The final value for skin Pco_2 was 42.3 mm Hg, with a 90 per cent response reached in 7.5 minutes. When the electrode was removed, a 2.5 cm wheal and 5 cm flare were present.

Four trials failed to reach a stable end point within a reasonable period of time; the average run length for this group was 33.2 ± 2.4 minutes, with a range of 27 to 40 minutes. The average rate of increase in Pco_2 at the end of each trial was $0.17 \pm .01$ mm Hg per minute. (Other trials showed indications of not approaching an

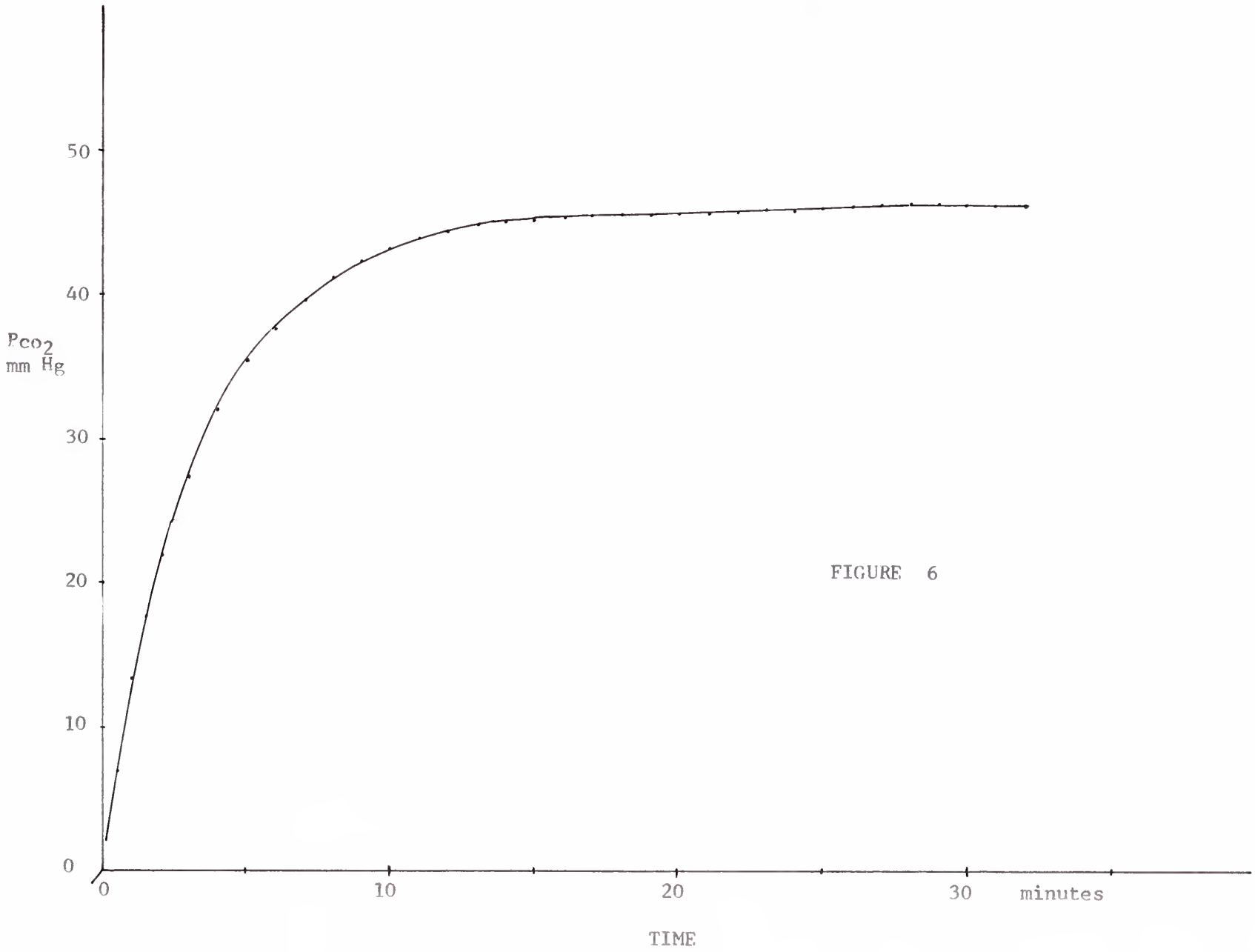

FIGURE 6

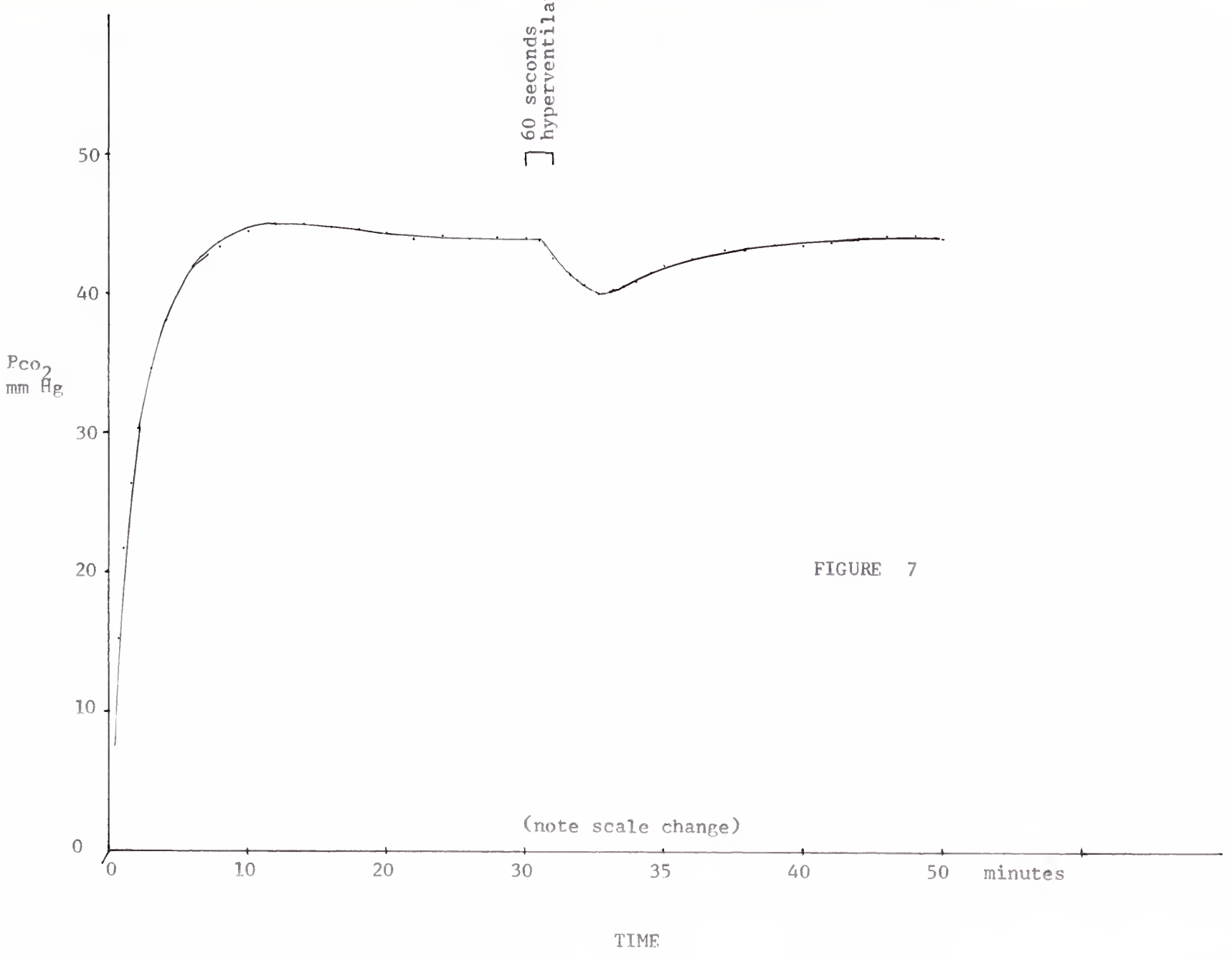
60 seconds hyperventilation
50
40
30
20
10
0
P_{CO_2} mm Hg
(note scale change)
0
10
20
30
35
40
50
minutes
TIME

FIGURE 7

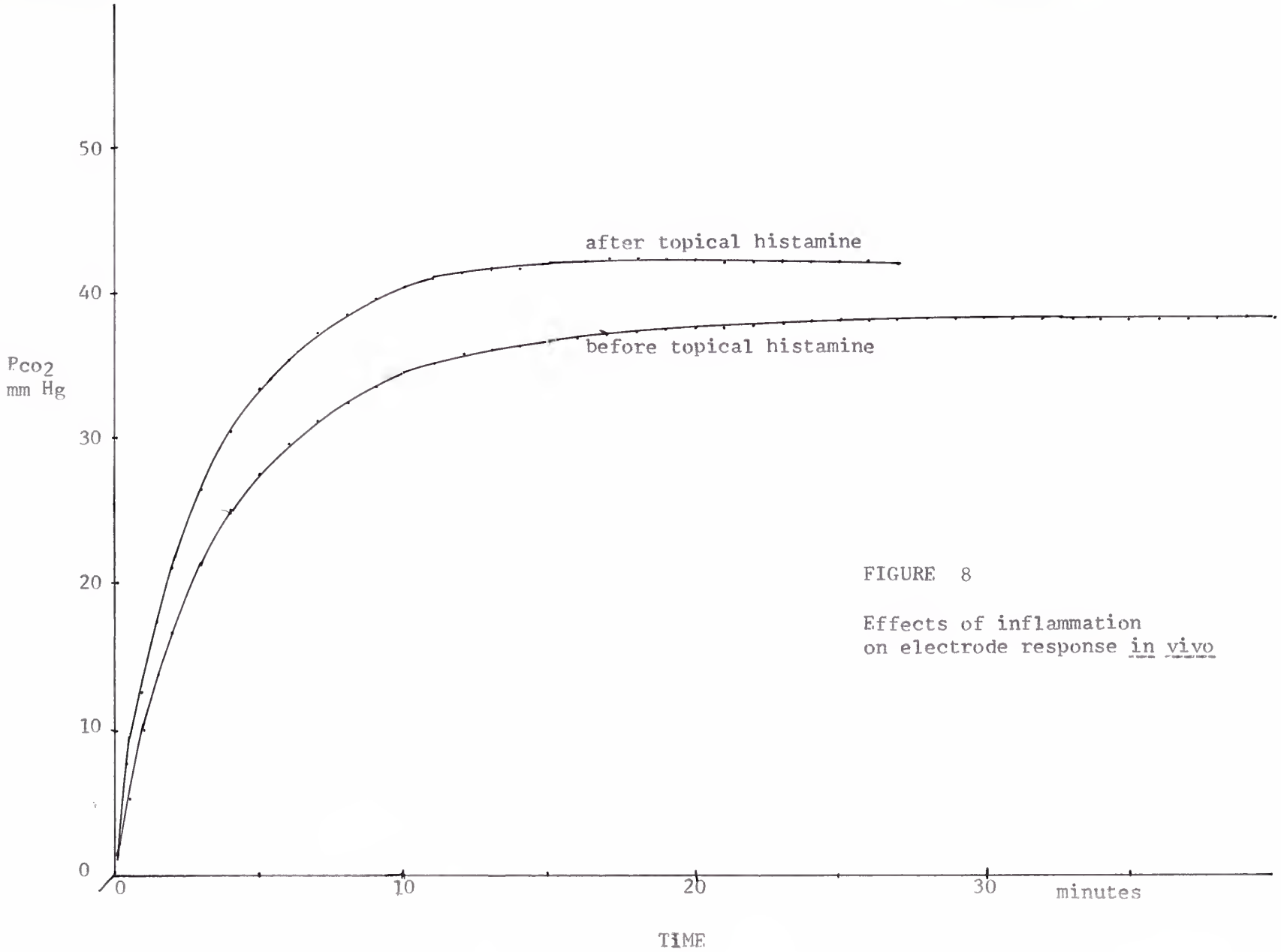

FIGURE 8

Effects of inflammation
on electrode response in vivo

end point, but these were either not of sufficient length to be included here or involved using the thinner washer with the possibility of skin-electrode contact affecting the results.) Figure 9 shows a typical example of this failure to reach an end point. It is clear from this diagram that instead of gradually approaching a final value in an exponential manner (see Figures 6,7 and 8), the Pco_2 continues to climb in an almost linear manner at a rate of approximately 0.15 mm Hg per minute and gives the impression that this rate of climb would continue almost indefinitely.

The single successful clinical trial of the electrode was performed on V.A., a 42-year-old white male with coronary artery disease, approximately five hours after undergoing aorto-coronary artery bypass grafts to the left anterior descending and left circumflex arteries. His respirations were artifidally assisted during this period, with a stable arterial Pco_2 ranging between 29 and 31 mm Hg. The Pco_2 electrode was applied to a site several centimeters below the umbilicus after removal of the stratum corneum as described earlier. All vital signs were reasonably stable during this period and the skin color and temperature at the electrode site and elsewhere showed no evidence of impairment of peripheral circulation. Examination of Figure 10 shows that the electrode first appeared to be approaching equilibrium at 37 mm Hg; at this point the patient was removed from the respirator and endotracheal suctioning performed. The skin Pco_2 again began to rise towards

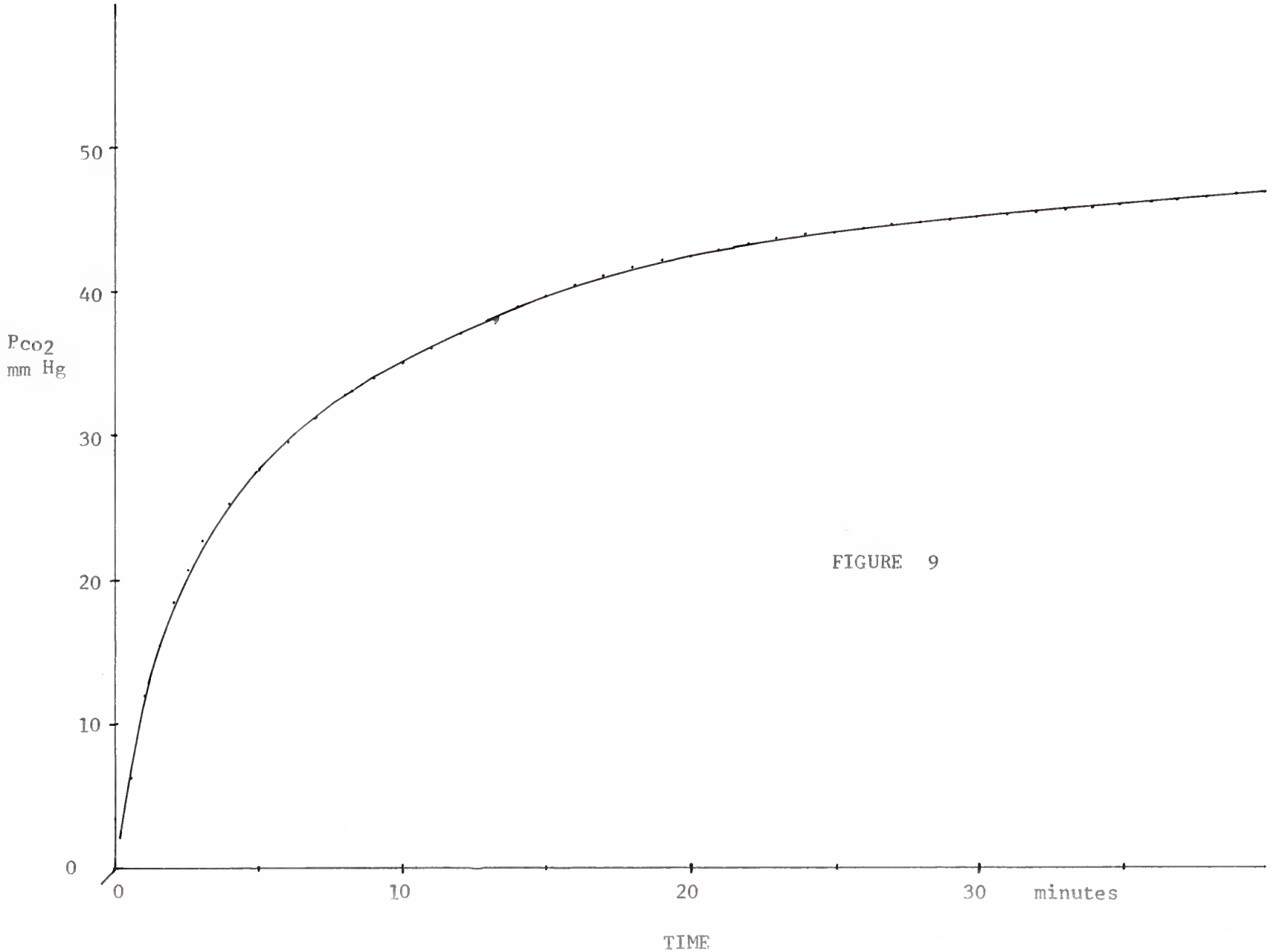

FIGURE 9

42 mm Hg. Another smaller rise occurred after his vital signs were taken (awakening and somewhat disturbing him) and the final value was approximately 43 mm Hg. The skin site showed only minimal erythema, and after four days had become slightly hyperkeratotic.

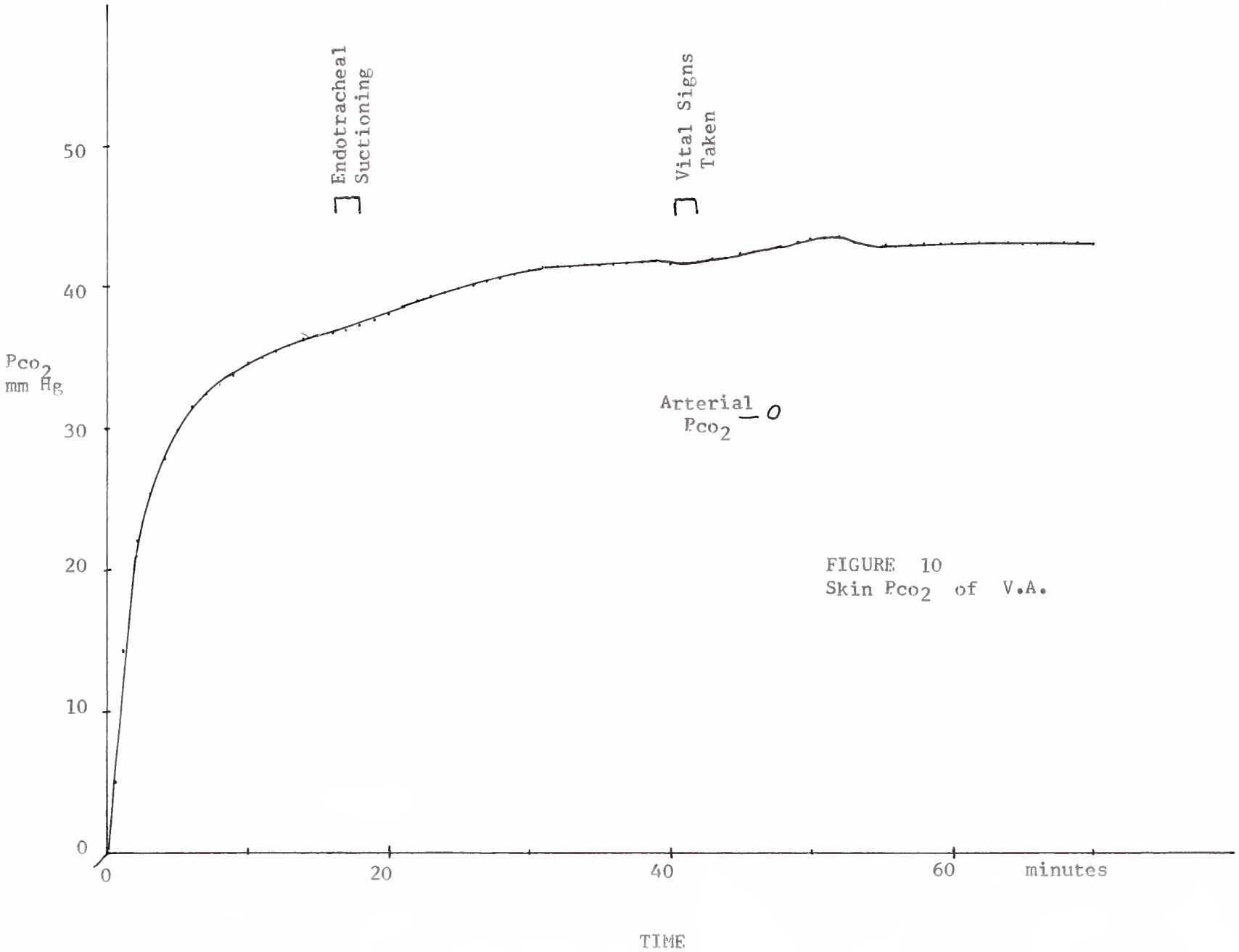

FIGURE 10
Skin Pco_2 of V.A.

DISCUSSION

Percutaneous Gas Diffusion. The skin protects the rather delicate organism from hostile environmental influences and provides an effective barrier against changes in the internal composition of the body. The barrier is not perfect, however, and permits the diffusion of most gases in quantities up to 2.7 per cent of that exchanged by the lungs (21). William Cruikshank, in 1779, was probably the first investigator to become aware of the diffusion of gases through the skin. As Abernethy relates,

> Mr. Cruikshank entertained the opinion, thatthe matter of perspiration, and that expelled from the lungs in breathing, were similar in their qualities. In his experiments, he collected the aqueous exhalation from the skin, but only slightly examined the aeriform matter: he agitated lime water in the air with which his hand had been surrounded, when the precipitation of the lime shewed the existence of fixed air; he has also observed that a candle burned dimly in this air. Such I believe was the extent of the information, which we have heretofore possessed on this subject (22).

In 1793, Abernethy (22) performed a series of ingenious experiments designed to provide more quantitative data on the excretion of "fixed air," or carbon dioxide. From measurements on his own hand and forearm, he concluded, "If then the perspiration of all parts were equal, seventy-seven dram measures of carbonic gas...would be emitted from the body, in the space of one hour."

Using his calculations for his body surface area, this figure can be converted to about 170 ml of carbon dioxide per square meter per hour, a result that compared favorably to more recent work (21). Since Abernethy's work, many investigators have studied the effects of temperature, humidity, age, and other factors on the diffusion of carbon dioxide and oxygen through intact skin. An excellent review of these studies is given by Rothman (23).

The possible sources for the excreted carbon dioxide are two: diffusion from the blood through the skin and production by the skin itself followed by direct diffusion outward. It is generally agreed that the diffusion process itself is simply a passive one, depending primarily on the permeability of the skin to the gas and on the difference in partial pressure of the gas from the tissue level to the outside. For a given individual, the diffusion rate tends to increase with increased temperature, arterial hyperemia and inflammation. The rate is decreased in the palms and soles, and with diminished skin blood flow (23). Decreased rates are also noticed in the elderly and in the newborn. The metabolic needs of normal skin are low and are supplied with a relatively small percentage of the total blood flow which it normally receives (24). It is therefore unlikely that the amount of carbon dioxide diffusing through the skin is significantly influenced by local production. Rothman (23) feels that "only in exceptional cases does the carbon dioxide production of the skin proper contribute to the delivery to the outside," and particularly

cites cutaneous inflammation as a possible cause of increased local production.

The principle used in this paper to estimate the skin Pco_2 relies on the attainment of equilibrium between the Pco_2 present in a small chamber and that of the tissue below. Assuming this equilibrium process to be governed by the laws of simple diffusion across a membrane, it follows that the length of time needed to reach equilibrium will depend on the permeability of the membrane (i.e., the skin), on its thickness, on the area of the membrane and on the volume ofthe chamber. As the equilibrium nears completion, the difference between the partial pressures of carbon dioxide on the two sides will dimnish, reducing the rate of diffusion. The result will be that the Pco_2 of the chamber will approach that of the skin beneath in an exponential manner.

In order for a monitoring device to be useful, it should respond to a change in the measured variable with some alacrity; a method with an excessively slow response would tend to be replaced by a faster, if otherwise less convenient, technique. In order to shorten the equilibrium time of the system described above, several steps may be taken based on the factors outlined. The area of skin used can be increased and the volume of the chamber decreased. These considerations have been discussed in an earlier section. The other rate-limiting factor, the permeability of the skin to carbon dioxide, may in part be overcome by altering the

barrier function of the skin. Although the diffusion of carbon dioxide through the skin is fairly rapid, Shaw et al. (25) found that carbon dioxide diffused about fourteen times as rapidly across exposed muscle as it did across intact skin. If it were possible to find the limiting factor that the skin presents to diffusion, perhaps that factor could be modified to increase the permeability.

The barrier function of the skin has already been considered in studies dealing with alterations in water and electrolyte loss and drug absorption. Malkinson (26) and others [see Rothman (23)] are of the opinion that the principle block to percutaneous diffusion lies in the region between the stratum corneum and the stratum granulosum. Others, such as Monash (27), attribute the barrier function of the skin to the entire thickness of the stratum corneum. By testing the barrier function after increasing thicknesses of stratum corneum have been removed (as will be described), it was found that the rate of absorption of superficially applied local anesthetic gradually increased as the stratum corneum became thinner (27).

The easiest and least traumatic means for removing the stratum corneum layer by layer, first introduced by Wolf (28) and studied in detail by Pinkus (29,30), involves the application of a piece of cellophane adhesive (Scotch Tape®) to an area of skin. After the application of a moderate amount of pressure, the tape is removed, carrying with it an almost continuous sheet of cornified cells. If this process is repeated, successive layers of cells

can be removed. If the number of cells removed per application is counted, it will be found that fewer cells are removed with each subsequent stripping. This was taken by Kligman (31) as evidence that the cohesiveness of the cells of the stratum corneum increased with the depth from the surface. The number of applications needed to completely remove the stratum corneum varies with the pressure used, the adhesiveness of the tape, and the thickness of the stratum corneum. On the forearm, it takes 25 to 30 applications to completely remove the layer (28,30).

As mentioned earlier, the removal of successive layers of stratum corneum causes a proportional increase in the absorption rate of local anesthetics (27). In addition, the transepidermal water vapor loss increases 40 to 50 times when the stratum corneum is completely removed (32). Increased absorption of topical steroids (31) and of topical histamine phosphate (33) have also been demonstrated on stripped skin. It is not difficult to draw the conclusion that most substances to which the skin presents a diffusion barrier should pass more easily through stripped skin than through intact skin. Figure 4 shows data relating the rate of response of the electrode system used in this paper to the number of strippings of forearm skin, which confirms the hypothesis that the stratum corneum provides a significant portion of the barrier to carbon dioxide diffusion. Thus, stripping the stratum corneum seems to be a convenient means

for increasing the rate of response of the system.

Tissue Pco_2. Because blood can be removed easily from the body under anaerobic conditions, blood Po_2 and Pco_2 can be measured easily *in vitro* with every assurance that the values obtained will be the same as they are *in vivo*. Measurements in other tissues have been obtained using several techniques. Thompson and Brown (34) studies carbon dioxide concentrations in rat tissue by sacrificing the animals and storing the various organs under anaerobic conditions before measurement. This type of measurement is fraught with error, because once removed, the tissue is deprived of its circulation but not its metabolism, altering the results. The technique is clearly not suited for sequential measurements or for human use.

Another technique that is somewhat less traumatic involves placing a bubble of gas within the body and assuming that its contents will eventually come to equilibrium with the partial pressures in the surrounding tissues. Campbell (35) reviewed the technique, which has been applied to the pleural and peritoneal cavities and to subcutaneous pockets created by the injection of a quantity of gas. The Pco_2 so measured subcutaneously in a variety of laboratory animals is generally between 45 and 55 mm Hg. On the forearm of man, it seems to be more nearly 40 mm Hg.

Niininoski and Hunt (36), and Myers *et al.* (37) modified this technique somewhat to provide a more continuous means of

monitoring. By means of coils of silicone rubber tubing implanted subcutaneously, they measured tissue gas levels in healing wounds. Again, they assumed that the gas within the tubing would equilibrate with the partial pressures of the gases in the surrounding tissue. The Pco_2 reported by Myers for the skin of pigs ranged between 41 and 53 mm Hg.

On the supposition that lymph would accurately represent the composition of the interstitial fluid bathing the tissue, Bergofsky *et al.* (38) measured the blood gas levels of lymph and found the Pco_2 to be invariably higher than venous levels by an average of 5 mm Hg. The Po_2 was found to be usually around 8 mm Hg, even in the presence of elevated blood levels. The principal disadvantages to the method are the difficulties in isolating the thoracic duct and the slow equilibration of central lymph gas tensions with acute changes in blood gas tensions.

With the development of electrodes sensitive to oxygen and carbon dioxide the measurement of tissue levels of these gases *in vivo* has been simplified. The Po_2 of skin and other tissues has been successfully measured using polarographic techniques (39,40) with implanted platinum electrodes. The Pco_2 electrode (described in detail in Appendix I) is sensitive to the Pco_2 present at its sensitive tip and is equally reliable on gaseous, liquid or tissue samples.

Severinghaus (41,42) used a Pco_2 electrode to measure tissue Pco_2 and found cerebral cortical Pco_2 in dogs to be about 55 mm Hg when the arterial Pco_2 was 40 mm Hg. He also measured the Pco_2 of liver and gut mucosa. He stated that the skin Pco_2 was found to vary from arterial levels to levels exceeding 130 mm Hg when sufficient pressure was applied by the electrode to cause blanching of the skin.

In 1959 Hertz and Siesjö (43) described modifications to the Pco_2 electrode devised by Stow et al. (44). They made two principal improvements over earlier versions: a special design permitting more rapid response and a flat, rather than convex, tip for easier application to tissue. In 1961 Siesjö (45) reported some further refinements of the apparatus along with results obtained on the cerebral cortex of cats. He found that the electrode itself was somewhat pressure sensitive, and devised an elaborate counterbalance for reducing this problem. He reported that the measurements were quite stable over periods of several hours (if the animal's respirations were kept constant) and were repeatable when the electrode was removed and replaced.

Gleichmann et al. (46,47), studying cerebral metabolism in dogs, used Hertz and Siesjö's electrode for measuring the cortical Pco_2. They assumed that the average capillary Pco_2 would be the simple arithmetic mean of arterial and venous (superior sagittal sinus) levels, and found that the tissue

Pco_2 measured by their electrode was a scant 1 mm Hg greater than that average. With calculations relating cortical metabolism, regional blood supply and the carbon dioxide diffusion coefficients in tissue, they were able to explain this small difference as the contribution made by local metabolism.

If, then, the increase in tissue Pco_2 due to local metabolism is so small in an actively metabolising tissue like the cerebral cortex, this is fairly good evidence that the Pco_2 measured on the skin surface will likewise reflect capillary levels accurately. One potential difficulty in this assumption is that the average intercapillary distance is quite small in the brain, while the superficial layers of skin have no direct blood supply, but receive their nutrients from the capillary plexus in the dermis. As Gleichmann et al. (47) showed, the difference between average capillary Pco_2 and average tissue Pco_2 will increase with increasing intercapillary distances. Although a good technique exists for isolating the venous return from the brain, there is none for that from the skin, and a quantitative estimate of the error caused by local production of Pco_2 cannot be easily determined.

Skin Pco_2. In the paper alluded to earlier, Johns et al. (20) used a Pco_2 electrode to measure skin Pco_2 in 11 patients with known arterial blood gases. They reported a statistical correlation between skin and arterial Pco_2:

$$\text{Arterial } Pco_2 = 1.08 \times \text{Skin } Pco_2 + 5 \pm 6.$$

This is a rather remarkable result, particularly in light of their earlier statement in the same paper that tissue Pco_2 was about 5 mm Hg higher than arterial Pco_2. The logical presumption, then, is that the above equation represents an error in printing, with "arterial" and "skin" interchanged. In their brief paper, they made no reference to any problems such as the drift encountered in this study and gave no details of their apparatus.

Severinghaus (41), as mentioned earlier, also used a similar technique to measure skin Pco_2, but noted that the values he obtained ranged from arterial levels to levels exceeding 130 mm Hg when sufficient pressure was applied to cause blanching of the skin.

In considering the results presented in this study, several conclusions can be derived. First, the Pco_2 electrode seems to perform quite well in vitro further confirming other work cited in Appendix I. Second, care must be taken in applying the electrode to the skin to prevent errors resulting from pressure on its sensitive tip, at least when using the type of electrode used in this study. Third, the time response of the electrode, when used on the investigator's skin, averaged 7.4 minutes for a 90 per cent response. Fourth, taking the results of the pig into consideration, the skin Pco_2 would seem to follow the arterial Pco_2 quite well, and the electrode responds accordingly.

Fifth, a slow upward drift in the reading of the electrode was noted with sufficient frequency to preclude it being an accidental problem.

The drift at present cannot be explained, although some hypotheses have been formulated. The necessity for maintaining an air-tight seal between skin and electrode may cause sufficient pressure to be exerted to compromise the local blood supply somewhat, resulting in a slow increase in Pco_2 towards venous levels. Another possible factor may be related to local inflammation caused by the stripping process. Since the electrode was generally applied immediately after the stripping process, the Pco_2 of the skin might increase simply due to increased local metabolism. (The application of topical histamine and the inducing of extreme inflammation was noted to cause a rise in skin Pco_2 of almost 4 mm Hg.) If the inflammation reached a peak slowly enough, this could be recorded by the electrode as a slowly increasing value, as observed. Further studies must be done to better isolate the cause of this drift, however.

Insufficient data was obtained to provide the basis for demonstrating a quantitative correlation between skin and arterial Pco_2. Assuming the arterial Pco_2 of the investigator to be approximately 40 mm Hg., the average skin Pco_2 was about 1.5 mm Hg higher. In the pig studied, the skin Pco_2 was 5 to 8 mm Hg higher than arterial Pco_2. For the one successful

clinical subject, the skin Pco_2 of the abdomen was 11 to 12 mm Hg higher than arterial levels.

In addition to further studies on arterial-skin Pco_2 correlation, other studies should be performed to estimate the response of the electrode to different types of skin and to determine the effects of anesthesia, shock and vasoconstricting medications on the arterial-skin Pco_2 difference. It would also be desirable to devise a better means of holding the electrode against the skin; the method used in this study is not particularly secure against movement unless it is applied excessively tightly. Perhaps the solution may lie in making a smaller, lighter Pco_2 electrode which would require less force to keep it perpendicular to the skin surface.

CONCLUSIONS

Several problems relating to the adaptation of a commercial Pco_2 electrode to measure skin Pco_2 have been identified. Some of these have been overcome, and others need further work. The performance of this device in a limited study suggests that it may have some application in the clinical monitoring of arterial Pco_2; even though an absolute correlation between skin Pco_2 and arterial Pco_2 has not been proven, the skin Pco_2 appears to follow changes in arterial Pco_2. Thus, when changes rather than absolute values are important, this technique may be of value.

APPENDIX I. Operation of the Pco_2 electrode.

Introduction. The Pco_2 is basically a thin layer of a bicarbonate solution separating a pH-sensitive glass electrode from a thin membrane (e.g., Teflon or silicone rubber) which is permeable to gases but not to ions. Since carbon dioxide is the only physiologically occurring gas which can alter the pH of the bicarbonate solution, exposure of the membrane to a sample containing carbon dioxide will result in a pH change proportional to the Pco_2, which will in turn be registered by the glass electrode and can thus be measured.

Historical Background. The "discovery" of the Pco_2 electrode seems to have occurred at least three times. In 1926 Gesell and McGinty (48) wanted a continuous method to record changes in expired carbon dioxide. They developed a method based on "the fact that the acidity of a watery solution varies with the partial pressure of carbon dioxide with which it is in contact." They used dog peritoneal membrane to separate their sample from a manganese dioxide electrode, which they used to measure pH. Although they found the method quite useful, the technique was not generally accepted and was apparently forgotten. Then in 1938 Blinks and Skow (49), studying photosynthesis, placed a glass electrode directly in contact with plant tissue with a thin film

of solution between. They observed prompt changes in pH when they changed the level of illumination the plant received and assumed that these changes were due mainly to changing levels of carbon dioxide concentration. They recognized that their electrode was also sensitive to other tissue constituents, and therefore did not attempt to obtain quantitative measurements. The technique was apparently again forgotten.

The Pco_2 electrode was rediscovered in 1954 by Stow and Randall (44,50), who described using a glass electrode covered with a thin film of water and separated from a sample of blood by a rubber membrane. The changes in potential of the glass electrode were found to vary in direct proportion to the logarithm of the Pco_2. They were impressed with the accuracy and reliability of the system and suggested its possible clinical usefulness. Stow and Randall's device did not suffer the fate of its predecessors, but became the basis for most present-day Pco_2 measurement systems.

In 1958 two important advances in the design of the Pco_2 electrode were reported. Gertz and Loeshka (51) replaced the rubber membrane with a thin polyethylene one and added sodium bicarbonate to the thin film of water, resulting in a faster response time and a greater sensitivity. At the same time, Severinghouse and Bradley (52) independently conducted extensive studies on the Pco_2 electrode, defining the optimum range of bicarbonate concentration and trying a variety of membrane materials. Most of the more recent efforts toward improving the Pco_2 electrode are based on the work of

Severinghaus, and he is generally given credit for the establishment of the Pco_2 electrode as a useful clinical tool. Although many other workers have studied the Pco_2 electrode, none has succeeded in making any significant improvements over Severinghaus' design.

Theory. According to Henry's Law, the amount of carbon dioxide which will dissolve in an aqueous solution is proportional to its partial pressure. In addition, the carbon dioxide in solution combines with water to form carbonic acid, which in turn dissociates into hydrogen, bicarbonate and carbonate ions; thus:

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \overset{K_1}{\rightleftharpoons} H^+ + HCO_3^- \overset{K_2}{\rightleftharpoons} H^+ + CO_3^= \qquad \ldots.(1)$$

where K_1 and K_2 are the first and second dissociation constants for carbonic acid.

If sodium bicarbonate is also present in the aqueous solution, the equations for the equilibrium constants and for electroneutrality yield the following relation (52):

$$\alpha P_{CO_2} = [H_2CO_3] = \frac{A_H^2 + A_H A_{Na} - K_W}{K_1\left(1 + \frac{2K_2}{A_H}\right)} \qquad \ldots.(2)$$

where A_H and A_{Na} are the activites of hydrogen and sodium K_W is the dissociation constant for water, and is the solubility constant of carbon dioxide.

If no sodium bicarbonate is present, this reduces to:

$$\alpha P_{CO_2} \approx A_H^2 / K_1 \quad , \text{ or,}$$

$$pH \approx \frac{pK_1 - \log(\alpha P_{CO_2})}{2} \qquad \ldots.(3)$$

since $pH = -\log A_H$ and $pK_1 = -\log K_1$. This is the basic relation describing the response of Stow and Randall's electrode (50,52).

If sodium bicarbonate is present in the solution in a concentration between 0.001 and 0.1 M, Severinghaus (52) showed both theoretically and experimentally that equation (2) can be approximated by:

$$\alpha P_{CO_2} \approx A_H A_{Na} / K_1 \quad , \text{ or,}$$
$$pH \approx pK_1 + \log (A_{Na} / \alpha P_{CO_2}) \qquad \ldots.(4)$$

This effectively doubles the pH change for a given change in log Pco_2 as compared with the use of distilled water, as in Stow's electrode. At higher levels of bicarbonate concentration, the pH response drops off somewhat due to the appearance of carbonate ions.

The relationship between pH and Pco_2 can be rewritten thus:

$$pH = pK_1 + \log A_{Na} - \log \alpha - \log P_{CO_2} \quad , \text{ or,}$$
$$pH = pH_0 - \log P_{CO_2} \qquad \ldots.(5)$$

where $pH_0 = pK_1 + \log A_{Na} - \log$. With a constant temperature and limited changes of pH, pH_0 can be considered a constant, so that a ten-fold change in Pco_2 should produce a change of one pH unit. Severinghaus (52) found that this is not strictly true, and the

sensitivity, S, defined as $-\ pH/\ \log Pco_2$, instead of being unity is actually slightly less, since equation (5) is only an approximation of equation (1). Rewriting equation (5) to take into account this fact,

$$pH = pH_o - S \log Pco_2 \qquad \ldots.(6)$$

For a given Pco_2 electrode with fixed bicarbonate concentration and temperature, S has been found to be quite constant with time and Pco_2.

Since the pH change of a dilute bicarbonate solution can be considered a unique function of the Pco_2, it is easy to devise a means for measuring the Pco_2 using this property. Figure // shows a highly schematic representation of a Pco_2 electrode. A bicarbonate solution is separated from the sample to be measured by a thin membrane, typically silastic or Teflon, which is impermeable to ions but permeable to gases. Since carbon dioxide is the only gas occurring physiologically in sufficient quantity to alter the pH, the membrane will effectively make the electrode sensitive only to Pco_2. The pH of the solution is measured with a glass electrode, whose potential varies directly with the pH by the Nernst relation (53,54):

$$V_{glass} = V_o - \frac{RT \ln 10}{F} pH \qquad \ldots.(7)$$

where V_o depends on the particular electrode, reference electrode and temperature; R is the gas constant, T is the absolute temperature

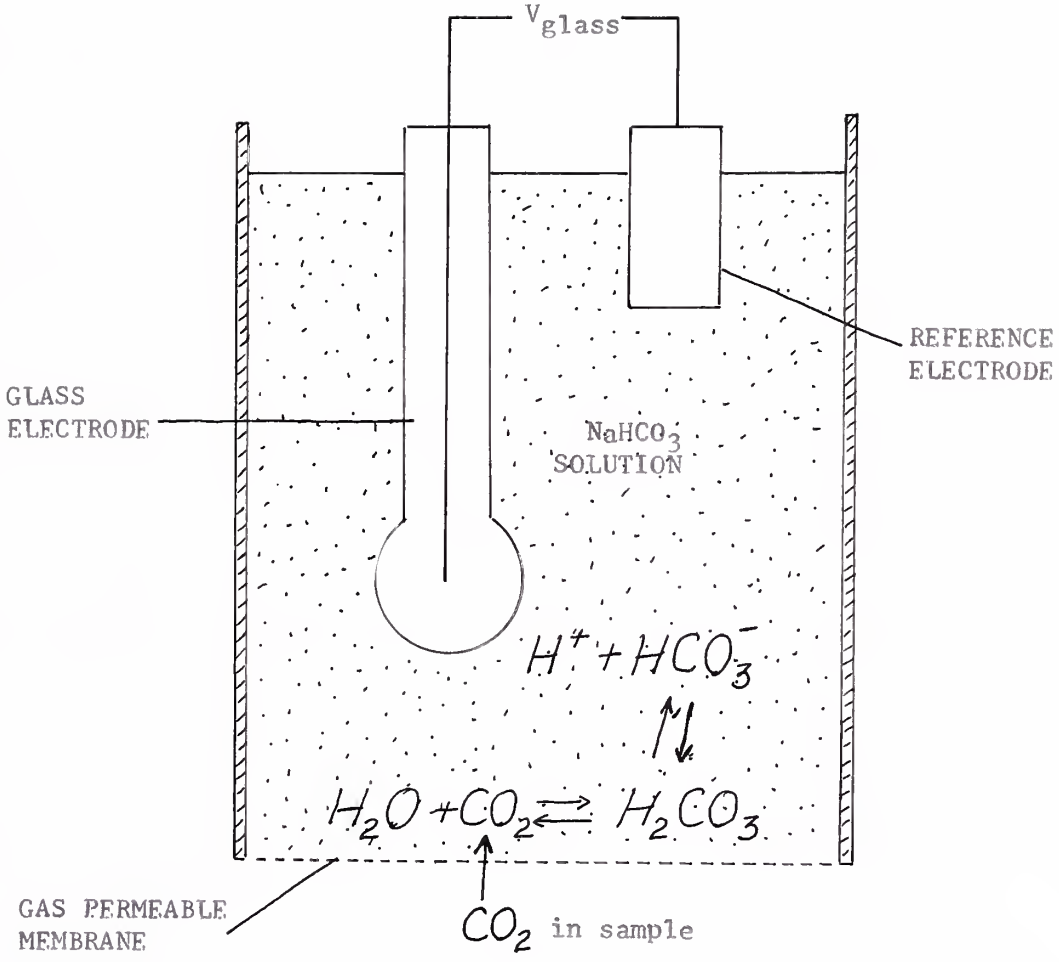

FIGURE 11

Scematic illustration of the operation of a P_{CO_2} electrode

and F is Faraday's constant. Substituting, this becomes:

$$V_{glass} = V_o - 0.1984 \times 10^{-3} T pH, \text{ or,} \quad \ldots.(8)$$

$$= V_o - 61.5 \times 10^{-3} pH, \quad \text{at } 37°C. \ldots.(9)$$

Substituting equation (6) into equation (9), we get the relationship between the potential of the glass electrode and the Pco_2:

$$V_{glass} = V_o - (0.1984 \times 10^{-3}) T (pH_o - S \log Pco_2), \text{ or,}$$

$$V_{glass} = V_o' - (0.1984 \times 10^{-3}) T S \log Pco_2 \quad \ldots.(10)$$

where $V_o' = V_o - (0.1984 \times 10^{-3})\ T\ pH_o$. Thus, there should be a linear relationship between the electrode potential and the logarithm of the Pco_2, and this has been experimentally confirmed by all whohave studied this (43,55,56,57,58). This electrode potential is easily measured and can be used to determine the level of Pco_2.

In order to successfully implement the concept of the Pco_2 electrode, certain practical design considerations are of importance. For any measuring device to be useful, it must be accurate, stable and reliable and should respond rapidly. When properly constructed and used, the Pco_2 electrode fills these criteria.

Practice: Several factors could limit the speed of response of the electrode; these include the diffusion rate of carbon dioxide through the membrane, its rate of equilibration with the

bicarbonate solution, and the response time of the glass electrode. The glass electrode is not a limiting factor, as it responds very rapidly.

The membrane, although chosen for its permeability to carbon dioxide, still presents a partial diffusion barrier and thereby places a limit on the rate of response of the electrode to changes in Pco_2. Much of the research on the Pco_2 electrode has been directed at finding the "ideal" membrane: one which is highly permeable to carbon dioxide, impermeable to water and electrolytes and mechanically rugged. Unfortunately, all these features have not yet been incorporated into a single membrane material, but reasonable compromises have been made. Polyethylene (59), Teflon (52), and silicone rubber (57) have all been used with success, but there are distinct differences among them which govern their selection for particular applications. Although polyethylene has been used by several investigators (51,59,60), it does not seem to offer any particular advantages over Teflon; in fact, the rate of diffusion of carbon dioxide through polyethylene is only about one-half that for Teflon of equal thickness (61,62). Silicone rubber is by far the most permeable to carbon dioxide [170 times faster than Teflon for the same thickness (62,63)], but suffers from fragility, being rather easily torn or punctured (62). Silicone rubber is also quite permeable to water vapor, which may cause undesired drying of the electrode. Teflon is quite strong, and can be used as a much

thinner membrane than can silicone rubber, which in part compensates for its lesser permeability. Most investigators find that Teflon is the nearest to the "ideal" material for general use, although where very rapid changes in Pco_2 are to be followed, silicone rubber is often used. However, as improved silicones are developed, it may be found that this material will come closest to fulfilling the criteria for the best material.

After passing through the membrane, the carbon dioxide must then dissolve and be hydrated to form carbonic acid; the carbonic acid must then be dissociated, and will affect the pH of the solution as described earlier. Although the hydration step might be expected to be a rate-limiting factor, and the addition of carbonic anhydrase to the bicarbonate solution would speed the reaction, Lunn and Mapleson (64) demonstrated that this is not a factor except when the Pco_2 is below 10 mm Hg. However, the carbon dioxide must diffuse throughout the bicarbonate solution for equilibrium to be reached, and this can slow the response of the electrode if the quantity of solution is large. In addition, a larger amount of solution will dissolve a greater quantity of carbon dioxide at the same partial pressure, and thus delay the equilibration as the additional gas diffuses through the membrane.

The fastest possible electrode should result, then, when the thinnest possible film of bicarbonate solution is placed between the membrane and the glass electrode. One way to accomplish this is to place the membrane in direct contact with the electrode,

relying on capillary action to maintain a thin film in place. This technique is unsatisfactory, resulting in somewhat erratic readings with a fairly marked drift, possibly because the glass electrode tip is slightly convex and the resultant pressure on the stretched membrane tends to squeeze the bicarbonate solution away from the electrode. Whatever the cause, most investigators have resorted to various means to maintain a fixed but small quantity of solution between membrane and glass by means of some kind of spacer. Cellophane dialyzing membrane (52), viscous methyl cellulose (62), surgical gauze (57), nylon mesh (65), special lens paper (62) (Gizeh or Joseph paper) and glass wool (62) have all beenused with success. Severinghaus (62), who has tried all the different techniques, prefers Joseph paper for fast response, stability and low drift.

Two other ways by which the bicarbonate solution affects the performance of the electrode are related to its concentration. Severinghaus (52) has studied these effects both experimentally and theoretically and found equilibrium is reached faster at lower bicarbonate concentrations. He also found that the sensitivity of the electrode (defined as $\Delta pH/\Delta \log Pco_2$) was at a maximum of almost unity between 0.001 and 0.1 M bicarbonate. This latter fact simply reflects the failure of the Henderson-Hasselbalch equation equation (4) to be a good approximation of equation (2) at high sodium bicarbonate concentrations.

Because of these facts and because the stability and drift of the electrode seem to be compromised at very low levels of bicarbonate, most investigators use bicarbonate concentration between 0.001 and 0.01 M for routine work, while using more dilute solutions (0.0001 M) when very rapid response is desired more than sensitivity and stability.

Since the glass electrode only furnishes a half-cell potential, another electrode whose potential does not vary with pH or Pco_2 must be used as a reference on which to base the measurements of the glass electrode potential. The reference electrodes most commonly used for this work are calomel (Hg-HgCl) or silver-silver chloride (Ag-AgCl). Since Stow's electrode was somewhat unstable and had a fair amount of drift, subsequent investigators frequently blamed the Ag-AgCl electrode for this,and would use calomel for a reference. However, Severinghaus (52) found that the addition of 0.1 M NaCl and a very small amount of $AgNO_3$ could stabilize the Ag-AgCl electrode. There do not appear to be any significant advantages in using the one over the other, except perhaps for the slight increased bulk and difficulty in preparing the calomel electrode.

Figure 12 shows a cross-section of a typical Pco_2 electrode fully assembled (Radiometer type E5036).

Performance. When all precautions have been taken as outlined above to make the Pco_2 electrode as fast and reliable as possible,

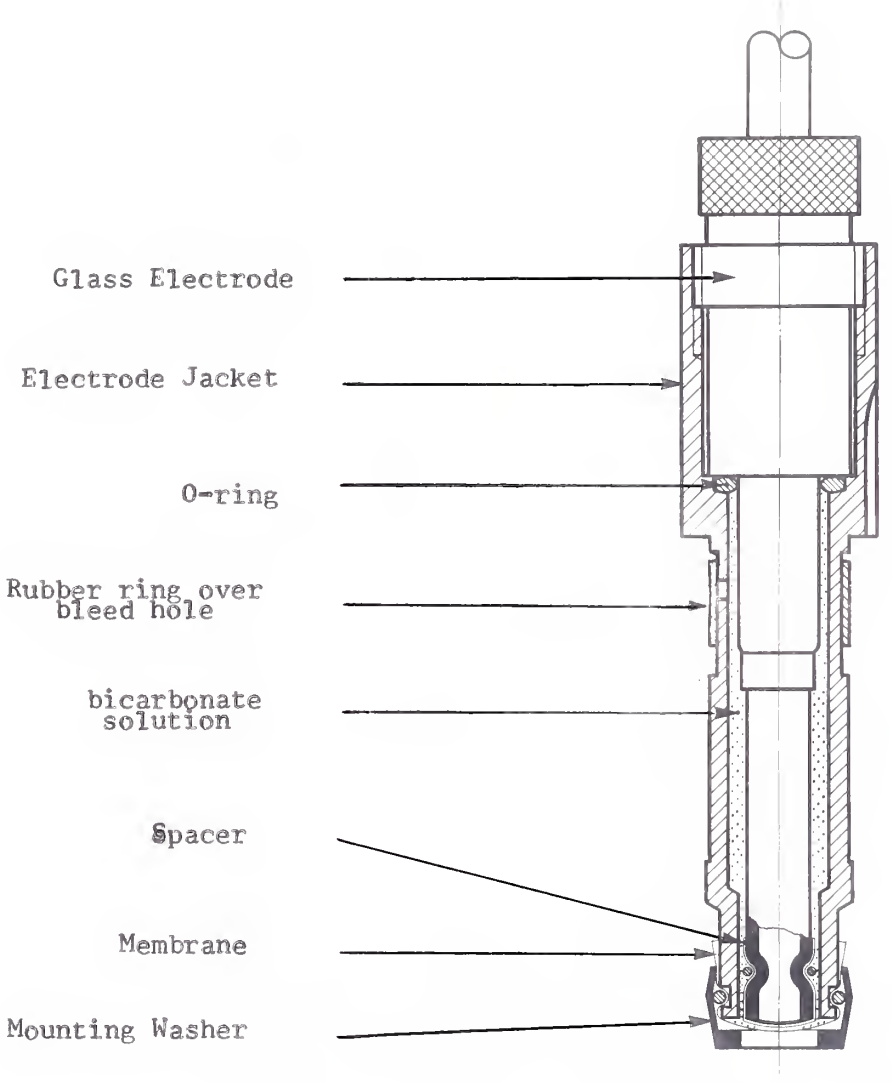

FIGURE 12

Cross-section of Pco_2 electrode
Radiometer type E5036
(adapted from instruction manual)

the result is a useful measurement device. Purcell and Rodman (65) compared the Pco_2 measured by the Pco_2 electrode with that obtained using the Van Slyke Manometric method for over 200 blood samples and concluded that the two methods usually agreed to within 1 mm Hg and only rarely differed by more than 3 mm Hg. Holmes et al. (67) compared the use of blood and gas at the same Pco_2 and found as had previous investigators that the Pco_2 electrode measures no difference. Bartschi et al. (60) compared the Pco_2 electrode, the Van Slyke technique and the Astrup micro-method with blood equilibrated to known values of Pco_2. They found that the Pco_2 electrode was the most satisfactory, having the least scattering of data and no directional error.

There are some potential difficulties with using the Pco_2 electrode. There tends to be a slow drift in the output of the electrode. This drift is usually less than 0.01 pH unit per hour (64) and seems to be only a change in V_0' [see equation (10)] . It may be due in part to the fact that the bicarbonate solution may dissolve an appreciable amount of alkali from the glass used in constructing the glass electrode (43,45). In addition, the electrode is remarkably temperature sensitive: the potentials of both glass (53,54) and reference electrodes (68), the pK of carbonic acid (69) and the solubility constant of carbon dioxide (70) all vary with temperature. For this reason, it is important that the electrode be maintained at a constant temperature. This will be discussed further in Appendix III.

Although there is a drift in the electrode potential, the slope of the electrode response, $\Delta V_{elect}/\Delta \log Pco_2$, is remarkably constant for a particular electrode, being dependent primarily on the bicarbonate concentration, the temperature, the type of spacer used between the membrane and glass electrode and perhaps the actual physical design of the electrode. For bicarbonate concentrations in the range of 0.0001 to 0.005 M, the sensitivity, $\Delta pH/\Delta \log Pco_2$, is typically between 0.88 and 0.94 (43,45,52).

Conclusion. The Pco_2 electrode, when used within its limitations, can be a very convenient method of measuring Pco_2 in gases or solutions. As an example to show what the characteristics of a typical commercially-made Pco_2 electrode are, the following are specifications from the manual for the Radiometer E5036 electrode:

CO_2 sensitivity	better than 90%
99% response time (for 2-fold change)	1-1.5 min with 11 Teflon membrane
Reference electrode	Ag-AgCl
Electrolyte solution	.005 M $NaHCO_3$, 0.02 M NaCl, Sat. $AgCl_2$

APPENDIX II. Electrode amplifier and Linearizing circuitry

As derived in Appendix I, the voltage developed by the Pco_2 electrode can be apprximated by:

$$V_{glass} = V_o' + K\ T\ S \log Pco_2, \qquad \ldots(1)$$

where V_o' is a constant dependent on the potential of the reference electrode, the temperature, the bicarbonate concentration, the first dissociation constant of carbonic acid and the characteristics of the particular glass electrode; K is RTln10/F = 0.1984 T mV; T is the absolute temperature; and S is the sensitivity of the electrode,

Since the above relationship is a nonlinear one, most commercial Pco_2 meters use a special nonlinear scale for read-out. This technique serves adequately in the laboratory for single samples, but in order to use a chart recorder or digital voltmeter for continuous monitoring, the signal must be linearized. A circuit was devised to accomplish this and has the secondary advantage of allowing the use of only a single calibrating gas for routine use, rather than the two gases required by most commercial units.

As shown in Figure 13, the circuit used to amplify and linearize the electrode output consists of three parts: a

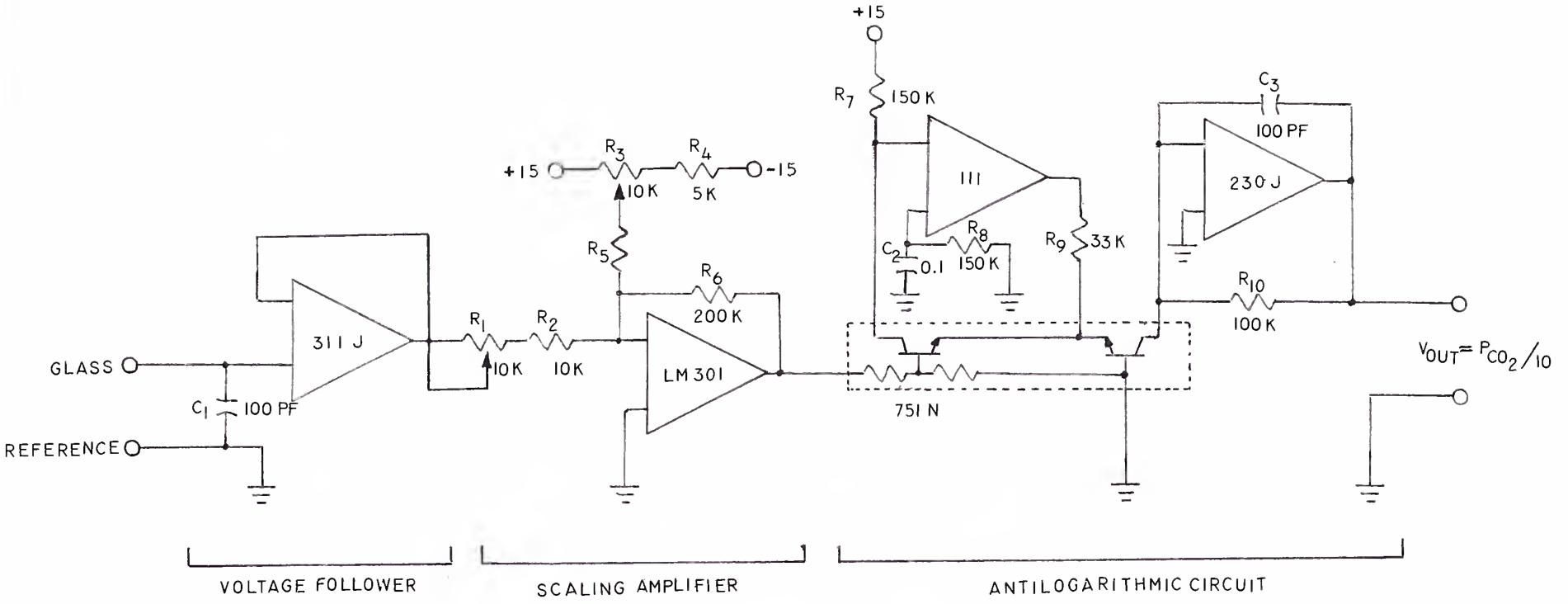

FIGURE 13

Pco_2 amplifier and linearizing circuit

voltage follower, a scaling amplifier, and an antilogarithmic circuit. Power for the operational amplifiers used in the circuit is obtained from a regulated power supply*. According to manufacturer's specifications, this unit provides 50 megohms of input isolation. Thus for patient safety, all circuitry is well isolated from the A-C supply.

The voltage follower is necessary because of the very high impedance of the glass electrode (about 6×10^8 ohms); it utilizes varactor bridge operational amplifier** in a noninverting unity gain configuration. This circuit has an imput impedance of 10^{14} ohms and has less than 10 v of input noise. C_1 is a low-leakage polystyrene capacitor used to improve the stability.

The second stage utilizes an antegrated circuit operational amplifier*** in an inverting scaling amplifier configuration. The output of this stage is:

$$-V_{301} = A\ V_{311} + V_{cal} \quad , \text{ or,}$$

$$= A\ (V_o' + K\ T\ S \log Pco_2) + V_{cal} \quad , \qquad \ldots(2)$$

where A is varied between 10 and 20 by adjustment of R_1, and V_{cal} varied between +3 and -3 volts by adjustment of R_3.

The final stage is the antilogarithmic circuit as described

---

* Analog Devices Model 902

** Analog Devices Model 311 J

*** National Semiconductor LM301

by Borlase and David (71). It relies on the exponential characteristic of a semiconductor junction in the input side of a feedback amplifier. The output of this final state is:

$$V_{out} = 10^{1-V_{301}}$$

$$= 10^{1+V_{cal}+A(V_o' + KTS\log Pco_2)}, \text{ or,}$$

$$= 10^{1+V_{cal}+AV_o'} (Pco_2)^{AKTS}, \text{ or,}$$

$$\ldots(3)$$

If A is adjusted to equal 1/KTS (approximately 16.2/S at 37°C) and Vcal is adjusted so that $V_{cal} + AV_o' = -2$, then:

$$V_{out} = Pco_{2/10} \text{ volts.}$$

$$\ldots(4)$$

Thus a range of 0-10 volts for V_{out} represents a linear range of Pco_2 from 0.100 mm Hg.

In use, A must be adjusted to correspond with the slope of the particular electrode's response ($A = \Delta \log Pco_2 / \Delta V_{glass} = 1/KTS$). This is done with two gases of known Pco_2; the ratio of the outputs of the circuit is adjusted with R_1 to equal the ratio of the Pco_2s of the gases. Assuming that the sensitivity of the electrode will remain constant (see Appendix I), this value should not need further readjustment unless the electrode is changed. However, there can be a significant drift in the electrode's baseline voltage, V_o', (see Appendix I); for this reason, V_{cal} should be checked periodically with a single known gas.

The potential sources of error are four-fold: deviations of the linearizing circuitry from a true antilogarithmic function, deviations in electrode response from the approximation of equation (1), errors in adjusting A and errors in calibration. As shown in Figure 14, the antilogarithmic circuit is quite accurate; it is also quite stable with time. As demonstrated in Appendix I, equation (1) is a valid approximation within the physiologic range of Pco_2. Calibration errors can be avoided by warming and humidifying the gas before passing it by the electrode. However, variations in AKTS may occur if component tolerances, electrode tip temperature, or sensitivity, S, vary.

Although temperature will affect V_0' as described in Appendix III, the factor KTS is not particularly sensitive to small changes in temperature; a $1^{o}C$ change in temperature changes KTS by 0.32 per cent. However, a change in AKTS from variations in component tolerances or electrode sensitivity could be considerably greater.

If the system is calibrated with a gas of Pco_2 of 60 mm Hg by adjusting V_{cal} for an output of 6.0 volts, then Figure 15 shows the magnitude of the error for Pco_2 of 30 or 90 mm Hg if AKTS is not unity [see Equation (3)]. For an error of 5 per cent in adjusting A, there is less than 4 per cent error at 30 mm Hg and less than 3 per cent error at 90 mm Hg. If truly great accuracy is desired, then one must adjust A with great care; if changes

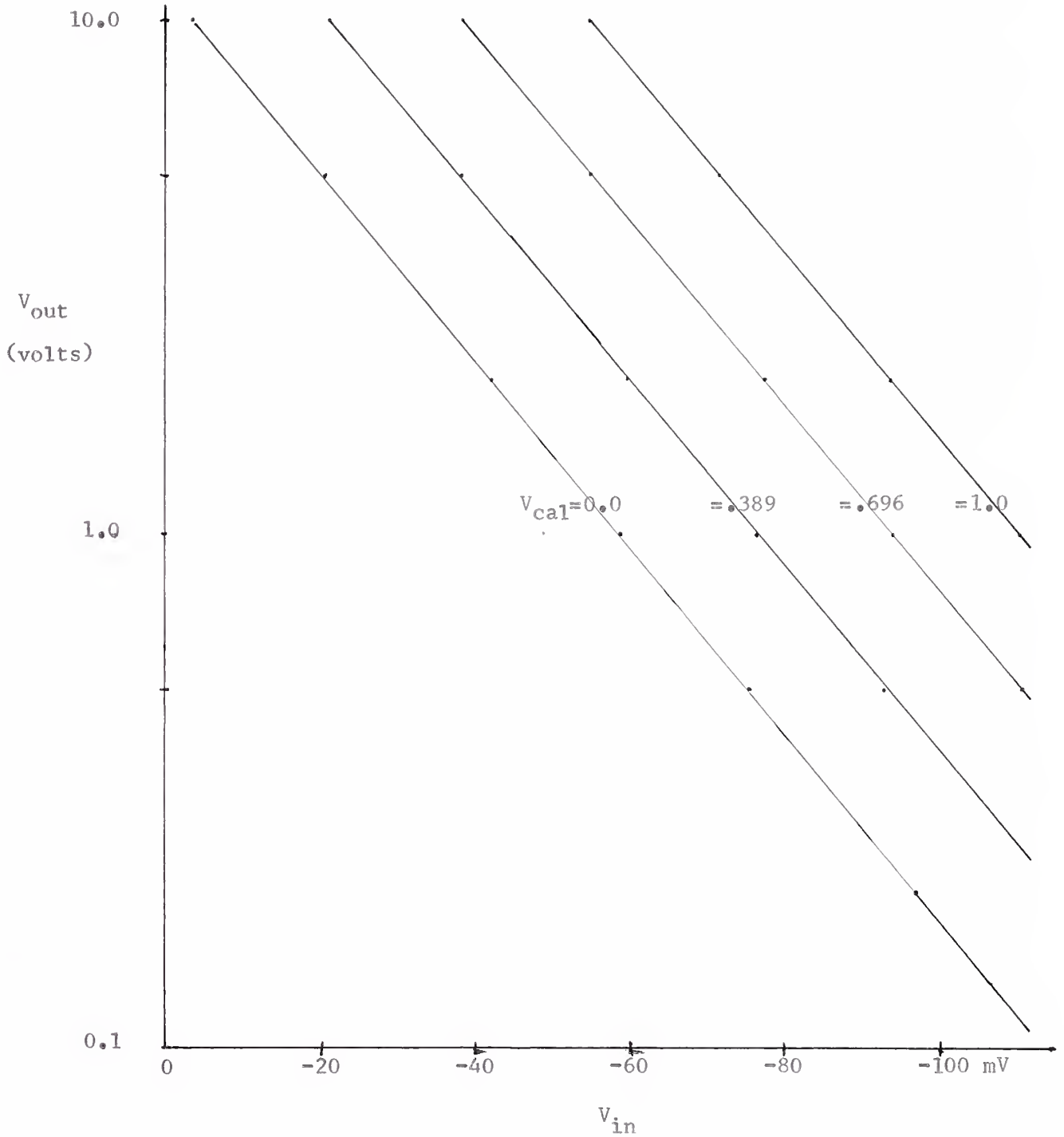

FIGURE 14

Performance of linearizing circuitry
(A=18.08)

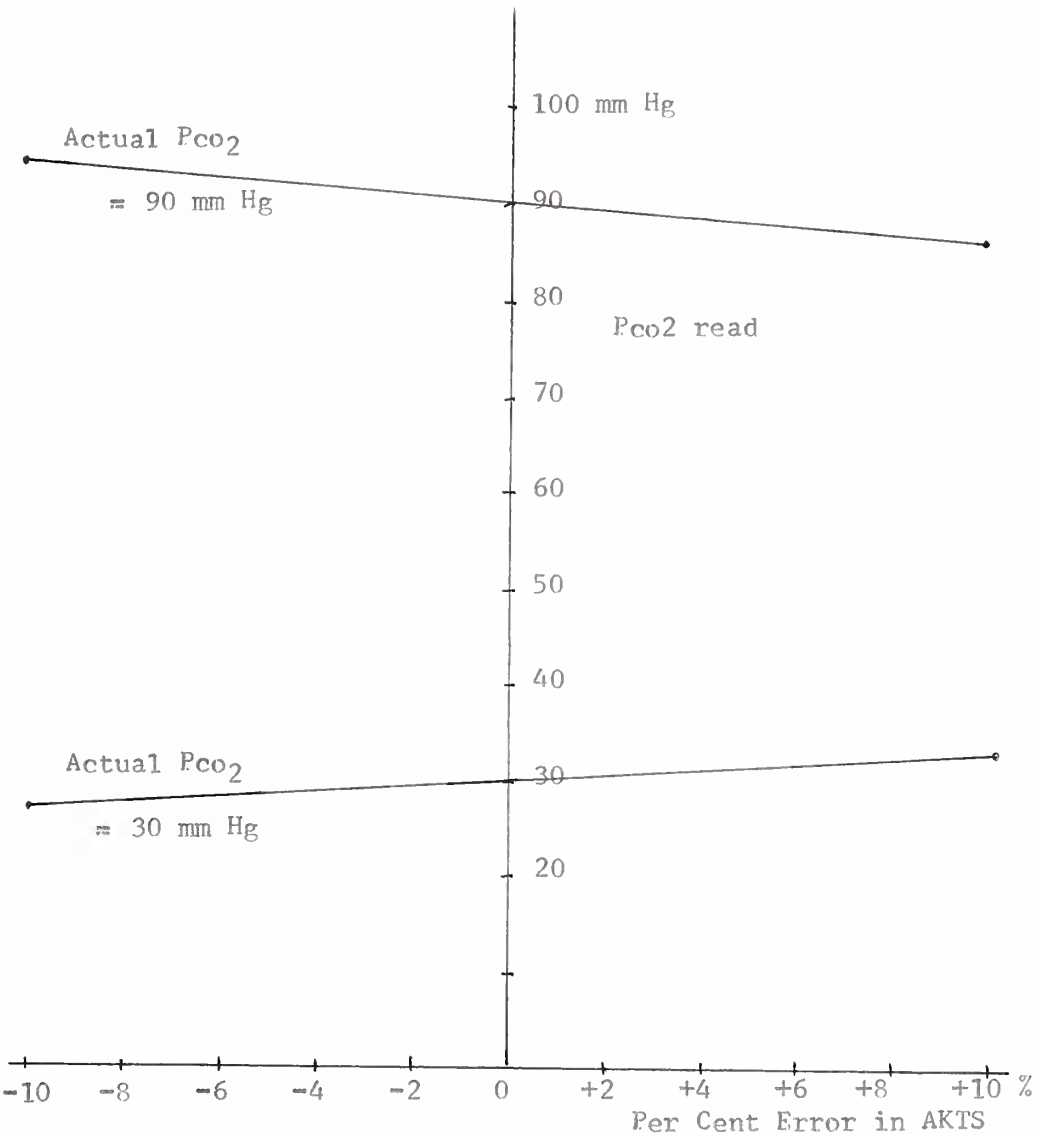

FIGURE 15

Calculated error for anti-log circuit

$$Pco_2 \text{ (read)} = 10 \times V_{out} = B(Pco_2)^{AKTS}$$

$$B = 10^{1+V_{cal}+AV_0'}$$

V_{cal} adjusted to read accurately at 60 mm Hg

in P_{CO_2} rather than the absolute value are important, then there can be somewhat less concern with adjusting A, and a single gas be used for routine calibration checks.

APPENDIX III. Electrode Temperature Control

General Considerations. As mentioned in Appendix II, the electrode baseline voltage, V_0' , is affected by temperature, although the slope, Δ Vglass/Δ log Pco_2, is not affected significantly over a limited range of temperature. Most of the factors which contribute to the electrode's potential are temperature sensitive: the glass electrode (53,54), the reference electrode (68), the dissociation constant of carbonic acid (69), and the solubility of carbon dioxide (70) all vary with temperature. The total magnitude of the error so produced varies with the concentration of the bicarbonate solution and choice of reference electrodes and has been reported as high as 8 per cent per degree Centigrade by Fatt (61), although others, such as Siesjö (45), report considerable lower values.

Approach. To try to minimize the temperature errors, a device was constructed which kept the electrode at a reasonably constant temperature. The method used had to permit operation of the electrode at least three to four feet away from any bulky

apparatus in order to permit its convenient application to a patient*. Any form of electric heating element placed directly on the electrode seemed unsafe in terms of shock hazard to the patient. Instead, a means of circulating heated water around the electrode via plastic tubing was developed. Because the tubing is exposed to ambient temperature as it travels from the water bath to the electrode, a certain amount of heat will necessarily be lost en route; the actual temperature of the electrode will then be less than that of the water bath by an amount depending on the ambient temperature and on the rate of flow of the water through the tubing.

The simplest approach was tried first--simply pumping the water from a water bath several degrees warmer than the desired electrode temperature. It was found that the flow rate to the electrode was not constant, due to inherent variations in the pump flow rate and occasional kinking of the plastic tubing, with the result that the electrode temperature was not constant.

This approach was modified to allow the temperature of the water bath to be controlled by the actual electrode temperature, as measured by a thermistor mounted near its tip. Again, this

*Siesjö (45) used a plastic box placed around the head of anesthetized animals into which heated air was circulated to keep the temperature of his electrode at the same temperature as the cortex. Such a technique was not considered suitable for the present study.

was not satisfactory, as the thermal time constant of the system was so slow that the system would respond sluggishly; attempts to speed the response led to considerable instability of the system. In addition, if the electrode exceeded its desired temperature, an exceedingly long time was required to allow the water bath to cool after the heater was shut off.

The final system, which has proved most satisfactory, uses a different and perhaps unique approach. The same basic technique of circulating preheated water is used as before; however, instead of trying to overcome the variations in electrode temperature with flow rate, these variations were used as the means of controlling the electrode temperature. The water bath is kept at a temperature several degrees higher than the desired electrode temperature. The temperature at the electrode tip, measured with a thermistor, is kept constant by varying the flow rate (and thereby the heat loss) to the electrode by varying the pump speed.

System Description. Referring to the schematic block diagram in Figure 16, a foam-insulated container with a six-liter capacity is the reservoir of preheated water for the electrode. The temperature of the water bath is maintained with a 100-watt fish tank heater*; the built-in thermostat is capable of regulating water bath temperature within about 1°C. A submersible pump** is placed

*Metaframe Corporation, Model 22
**Model E200, Proven Pump Division, Western Brass Works

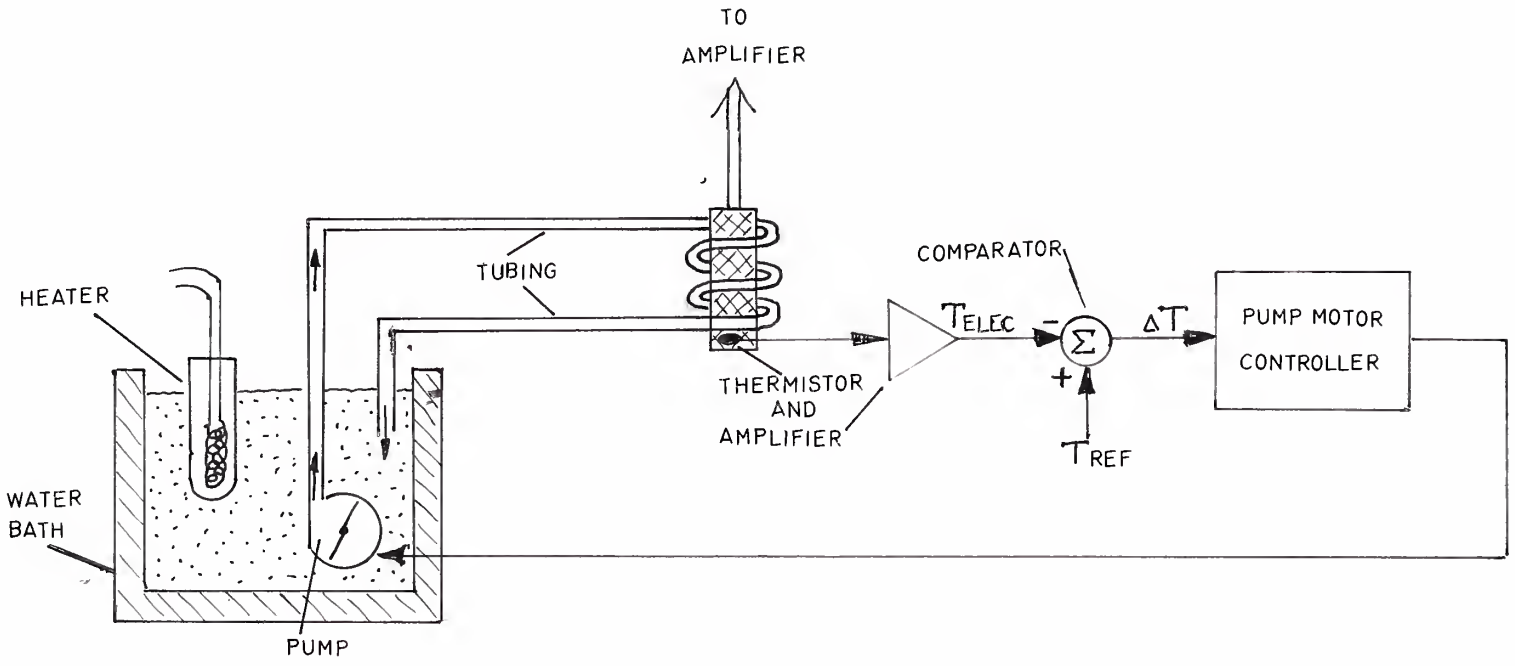

FIGURE 16

Temperature Controller
block diagram

within the water bath to pump the water to the electrode. This pump has the high capacity necessary to force the water through the high resistance of the tubing (about ten feet of 1/8 inch diameter). At present, this tubing is simply coiled around the electrode assembly, but a double-walled chamber to surround the electrode could easily be constructed for the water flow.

The temperature of the electrode is monitored with a thermistor* mounted beneath the tubing near the electrode tip. The resistance of the thermistor changes with temperature and is converted to a voltage with a simple bridge amplifier circuit. This voltage is compared with an adjustable reference voltage which will correspond with the desired temperature. This difference signal is amplified and used to drive a proportional motor controller, which in turn varies the rate of water flow through the tubing.

In operation, a drop in electrode temperature below the preset reference level causes the difference signal to increase, increasing the pump flow rate. This increased flow allows less cooling of the water as it is transported to the electrode, and the electrode temperature increases. If the system is properly adjusted, no overshoot will occur, but an equilibrium will be established where there is a small but constant difference signal creating a constant flow sufficient to maintain this difference.

*Yellow Springs Instruments 44006

Circuitry. Figure 17 shows the circuit for the thermistor bridge amplifier and difference signal amplifier. Two integrated circuit operational amplifiers* are used for this circuit. The first stage accepts as input the voltage found at the junctions of R_1 and R_2; this voltage is adjusted to zero with R_3 when the thermistor temperature is 30°C. R_1 and R_2 are used to reduce the power dissipation of the thermistor to approximately 1 μW. As the thermistor temperature increases, its resistance decreases, causing the input to the operational amplifier to decrease. This voltage change is amplified, R_8 being used to set the output of the amplifier to 10 volts for a thermistor temperature of 40°C. A voltmeter connected to the output of this stage can be used to display the electrode temperature: a scale of 0-10 volts corresponds to a temperature range of 30-40°C.

The second state of this circuit compares the output of the first stage with a reference signal, set by R_{11}, and multiplies the difference by the amplifier gain, G. G can be varied upwards from a minimum of about 0.6 by adjustment of R_{15}. The output of this stage, $V_{control}$, becomes the input of the motor controller.

Figure 18 shows the pump motor controller circuit. At the heart of this circuit is a functional integrated circuit** (72).

*Motorola MC1741
**RCA CA3059

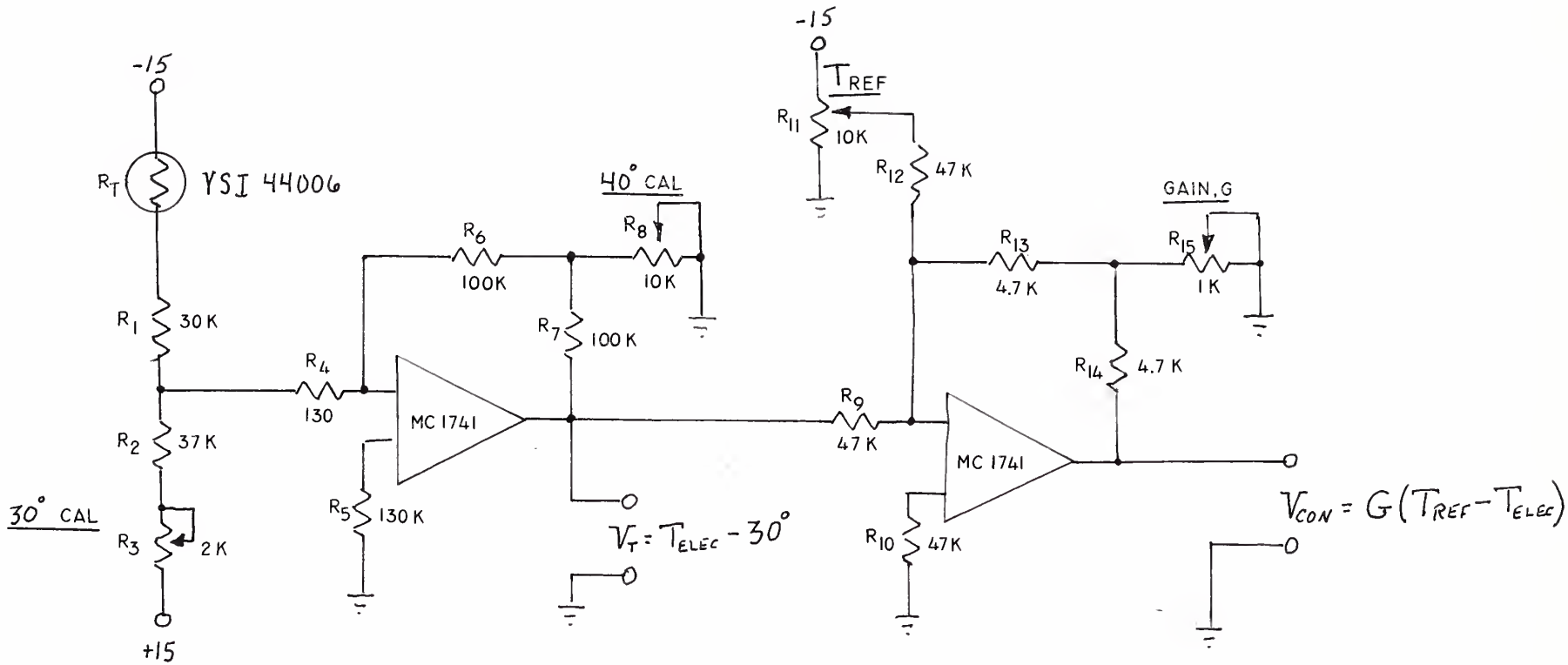

FIGURE 17

Temperature sensing and reference circuit

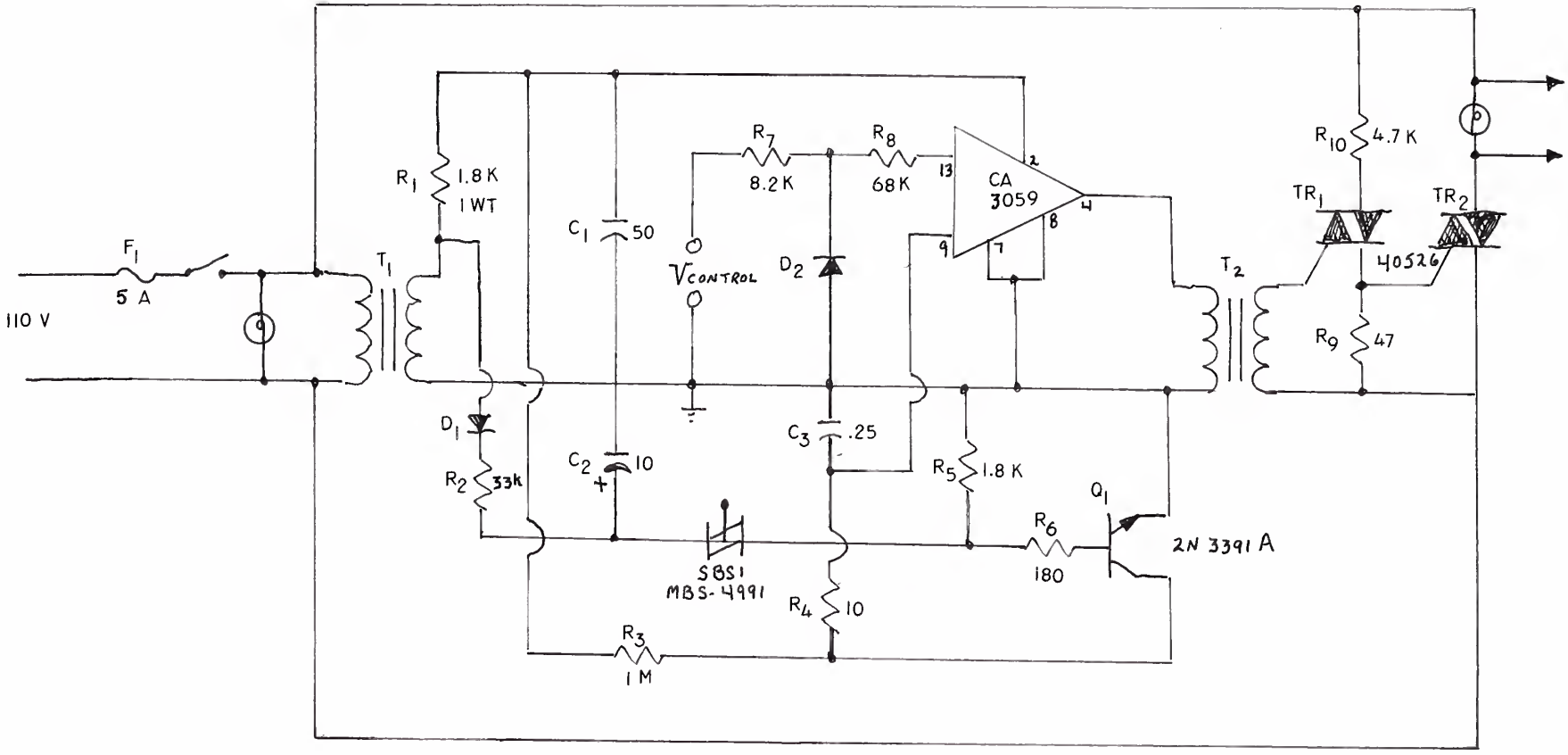

FIGURE 18

Pump motor controller circuit

The operation of this device is rather complex, but whenever the voltage on terminal 13 exceeds that on terminal 9, a pulse is produced on terminal 4 each time the power line voltage equals zero (i.e., 120 times a second). This output pulse triggers a triac* through transformer T_2**. This triac triggers a second triac, TR_2, in such a way that power is supplied to the pump motor (a highly inductive load) when the power-line voltage is at a peak and the current consequently zero. Figure 19 shows the temporal relations of the trigger pulses, the power line voltage and the motor current.

In order to make a proportional controller, the input to terminal 9 of the integrated circuit is a ramp function. Trigger pulses will only be generated for whatever portion of the ramp cycle that $V_{control}$ exceeds the ramp voltage, as depicted in Figure 20. Thus, for a value of $V_{control}$ greater than the maximum ramp voltage, trigger pulses will be produced at a maximum rate of 120/second, and for a small $V_{control}$, pulses will only be produced during the early portion of the ramp cycle. (D_2, R_7 and R_8 prevent the total absence of trigger pulses so that the water flow never completely ceases.)

The ramp is generated as C_3 charges through the combination of R_3 and R_4 and is discharged through R_4 and Q_1, when Q_1 is turned on. Q_1 is turned on about twice a second by a silicon bilateral

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*RCA 40526

**Lafayette 99-6129

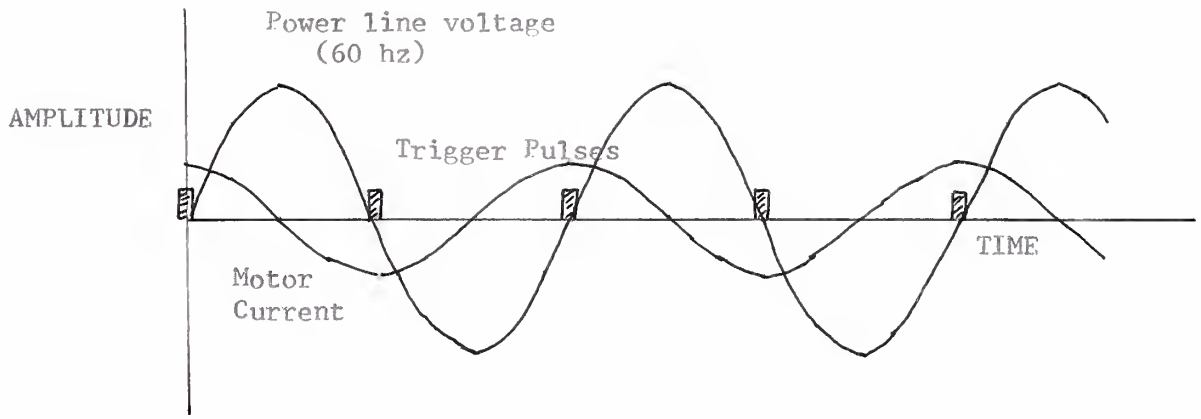

FIGURE 19
Current, voltage, and trigger (CA 3059)
pulse relationships

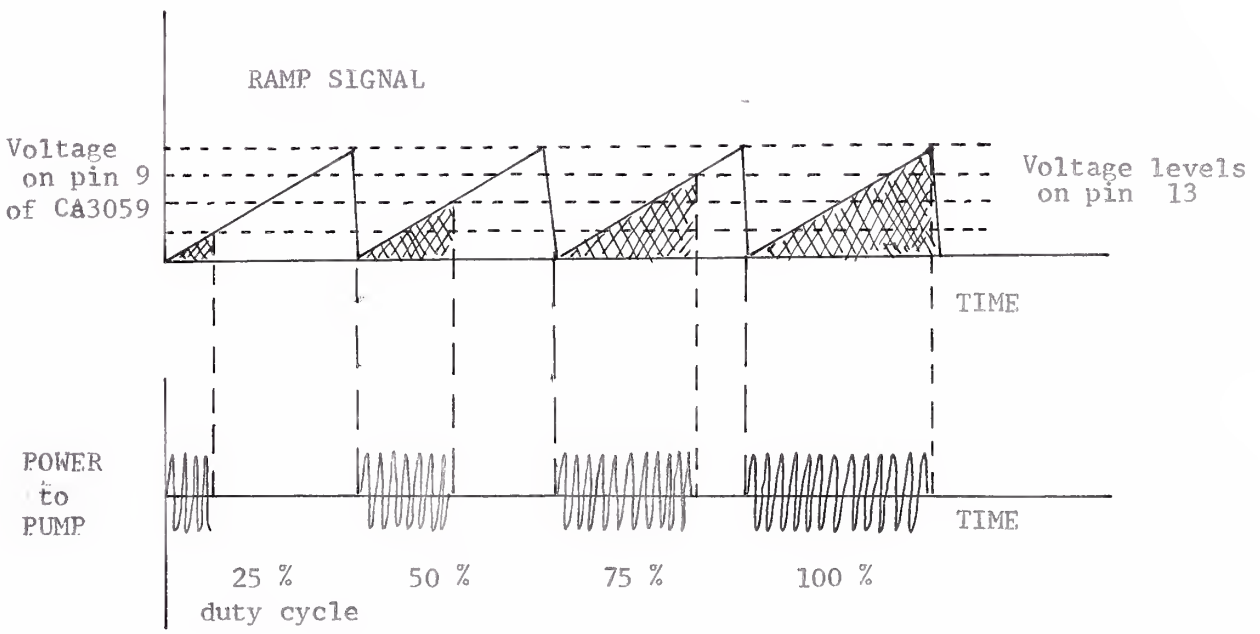

FIGURE 20

Pump power as a function
of ramp and input
voltages

switch, 5BS1,* a four-layer device which conducts when the voltage across it exceeds 8 volts. This voltage develops as C_2 is charged through D_1 and R_2.

Note that transformers T_1 and T_2 allow the input, $V_{control}$, to be well-isolated from the power line.

Performance. Figure 21 shows the performance of the pump motor controller by plotting the water flow rate against $V_{control}$. Figure 22 demonstrates the typical increase in electrode temperature with increasing flow. The water bath temperature is maintained between 3 and 4°C above the desired electrode temperature, and the gain, G, of the temperature reference amplifier is set as high as possible without causing instability (typically G=6-10). With these precautions, the system has proved capable of maintaining the electrode temperature to within $\pm$ 0.2°C.

*Motorola MBS 4991

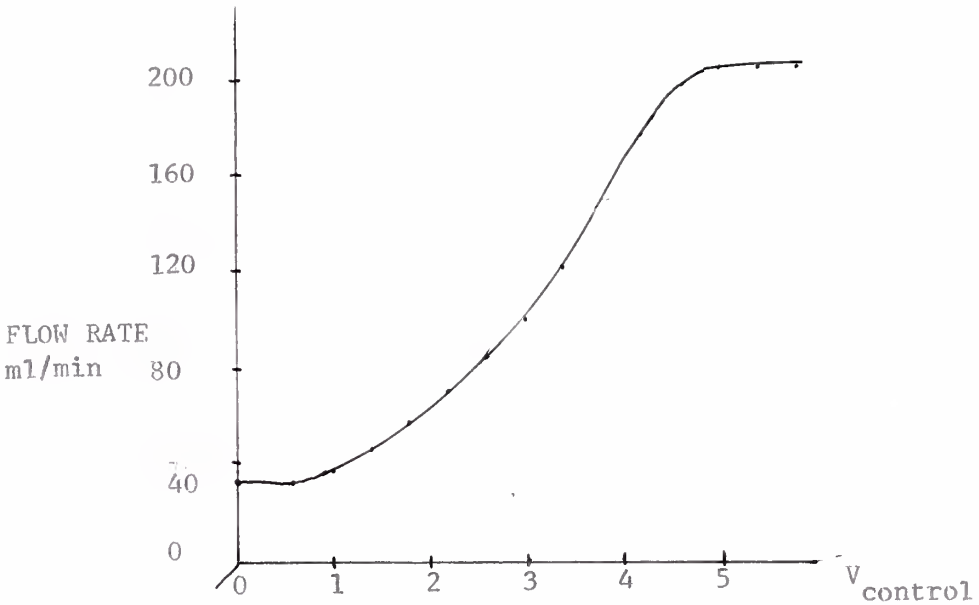

FIGURE 21
Pump flow rate vs control voltage

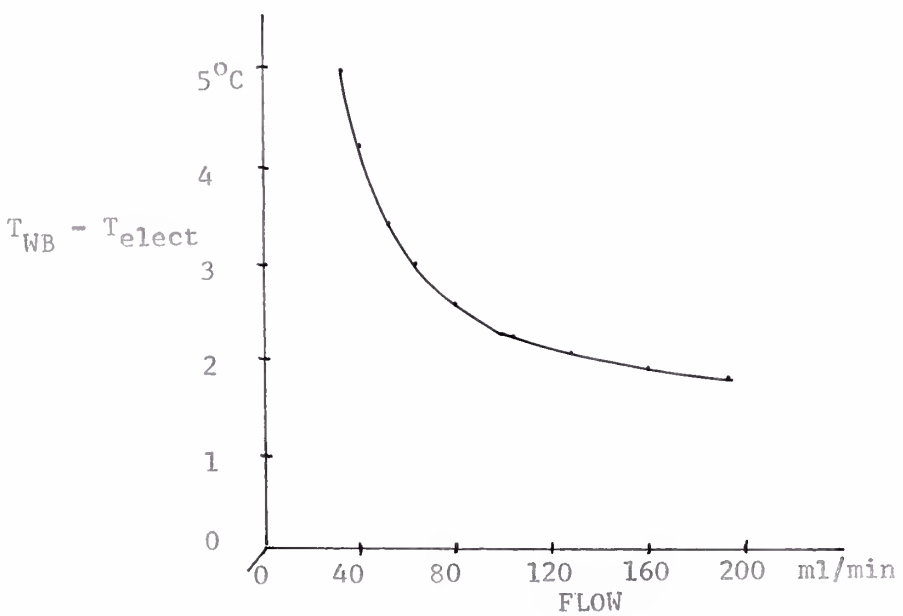

FIGURE 22

Heat loss vs. pump flow rate

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