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An intragastric pH and motility monitoring and automatic titration system

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AN INTRAGASTRIC pH AND MOTILITY MONITORING

AND AUTOMATIC TITRATION SYSTEM

BY

. BARRY F. MAYCOCK, 1940

A

THESIS

submitted to the faculty of

THE UNIVERSITY OF MISSOURI AT ROLLA

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Approved by

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ABSTRACT

Knowledge of the effects of prolonged states of weight-lessness on the physiological activities of gastric motility and acid secretion will aid in the planning of future space flights, since aberrations in these activities could affect the performance of astronauts. Investigation of these activ- ities requires monitoring of the pressure and pH in the stomach and titration of the gastric contents. Since pre- vious methods and equipment used for performing these func- tions are inadequate for this investigation, the equipment whose design and operation are discussed in this thesis was developed. This equipment includes an ingestible sensor capsule which is tethered in the stomach, a modulation unit which can modulate a transmitter to permit mobility of the subject, and an automatic titration unit.

PREFACE

The author wishes to express his gratitude to
Dr. Malcolm Peterson and Dr. Rodolpho Guillen of the
Gastroenterology Division of Washington University Medical
School for their aid in obtaining the _in vivo_ test results
reported in this thesis.

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I. INTRODUCTION

This thesis describes electronic equipment designed by the author as an employee of the McDonnell Astronautics Company to support the gathering of clinical baseline data for a medical experiment conducted by Dr. Malcolm Peterson of Washington University in St. Louis. The experiment will be sponsored by the National Aeronautics and Space Administration and is designed to investigate the effects of prolonged states of weightlessness on gastric motility and acid secretion. Knowledge of these effects will aid in the planning of space flights where an astronaut's performance might be compromised by aberrations in physiological activities. The investigation will be performed on a 10 to 14 day space flight by monitoring the pressure in the stomach as an indication of motility and by titrating gastric acid secretion. The latter requires monitoring the pH of gastric contents and introducing known amounts of a known alkaline solution into the stomach. The equipment described consists of an ingestible sensor capsule to measure the pH and pressure, a modulation unit to modulate a transmitter with the pH and pressure information, and an automatic titration unit.

II. LITERATURE REVIEW

A. INTRAGASTRIC PRESSURE MEASUREMENT

Early methods of measuring intragastric pressure usually consisted of systems utilizing catheters inserted through the esophagus with either a balloon on the end or an open end. The pressure was measured externally by optical, water, and Bourdon-tube manometers or by strain-gage transducers[1]. The primary disadvantage of these techniques is that they render the patient immobile during the measuring period and in some cases require a stationary relationship between patient and equipment.

In 1957, two groups, one headed by J. T. Farrar[2,3,4] and the other by R. S. Mackay and B. Jacobson[2,5,6], independently developed radio capsules which transmitted the stomach pressure from inside the stomach to an external receiver. Both groups used a bellows or diaphragm which was mechanically coupled to a ferrite core. As pressure fluctuations displaced the bellows, the core was moved in relation to a coil, producing a variable inductance which frequency modulated a transmitter. Mackay and Jacobson's capsule also transmitted temperature information by pulsing the frequency-modulated signal at a rate which was dependent on the temperature.

Similar capsules were developed by von Ardenne and Sprung in 1958[2], R. F. Russ and H. S. Wolff in 1960[2,7], Jacobson and Nordberg in 1961[2], and B. W. Watson, B. Ross, and A. W. Kay in 1962[2,8]. All of the above capsules

suffered from either a short life, a short transmission range, or both. Life was usually limited to 1 or 2 days with a typical transmission range of 1 m. The necessity of a small battery was the limiting factor on both, although a life of longer than 1 or 2 days was not usually required since the capsule would pass through the gastrointestinal tract in the natural manner in that period of time. Jacobson and Nordberg did develope a capsule with a 90 day life, but its transmission range was only 15 to 30 cm. Farrar developed a passive capsule which received radiated energy at one frequency and reradiated it at another frequency which was dependent on the pressure. Both Farrar and Mackay tethered capsules in the stomach at the end of threads which extended through the esophagus and were anchored to a tooth. This allowed them to control the position of the capsule in the gastrointestinal tract and obtain measurements over long periods of time, restricted only by battery life. Mackay suggested the use of power lines in the tether giving an unlimited life, subject only to electrical and mechanical failure.

B. pH MEASUREMENT

1. <u>Definition</u> <u>and</u> <u>Measurement</u> <u>of</u> <u>pH</u>[9,10] - The relative strength of an acid solution is a function of the hydrogen-ion concentration in the solution. This concentration, in gram equivalents per liter, can vary from 1 or greater for very strong acids, to 10^{-7} for neutral solutions. A neutral solution is one in which the hydrogen-ion

concentration is equal to the hydroxyl-ion concentration. In aqueous solutions, the product of the hydrogen-ion concentration and the hydroxyl-ion concentration is always equal to 10^{-14}. Those solutions in which the hydroxyl-ion concentration is greater than the hydrogen-ion concentration are called basic or alkaline solutions. Basic solutions therefore have hydrogen-ion concentrations ranging from 10^{-7} to 10^{-14}. The use of decimal notation to express hydrogen-ion concentration is rather inconvenient, so in 1909, Sorenson, a Danish biochemist, proposed the use of the pH scale. The pH of a solution is defined as the negative common logarithm of the hydrogen-ion concentration in that solution. This system results in a scale of small positive numbers, ranging from 0 for strong acids to 7 for neutral solutions to 14 for strong bases.

Measurement of pH can be accomplished by several methods, the most familiar of which is probably the use of organic colorimeter indicators such as litmus paper. Since the utility of these methods is limited, particularly where continuous pH measurement of a changing solution is required, electrometric methods of pH determination have become quite popular. With electrometric methods two electrodes are immersed in the solution whose pH is to be measured, and the electric potential between these electrodes is monitored. One of the electrodes is a pH-sensitive electrode whose potential with respect to the solution is a function of pH. The other electrode is a reference electrode whose potential

with respect to the solution is constant.

The first pH-sensitive electrode was the hydrogen electrode whose potential is developed when pure hydrogen gas is bubbled around an inert metal. This electrode, while still used as the primary reference for the pH scale, has the disadvantages of complicated operation and a 15 to 45 minute stabilization period. Another pH electrode is the quinhydrone electrode configuration in which an excess of solid quinhydrone is introduced into the solution to be measured and a platinum or gold electrode is used. This configuration establishes equilibrium in 1 to 5 minutes, has a limited pH range of 0 to 8, is sensitive to salt-ion concentrations, and has the inconvenient requirement of adding quinhydrone to the solution. A third pH electrode is the antimony electrode which has a rapid response to pH change and requires nothing but the electrode itself to be introduced into the solution. Its disadvantages are nonlinearity and lack of reversability. The pH electrode most responsible for the popularity of electrometric pH measurement is the glass electrode. This electrode has a response on the order of hundreds of milliseconds, is least affected by oxidizing agents of the four electrodes, and is quite durable. Its disadvantages are its high electrical resistance and a nonlinearity at the extreme ends of the 0 to 14 pH scale.

Two types of reference electrodes commonly used are the calomel electrode and the silver-silver chloride (Ag/AgCl)

electrode. Both of these electrodes are immersed in a saturated potassium chloride (KCl) solution which in turn forms a liquid junction with the solution being measured. The Ag/AgCl electrode has the better stability of the two for temperatures greater than $80^{\circ}C$ and as high as $100^{\circ}C$.

2. <u>Intragastric pH Measurement</u> - Before the advent of radio capsules, the pH of gastric contents was generally measured by one of two methods: gastric emptying by tube aspiration with external measurement of pH; and the use of glass electrodes designed for insertion through the esophagus and connected directly to a laboratory meter. The disadvantages of the first method, besides the obvious discomfort to the patient and the requirement to be prone, are the time delay in acquiring the measurement and the fact that the pH value obtained is merely an average value since considerable time is required to empty the stomach. The second method also restrains the patient considerably since the electrode requires a rather stiff shielded cable and connects to the laboratory meter.

In addition to developing one of the first pressure-sensitive radio capsules, Mackay and Jacobson also developed one of the first pH-sensitive capsules[2,6]. In this unit a plastic underwent mechanical changes with changes in pH. This mechanical change was coupled to a ferrite core whose motion relative to a coil frequency modulated a transmitter. The accuracy of this capsule was very poor.

In 1958, von Ardenne and Sprung developed a pH capsule

which used an antimony pH-sensitive electrode and an AgCl wire in sodium chloride (NaCl) solution for the reference electrode[2]. The potential developed across the electrodes modulated a transmitter. The capsule had a pH sensitivity which was of the same order of magnitude as its temperature drift and suffered from the defective response which is inherent in the antimony electrode.

In 1960, Russ and Wolff developed the first capsule utilizing the highly accurate glass pH electrode which had previously been shunned because of its high impedance[2,7]. The reference electrode was an Ag/AgCl electrode in contact with KCl crystals which were separated from the solution by a porous plug. This capsule suffered from drift with bias voltage and was limited to a life of 5 days by the battery.

During the early 1960's, H. G. Noller developed a capsule which was unique in that instead of using the standard commercial battery, electrical energy was obtained from a cell consisting of a magnesium electrode and an AgCl electrode in NaCl solution[2]. Since the cell compartment was in contact with the solution being measured through a semipermeable membrane, the AgCl cell electrode also served as the reference electrode for pH measurement. Unfortunately, the cell was capable of providing only 2.5 hours of operation and antimony was employed as the pH-sensitive electrode.

A passive pH capsule which utilized an external radio-frequency energy source similar to Farrar's passive pressure

capsule was developed by J. Nagumo et al. in 1962[2,11].
The capsule had an antimony and Ag/AgCl with KCl electrode
combination and suffered from the usual antimony problems.
A thread tether was used to fix the position of the capsule
in the gastrointestinal tract.

In 1964, Y. B. Babskiy reported a capsule which used
an antimony pH electrode and a reference electrode consisting
of an AgCl cup containing a solution of NaCl and AgCl[12].
The capsule was tethered on the end of a catheter which, in
addition to fixing the position of the capsule, allowed
removal of gastric juice to compare capsule readings with
those given by a standard laboratory meter.

Perhaps the best capsule with regard to stability and
accuracy was reported by K. Kitagawa et al. in 1966[13].
This capsule used a glass pH electrode and an Ag/AgCl ref-
erence electrode. Stability was reported to be ± 0.1 pH over
a 30 day period when operating in buffer solutions. The
capsule probably did not operate on one battery for this
period, since its current drain ($250 \mu A$) and the battery
employed (Mallory RM312, 36 mAh capacity) indicate a 6 day
life. The current drain also indicates a very short trans-
mission range. A stainless steel basket cover was used over
the electrode to prevent electrode contact with mucosa which
would result in erratic readings as noted by Bircher et.al.[14].

C. INTRAGASTRIC TITRATION

The classical method of titrating gastric contents in
order to determine the acidity involves emptying of the

stomach by tube aspiration and titrating the contents in the laboratory. Either a colorimeter indicator or a pH meter is used to indicate the end point or neutralization of the titration. The acid concentration is usually expressed in milliequivalents per liter or the number of ml of 0.1 N sodium hydroxide (NaOH) required to neutralize 100 ml of gastric juice. This is equivalent to the number of ml of 0.1 N hydrochloric acid (HCl) present in 100 ml of the gastric juice[15].

In 1960, Noller[16] began using a pH-sensitive radio capsule to indicate the end point of titrations performed on gastric juice in the stomach. His titration method involved introducing a known volume of sodium bicarbonate (NaHCO$_3$) into the stomach, causing the pH to reach alkaline levels, and then noting the time required for the stomach to return to its original acidic pH. This time was called the alkali-test time and was a measure of the gastric acidity.

In 1964, A. M. Connell and T. E. Waters[14] performed titrations similar to those of Noller's, with the exception of using smaller amounts of alkaline solution and substituting potassium bicarbonate (KHCO$_3$) as the alkaline solution. The use of smaller amounts reduced the test time and therefore reduced the effect of emptying of the stomach into the intestine. The use of KHCO$_3$ tended to inhibit this emptying rate.

III. EQUIPMENT REQUIREMENTS

The primary requirements of the equipment are to
monitor the pressure in the stomach, to monitor the pH of
the gastric contents, to modulate a transmitter with the
above information, and to automatically titrate the stomach
acid. The pressure fluctuations from which motility is to
be inferred, vary in the range from 0 to 100 mmHg at rates
up to 5 c/min. Since only the rate of these fluctuations
is of interest, no accuracy of measurement of the actual
pressure is required. The pH range to be monitored is 1 to
10 with an accuracy goal of ± 0.1 pH unit. The automatic
titration system must be capable of injecting an alkaline
solution into the stomach when the pH falls below a given
value, and discontinuing the injection when the alkaline
solution causes the pH to rise above another given value.
Since the limits within which the pH must be maintained will
be determined during the clinical studies, the limits must
be adjustable. The equipment must be capable of operating
for 14 days.

IV. EQUIPMENT DEVELOPMENT AND ANALYSIS

A. SYSTEM APPROACH

The system can be divided into three pieces of equipment: the sensor capsule, the transmitter modulation unit, and the automatic titration unit. The pH and pressure in the stomach are monitored by the sensor capsule which is tethered in the stomach. Signals from the sensor capsule representing pH and pressure are used by the modulation unit to control respectively the pulse rate and width of a pulse train which modulates a transmitter. The pH information from the modulation unit is sensed by the titration unit and controls a constant-speed pump. When the pH drops to a low pH level, the pump is activated and begins pumping a known alkaline solution into the stomach. When the pH reaches a high level, the pump is deactivated, allowing the gastric acid secretion to drive the pH level low again, causing the cycle to repeat.

B. SENSOR CAPSULE

The sensor capsule contains a pH-sensitive glass electrode, an Ag/AgCl with KCl reference electrode, a pH preamplifier, and a pressure-sensitive transducer. The capsule is restrained in the stomach for 14 days by a tether consisting of three tubes. One contains the wires which provide power to the capsule electronics and transmit the pH and pressure signals to the modulation unit. Another tube is used for pumping the alkaline solution into the stomach. The third tube is used to periodically flush air or water

around the glass electrode in order to prevent clogging of the basket by solids in the gastric contents which would inhibit measurement. The capsule has a teflon shell, 2.6 cm long and 0.8 cm in diameter, with a basket guard at one end which prevents the glass electrode from contacting mucosa and providing erratic measurement.

Of the four pH-sensitive electrodes discussed previously, the glass electrode is the logical choice. The hydrogen and quinhydrone electrodes are both impractical, requiring the introduction of hydrogen and quinhydrone respectively into the stomach. The antimony suffers from nonlinearity and lack of repeatability. A commercially available glass electrode, the Beckman Model 39042, is used after its stem has been shortened to reduce its size.

The Ag/AgCl reference electrode is preferred over the calomel electrode because of its simpler construction, using an Ag/AgCl wire rather than a calomel paste in conjunction with the KCl liquid junction. Construction of the electrode consists of filling a small glass tube with KCl crystals, sealing the Ag/AgCl wire in one end, and sealing a piece of fine porosity glass frit into the other end. The glass frit allows the KCl crystals to absorb liquid, providing the liquid junction, and also reduces the diffusion rate of the KCl crystals into the solution being measured, resulting in long life.

Because the output impedance of the electrode pair is several hundred megohms, a preamplifier must be located in

the capsule to reduce noise problems. The preamplifier uses a field-effect transistor (FET) with a resistor between source and ground. When the pH electrode pair potential is applied between gate and ground, the amplifier acts as a pH-controlled current source, where the FET drain current is given by:

$$I(pH) = I_o - \frac{g_m R_s}{(1 + g_m R_s)} \cdot \frac{\Delta V_{pH}(pH)}{R_s} \qquad (1)$$

where:

I_o is the drain current at 0 pH and is a function of the FET pinch-off voltage

g_m is the FET forward transconductance

R_s is the source resistor

pH is the solution pH

ΔV_{pH} is the change in voltage of the electrode pair per pH unit

Typical values are:

$I_o = 4.55 \mu A$

$g_m = 100 \mu mho$

$R_s = 360 k\Omega$

$\Delta V_{pH} = 0.059$ V/pH unit

Substitution of the above values into equation (1) yields:

$$I(pH) = 4.55 - 0.16(pH) \quad \mu A \qquad (2)$$

The pressure transducer, a Pitran Model PT-1 manufactured by Stow Laboratories, is a low-gain transistor modified to exhibit change in current gain with change in pressure. The modification consists of replacing the top of the

transistor can with a flexible diaphragm and connecting a pin between the diaphragm and the transistor base-emitter junction. Displacement in the diaphragm due to pressure change is coupled through the pin to the base-emitter junction, where the resulting stress causes a change in the current gain.

C. MODULATION UNIT

The modulation circuitry is shown in Figure 1. Transistors Q_1, Q_2, Q_3, resistors R_1, R_2, R_3, and capacitor C_1 form a relaxation oscillator whose frequency is a function of $I(pH)$. Operation is as follows. Initially C_1 is discharged and R_1 has a voltage across it as determined by the constant-current source formed by Q_3 and R_3. Q_1 and therefore Q_2 are cutoff, allowing $I(pH)$ to charge C_1 until the voltage across C_1 is large enough to forward bias the base-emitter junction of Q_1 causing it to conduct. The collector current of Q_1 drives Q_2 which in turn provides additional drive to Q_1, resulting in a regenerative action which discharges C_1 until the collector current of Q_2 becomes less than the current of the current source. The current source then begins to draw more current through R_1, cutting off Q_1 and Q_2. The process is repeated at a frequency given by:

$$f(pH) = \frac{I(pH)}{C_1 \Delta V_{C_1}} \qquad (3)$$

where ΔV_{C_1} is the change in voltage across C_1 during a cycle and is:

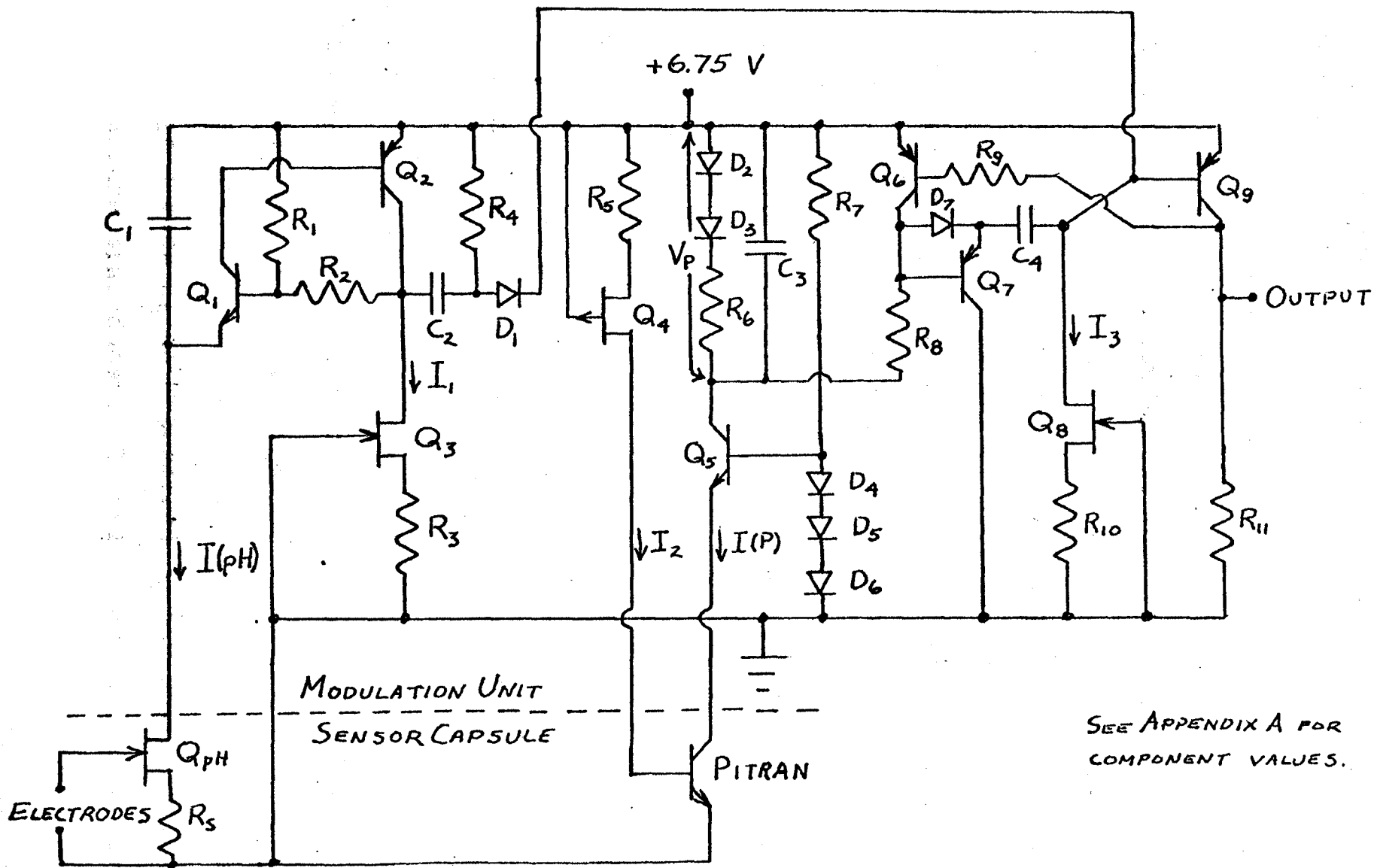$$\Delta V_{C_1} = I_1 R_1 + V_{BE1} - (V_{CE2} + V_{BE1}) = I_1 R_1 - V_{CE1} \qquad (4)$$

FIGURE 1 — SENSOR CAPSULE AND MODULATION UNIT

where V_{BEX} and V_{CEX} are the base-to-emitter and collector-to-emitter voltages respectively of Q_X. Substitution of typical values yields:

$$f(pH) = 2.28 - 0.08(pH) \quad kHz \qquad (5)$$

The output of the relaxation oscillator is differentiated and gated to a monostable multivibrator consisting of Q_6, Q_7, Q_8, Q_9, R_8, R_9, R_{10}, R_{11}, C_4, and diode D_7. The multivibrator is a standard circuit with the exception of Q_7, D_7, Q_8, and R_{10}. Q_7 and D_7 provide a fast recovery time by recharging C_4 with an amplified current allowing a high duty cycle. Q_8 and R_{10} provide a constant discharge rate to C_3 resulting in a pulse width which is independent of supply voltage variations and which is a linear function of V_p as follows:

$$T(P) = \frac{C_3 \Delta V_{C3}}{I_3} \qquad (6)$$

where $T(P)$ is the pulse width and ΔV_{C3} is the change in voltage across C_3 each cycle as given by:

$$\Delta V_{C3} = (V_p - V_{BE7} - V_{BE9}) - (V_{CE6} + V_{D_7} - V_{BE9})$$
$$= V_p - V_{BE7} - V_{CE6} - V_{D_7} \qquad (7)$$

where V_{D_7} is the voltage across diode D_7 and V_p is as shown in Figure 1. Substitution of typical values yields:

$$T(P) = 145 V_p - 159 \quad \mu s \qquad (8)$$

V_p is determined by the voltage across D_2 and D_3 plus the voltage across R_6 as determined by the collector current of the pressure transducer. D_2 and D_3 are used for temperature compensation of V_{BE7} and V_{D_7}. Q_4 and R_5 form a current source which provides a constant base current to the pressure

transducer independent of supply voltage variations. Q_5, R_7, D_4, D_5, and D_6 provide a regulated voltage to the collector of the pressure transducer. This improves the linearity of the collector current as a function of pressure. If the collector voltage were allowed to vary with V_p, the change in collector-to-emitter voltage divided by the collector resistance would result in collector-current variations not directly related to pressure variations. These changes are significant with this transistor because of its low current gain and operating current. Immunity to bias voltage variations is also provided by this type of biasing. A curve of collector current versus pressure is shown in Figure 2. If this curve is expressed as:

$$I(P) = 395 - 1.95P \quad \mu A \tag{9}$$

where P is the pressure in mmHg, the equation for V_p using actual values is:

$$V_p = 2.15 - 0.0047P \quad V \tag{10}$$

The final expression for pulse width as a function of pressure is then:

$$T(P) = 153 - 0.64P \quad \mu s \tag{11}$$

D. AUTOMATIC TITRATION UNIT

The automatic titration unit is shown in Figure 3 and consists of a frequency-to-dc voltage converter, a Schmitt trigger, a peristaltic pump, and a pump speed control loop. The frequency-to-dc voltage converter linearly converts the pH-dependent frequency to a dc voltage. The Schmitt trigger senses the dc voltage representing pH and activates the pump
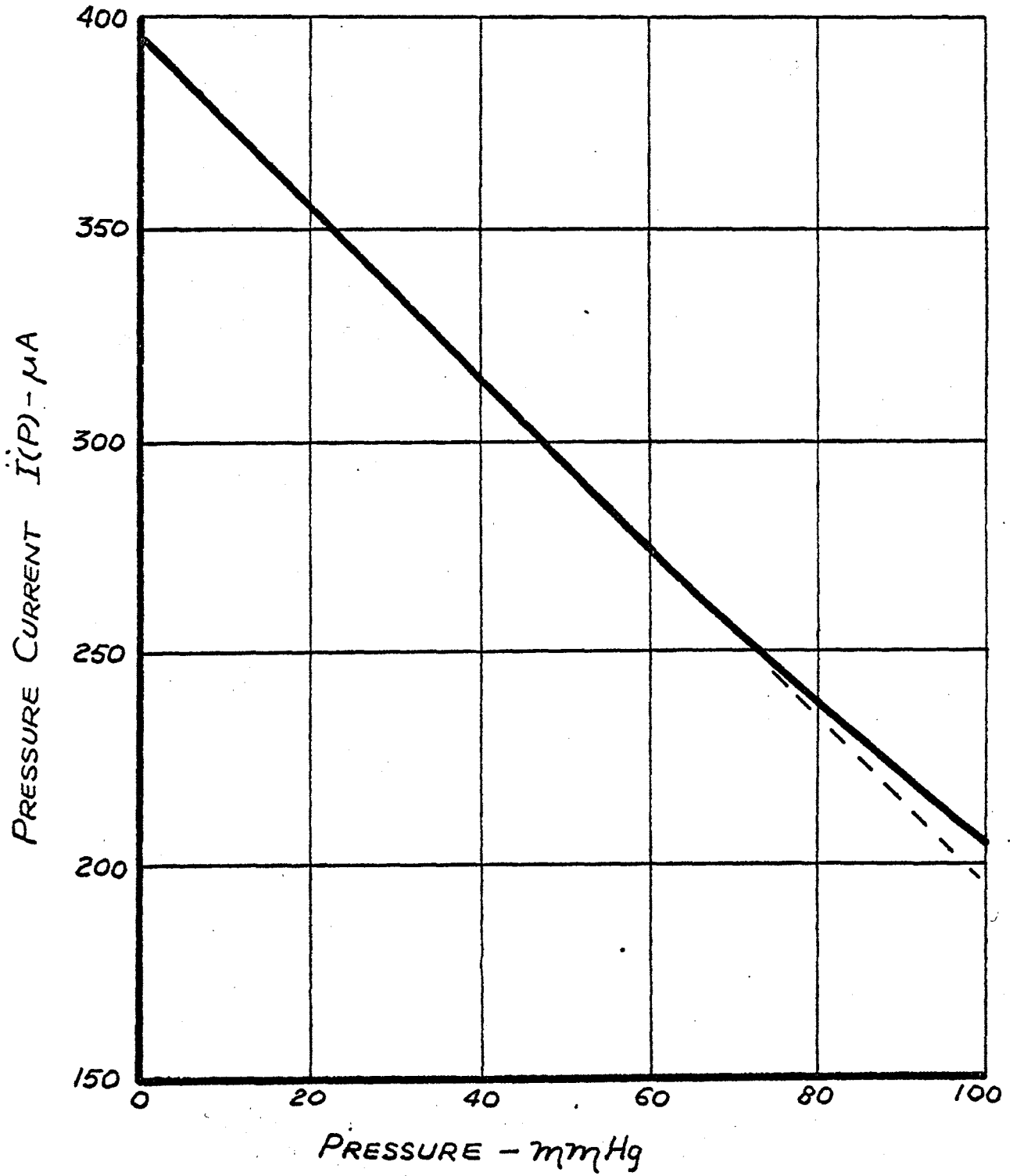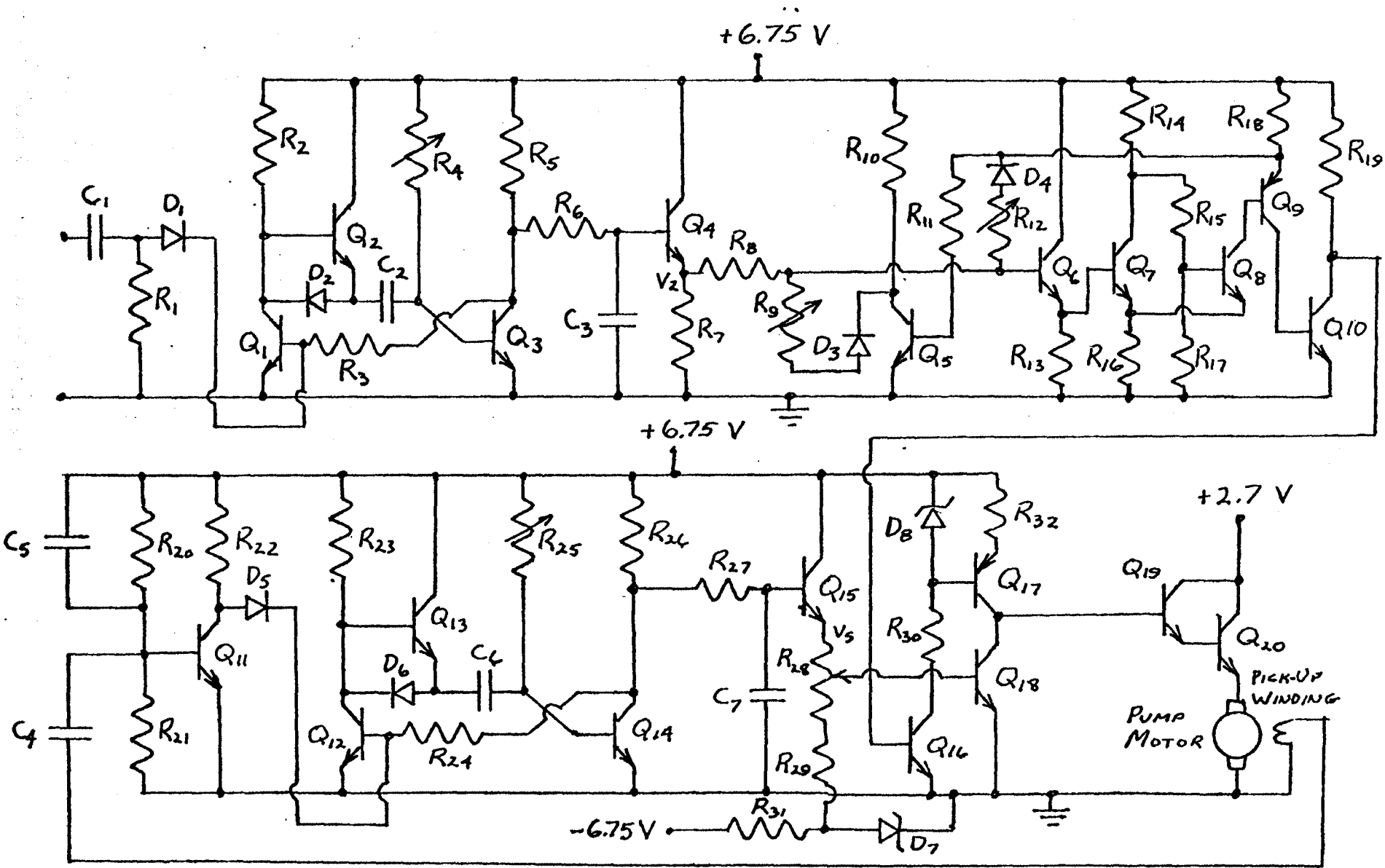
FIGURE 2 - PRESSURE CURRENT RESPONSE

FIGURE 3—AUTOMATIC TITRATION UNIT

SEE APPENDIX B FOR COMPONENT VALUES.

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when the voltage indicates a predetermined upper pH level
has been reached, and deactivates the pump when a predeter-
mined lower pH value has been reached. Since the speed,
and therefore the pumping rate, of the peristaltic pump is
maintained constant by the speed control loop, only the
time that the pump has operated must be known to specify
the amount of alkaline solution that has been pumped into
the stomach.

The frequency-to-dc voltage converter operates as
follows. The incoming pulses are differentiated and gated
to trigger a constant-pulse-width monostable multivibrator
consisting of Q_1, Q_2, Q_3, and their associated components.
R_6 and C_3 average the output of the monostable multivibrator
and Q_4 acts as a buffer amplifier. The voltage at the
emitter of Q_4 is:

$$V_2 = V_1 T_1 f(pH) - V_{BE}4 \qquad (12)$$

where V_1 and T_1 are the amplitude and width respectively of
the monostable multivibrator output pulses. Substitution
of typical values yields:

$$V_2 = 1.73 f(pH) - 0.7 \quad V \qquad (13)$$

In order to allow for experimentation with various
combinations of upper and lower pH levels during clinical
studies, a variable-hysteresis Schmitt trigger is used[17].
Here Q_7 and Q_8 form an ordinary Schmitt trigger with upper
and lower trigger levels of V_U and V_L respectively as seen
at the base of Q_7. Q_6 acts as a buffer amplifier to pre-
vent loading of the hysteresis control circuitry which

operates as follows. If Q_8 is cutoff, meaning that the circuit has received the upper trigger level most recently and is now awaiting the lower trigger level, Q_5 is saturated, D_3 is forward biased bringing R_9 into the circuit, and D_4 is back biased removing R_{12} from the circuit. The lower trigger level as seen at the emitter of Q_{14}, T_L', is changed as a result of the divider action of R_8 and R_9 and can be controlled by R_9 according to:

$$T_L' = \frac{R_8 + R_9}{R_9} T_L \qquad (14)$$

if various transistor and diode voltages are neglected. Similarly, when the Schmitt trigger is in the other state, Q_8 is saturated, Q_5 is cutoff, D_3 is back biased removing R_9 from the circuit, and D_4 is forward biased bringing R_{12} into the circuit. The upper trigger level as seen at the emitter of Q_4, T_U', is changed as a result of the divider action of R_8 and R_{12} and can be controlled according to:

$$T_U' = \frac{R_8 + R_{12}}{R_{12}} T_U \qquad (15)$$

if various transistor and diode voltages are neglected. This technique allows independent adjustment of the upper and lower pH levels. Q_9, Q_{10}, and Q_{16} activate or deactivate the pump, depending on the state of the Schmitt trigger.

The speed regulation of the pump is accomplished as follows. The pump motor is a permanent magnet motor to which a pick-up pole and winding have been added. Each time an armature pole passes the pick-up pole, a pulse is generated in the pick-up winding. These pulses are amplified by Q_{11} and their frequency is converted to a dc voltage at

the emitter of Q_{15} in a manner similar to the pH frequency-to-dc voltage conversion discussed above. The voltage at the emitter of Q_{15} is related to the motor speed as:

$$V_S = 3V_3T_3S - V_{BE15} \qquad (16)$$

where V_3 and T_3 are the amplitude and width respectively of the monostable multivibrator pulses and S is the speed of the motor. The factor 3 occurs because the armature has 3 poles, and therefore 3 pulses are produced for each revolution of the motor. V_S, and therefore the motor speed, are regulated as follows. D_8, Q_{17}, R_{30}, and R_{32} constitute a constant-current source, the output of which can either be shunted to ground through Q_{18} or provide drive to the motor through Q_{19} and Q_{20}. If V_S becomes smaller, indicating a reduction in speed, Q_{18} shunts less current to ground, allowing more drive to the motor, and causing an increase in speed and V_S. If V_S increases too much, indicating a high motor speed, Q_{18} shunts more current to ground, decreasing the drive to the motor, and causing a reduction in speed and V_S. D_7 provides the reference for the regulator and determines the speed for a given setting of R_{28}. Adjustment of R_{28} changes the speed to the desired pumping rate.

V. EXPERIMENTAL RESULTS

A. pH MEASUREMENT

Each sensor capsule has a different pH response, due primarily to differences in the pinch-off voltages of the individual FET's. The pinch-off voltage affects the 0 pH drain current, I_o. Other variables between various sensor capsules are the FET transconductance, gm, and the source resistor, R_s. The former affects the variable term of I(pH), while the latter affects both terms. Figure 4 is a plot of I(pH) for the sensor capsule used in the _in vivo_ tests discussed in the remainder of this section. The data for this curve was obtained from laboratory measurements using buffered pH solutions maintained at 37°C, the normal body temperature. The actual curve can be approximated by the linear curve:

$$I(pH) = 4.55 - 0.148(pH) \quad \mu A \tag{17}$$

The response becomes nonlinear in the alkaline region above pH 8; this was expected as noted earlier in this paper.

The response of f(pH) is shown in Figure 5, using the same sensor capsule as above with the modulation unit, and again using buffered solutions maintained at 37°C. The curve can be approximated by:

$$f(pH) = 2.155 - 0.07(pH) \quad kHz \tag{18}$$

Again the same departure from linearity is noted in the alkaline region. The pH temperature coefficient of this capsule is 2.5 Hz/°C representing 0.036pH unit/°C. Long term drift data obtained from other capsules and breadboard
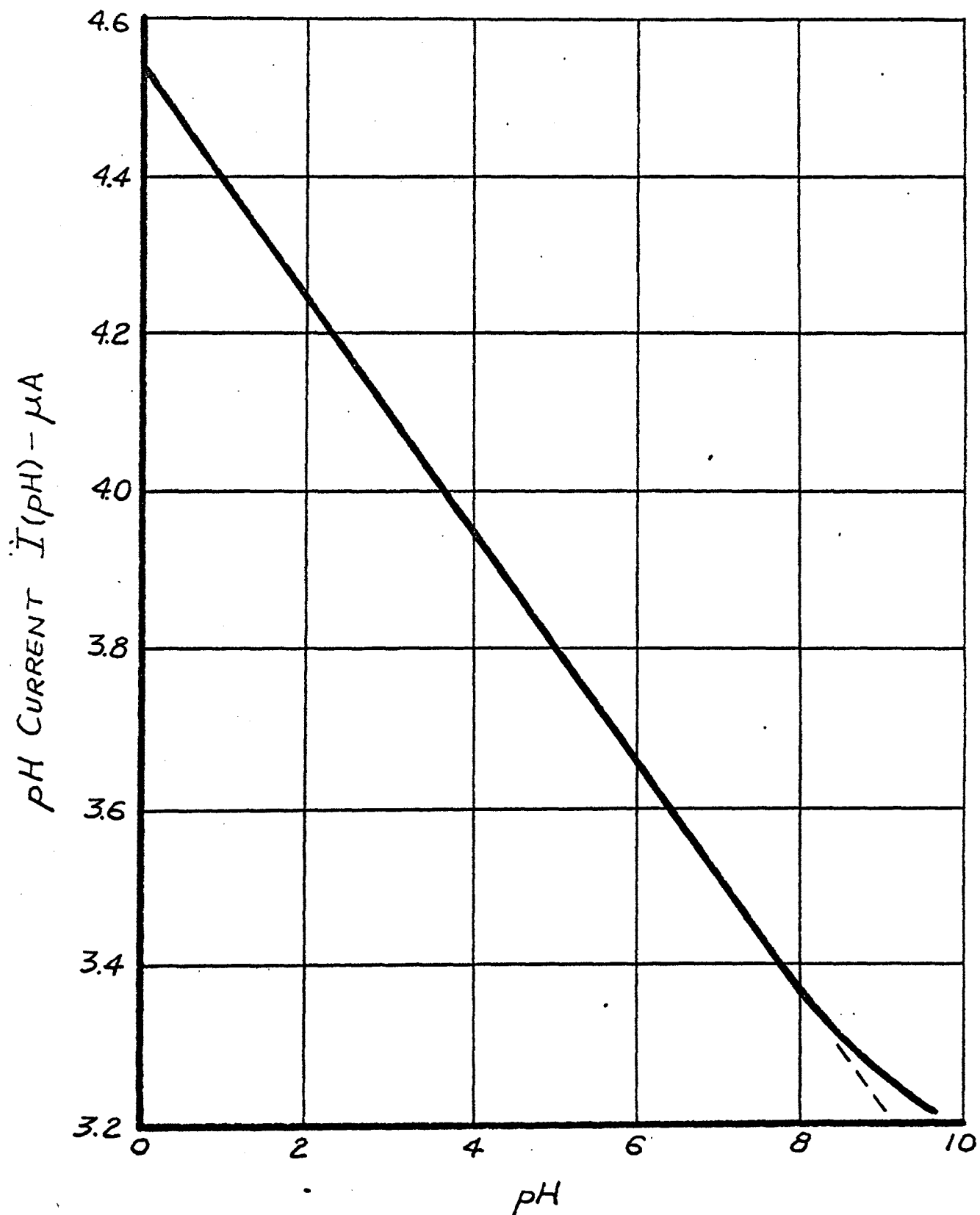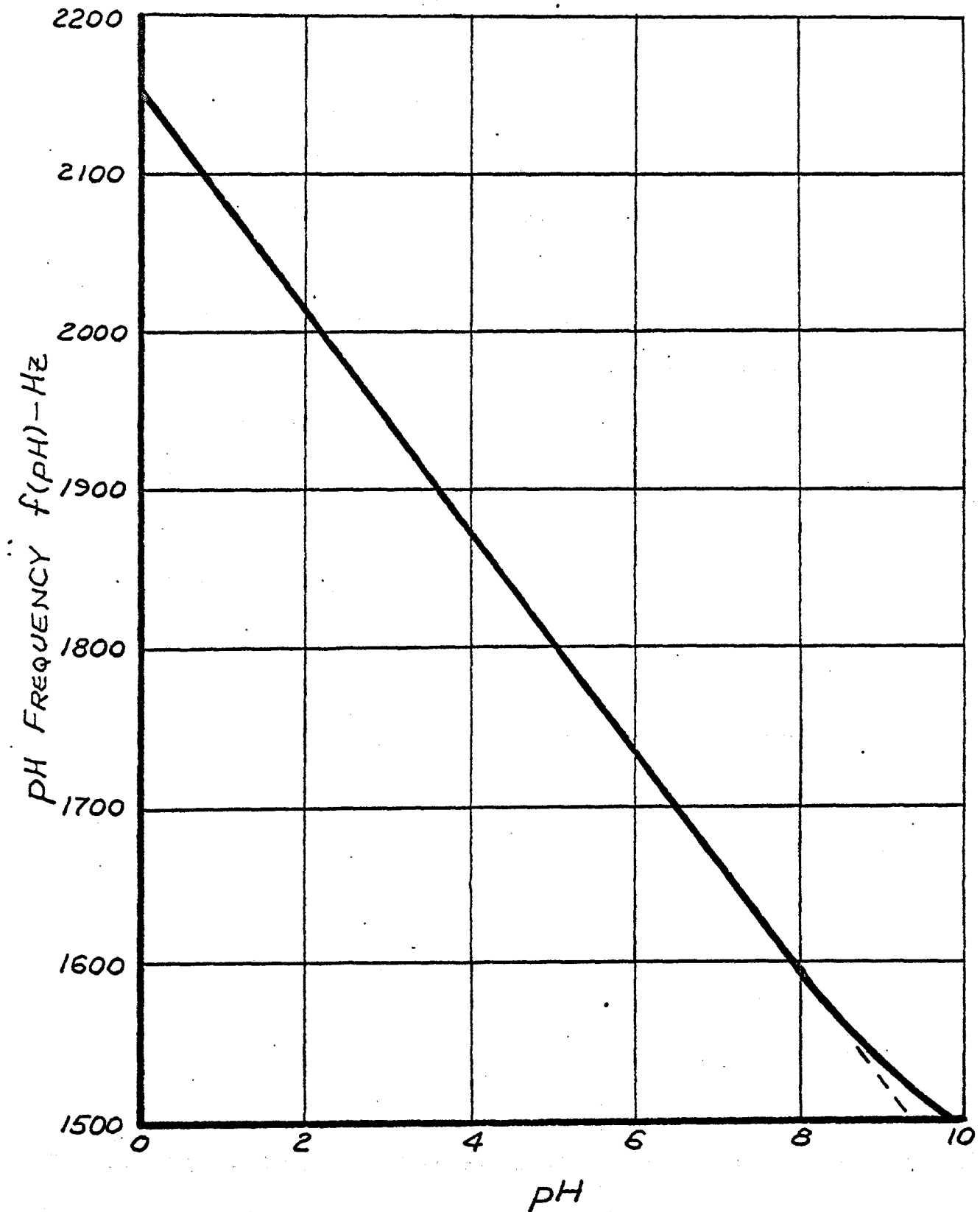
FIGURE 4- pH CURRENT RESPONSE

FIGURE 5 — pH FREQUENCY RESPONSE

capsules indicate random drift over a 0.2pH range for periods up to several days, with some breadboard capsules demonstrating drift less than 0.1pH over a 2 week period.

The useful life of the capsule is limited by two items, the reference electrode and the encapsulating material. The reference electrode produces a constant potential only if the KCl solution contained in it remains saturated. When the capsule is placed in a solution to be measured, the KCl solution in the reference electrode becomes diluted as KCl diffuses into the solution being measured. The use of the glass frit has reduced this loss to the extent that reference electrodes of the size compatible with the sensor capsule have operated as long as 21 days with breadboard capsules.

The problem concerning encapsulating materials, which has not been completely solved, is one of moisture absorption. As the capsule soaks in a solution, moisture is absorbed by the encapsulating material, reducing its insulating effectiveness. Although the conductivities of the moisture leakage paths are quite low, the impedances associated with the pH measuring circuit are quite high, and deterioration of the capsule operation results. The moisture leakage problem manifests itself in two ways: leakage between the FET gate and source or the solution, and leakage between the FET drain and the solution. The first type reduces the effective ΔVpH of equation (1) by loading the glass electrode. The second type produces a leakage path in parallel with the

pH-sensitive current source resulting in an apparent increase in I_o of equation (1). The most promising encapsulating materials have been the silicone rubbers, of which several types have been tried. Lifetimes up to 28 days have been obtained with the silicone rubbers, but these results have by no means been repeatable. The use of the teflon capsule shell has improved the situation by reducing the surface area exposed to soaking. When the teflon shell is used, the capsule components are potted in a silicone rubber slug which is then coated with silicone grease and forced into the teflon shell. The grease inhibits the leakage of moisture between the teflon shell and the rubber slug.

B. PRESSURE MEASUREMENT

The response of the pressure transducer is shown in Figure 2. When the sensor capsule is used in conjunction with the modulation unit, the pulse width as a function of pressure is as shown in Figure 6. The curve can be approximated by:

$$T(P) = 162 - 0.72P \quad \mu s \tag{19}$$

The nonlinearity of the actual response at high pressures is inherent in the pressure transducer. The temperature coefficient of the pressure response is -8 mmHg/^{o}C. The long term drift at constant temperature is within 5 mmHg.

The temperature coefficient could be improved to approximately -1 mmHg/^{o}C by venting the inside of the pressure transducer to atmospheric pressure. It is presently sealed
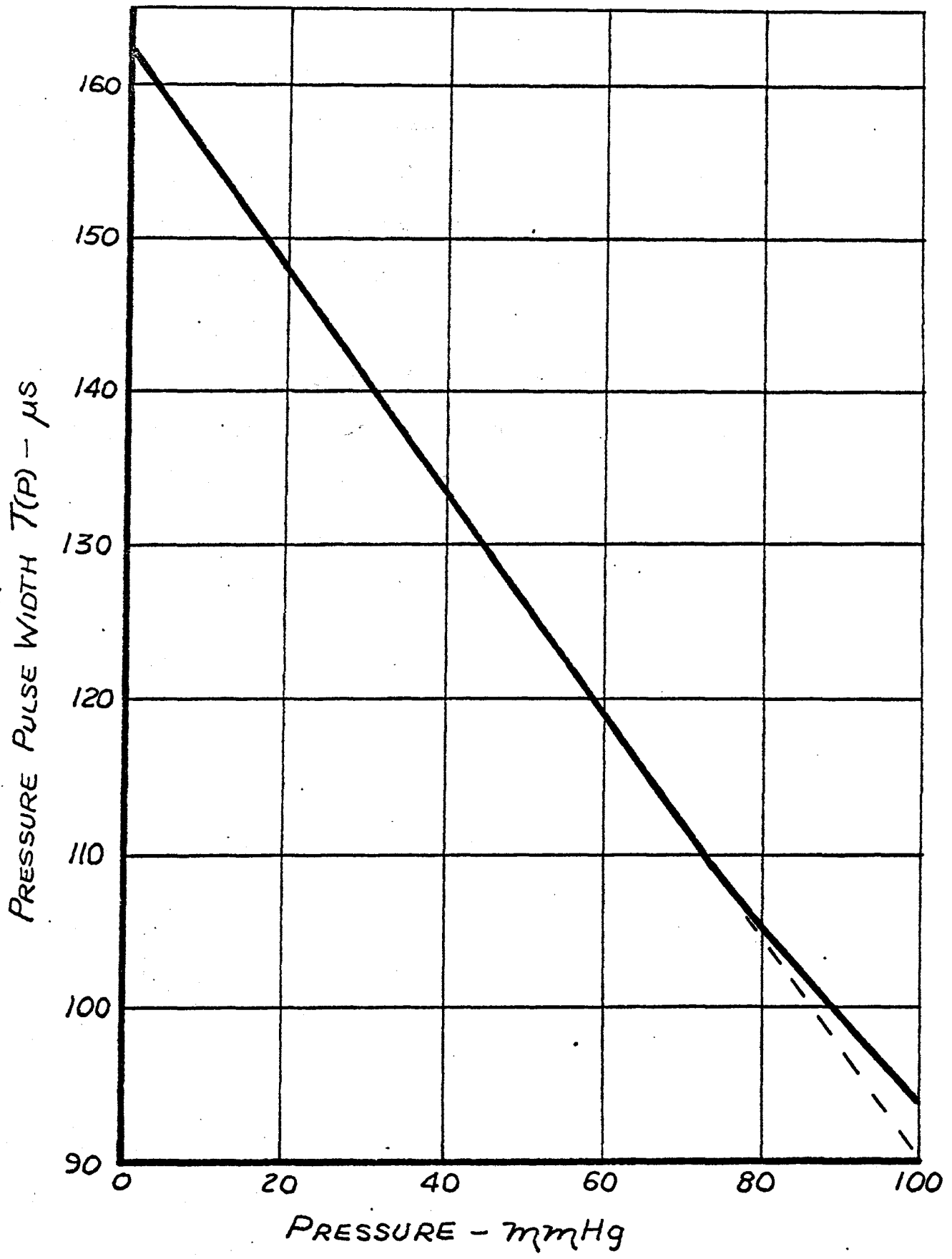
FIGURE 6 — PRESSURE PULSE WIDTH RESPONSE

at atmospheric pressure and an increase in temperature
results in air expansion, which appears as a decrease in
external pressure.   The venting could be accomplished via
the tether, although it might introduce an additional leak-
age problem.   The improved accuracy may not be necessary,
since only the detection of the presence of motility waves
at a rate of 3 c/min is desired and temperature fluctuations
will probably not occur at this rate.

In vivo tests thus far have been disappointing with
respect to motility detection.   Pressure fluctuations of 5
to 10 mmHg due to respiration, 40 to 50 mmHg due to coughing,
and up to 100 mmHg due to bearing down as in a bowel move-
ment are readily observed.   However, no fluctuations which
might be attributed to motility have been observed.   This
problem is not without precedent.   Farrar[3], Connell[18,19],
and Wolff[20] have reported monitoring pressure fluctuations
as large as 80 mmHg attributed to motility with the use of
radio capsules.   However, Connell discovered that the pres-
sure fluctuations he monitored were actually changes in
signal strength from the radio capsule which were caused by
a unidirectional antenna and movements of the capsule due to
motility.   A. N. Smith and M. Ridgway[21] overcame the uni-
directionality problem by the use of a multiple antenna
array.   Their findings indicate that pressure fluctuations
due to motility are more likely to be observed in the pyloric
section of the stomach than in the body of the stomach, pos-
sibly due to the narrowness of the pyloric section.

Studies by others[1,22,23] with open tip catheters and balloons have indicated that pressure fluctuations due to motility on the order of 20 mmHg might be expected in the pyloric section while little or no fluctuation may appear in the body of the stomach. These effects will be studied during the clinical baseline tests and are not of primary concern for the purposes of this thesis. Tests thus far have demonstrated that the technical aspects of the pressure channel operation are satisfactory.

C. AUTOMATIC TITRATION

Titration tests using the entire system in the laboratory and _in vivo_ have indicated satisfactory performance of the automatic titration unit. Turn on and turn off levels for the pump are repeatable to within 0.1 pH unit. A plot of a laboratory titration is shown in Figure 7. In this titration 0.1 N NaOH was titrated against 0.1 N HCl, with the upper and lower pH levels set at 6.8 pH and 2.4 pH respectively.

The results of an _in vivo_ titration are presented in Figure 8. Here the alkaline solution used was 1 M $NaHCO_3$ and the upper and lower pH levels were set at 6.6 pH and 1.5 pH respectively. When the automatic titration system was activated, the pump turned on immediately since the pH was initially at 1.0. 188 ml of the $NaHCO_3$ were required to raise the pH of the gastric contents to 6.6, turning off the pump. The acid secreted by the stomach then drove the contents to pH 1.5 and the pump turned on again, causing
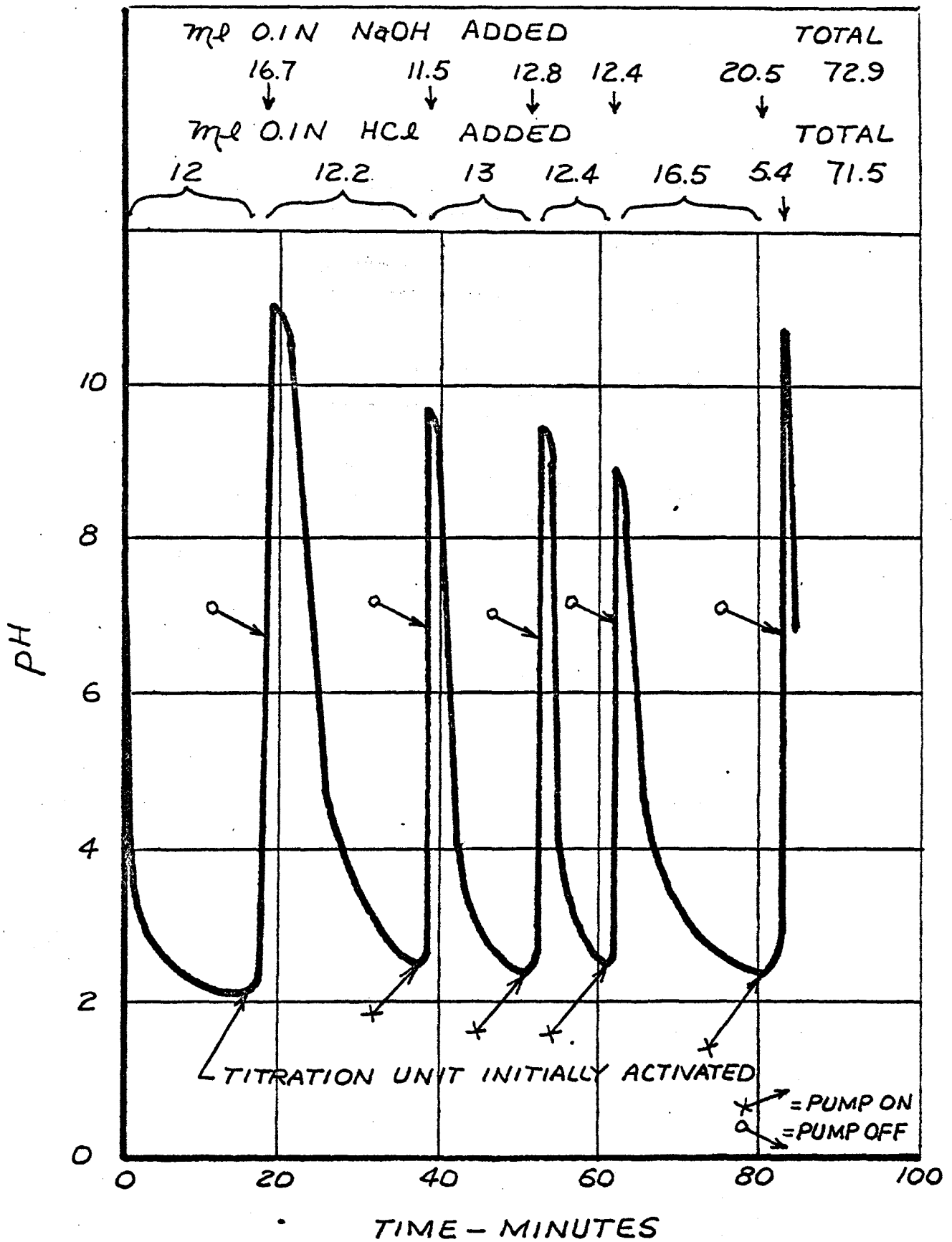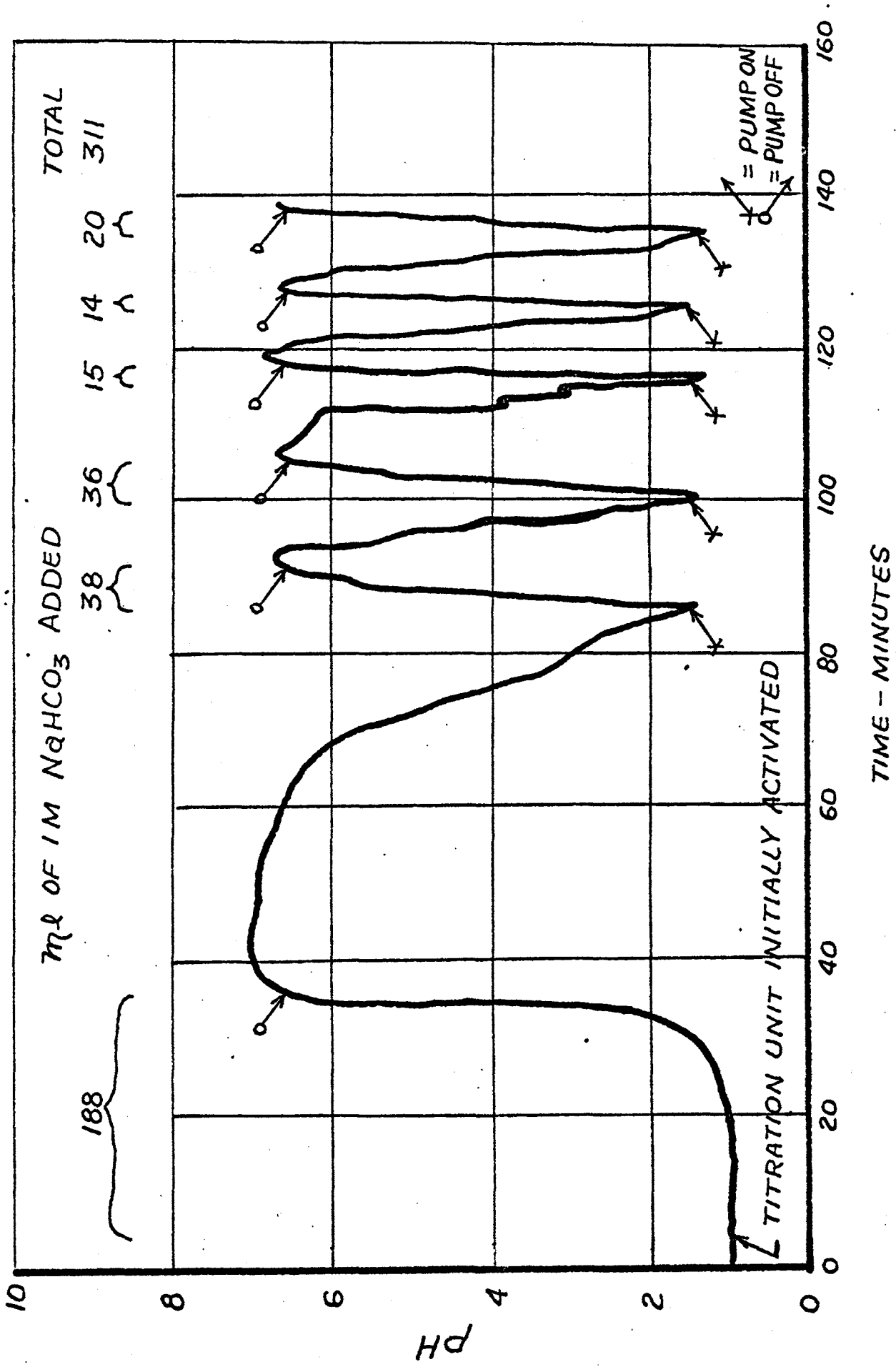
FIGURE 7—LABORATORY TITRATION

FIGURE 8 - IN VIVO TITRATION

the cycle to repeat.

Although the regulation of the pumping rate has been measured to be normally within 3% when only the speed control loop and the pump are operating, several periods of poor regulation were noted during operation of the entire system. This has been traced to interference from the pH frequency causing misfiring of the regulator's frequency-to-dc converter. This problem has been reduced by placing capacitors from the collectors of the switching transistors to ground, eliminating the high-frequency radiation components due to fast switching times.

VI. CONCLUSIONS

Although not all of the equipment performance requirements have been met on a consistent basis, the capability of meeting each requirement has been demonstrated. The greatest need for improvement is a longer capsule lifetime which must be achieved with improved capsule materials and/or construction techniques to reduce moisture absorption. Reduction of pH frequency drift is also desired; this problem may be associated with moisture absorption since breadboard capsules have demonstrated better drift characteristics than potted capsules. Performance of the pressure channel and automatic titration unit have been technically satisfactory, although there appears to be some question as to the validity of using pressure to infer motility. This will be resolved by further testing and is not a primary concern of this thesis.

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APPENDIX A

The component values for the circuit of Figure 1 are:

$R_1 = 6.8$ kΩ

$R_2 = 82$ Ω

$R_3 = 5.26$ kΩ

$R_4 = 100$ kΩ

$R_5 = 10$ kΩ

$R_6 = 2.4$ kΩ

$R_7 = 75$ kΩ

$R_8 = 430$ kΩ

$R_9 = 330$ kΩ

$R_{10} = 51$ kΩ

$R_{11} = 33$ kΩ

$R_s = 360$ kΩ

$C_1 = 1000$ pF

$C_2 = 500$ pF

$C_3 = 25$ μF

$C_4 = 6800$ pF

Q_1 and $Q_5 = $ 2N930

$Q_2 = $ 2N327A

Q_3 and $Q_8 = $ 2N3819

$Q_4 = $ 2N2498

Q_6, Q_7, and $Q_9 = $ 2N995

$Q_{pH} = $ KW3686

All diodes = 1N645

APPENDIX B

The component values for the circuit of Figure 3 are:

R_1 = 100 kΩ	R_{19} = 56 kΩ	C_5 = 1000 pF
R_2 = 68 kΩ	R_{20} = 680 kΩ	C_6 = 0.133 μF
R_3 = 330 kΩ	R_{21} = 100 kΩ	C_7 = 0.1 μF
R_4 = 100 kΩ	R_{22} = 68 kΩ	Q_1, Q_2, Q_3, Q_4,
R_5 = 33 kΩ	R_{23} = 68 kΩ	Q_5, Q_6, Q_7, Q_8,
R_6 = 100 kΩ	R_{24} = 330 kΩ	Q_{10}, Q_{11}, Q_{12},
R_7 = 10 kΩ	R_{25} = 330 kΩ	Q_{13}, Q_{14}, Q_{15},
R_8 = 56 kΩ	R_{26} = 68 kΩ	Q_{16}, and Q_{18} =
R_9 = 100 kΩ	R_{27} = 470 kΩ	2N930
R_{10} = 56 kΩ	R_{28} = 25 kΩ	Q_9 = 2N995
R_{11} = 56 kΩ	R_{29} = 200 kΩ	Q_{17} = 2N1132
R_{12} = 25 kΩ	R_{30} = 6.8 kΩ	Q_{19} = 2N1613
R_{13} = 100 kΩ	R_{31} = 1 kΩ	Q_{20} = 2N3585
R_{14} = 33 kΩ	R_{32} = 6.8 kΩ	D_1, D_2, D_3, D_4,
R_{15} = 100 kΩ	C_1 = 150 pF	D_5, and D_6 =
R_{16} = 22 kΩ	C_2 = 0.01 μF	1N645
R_{17} = 180 Ω	C_3 = 1 μF	D_7 = 1N751A
R_{18} = 33 kΩ	C_4 = 2200 pF	D_8 = 1N748

VITA

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