

UNIVERSITY OF CAPE TOWN

A BLOOD-PERFUSION FLOWMETER

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A thesis submitted in fulfilment  
of the requirements for the degree  
of M.Sc. in Electrical Engineering.

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## Introduction

A variety of methods have been used for measuring blood flow in large vessels. However, almost all of these methods are unsuitable for measuring perfusion flow in tissue.

Basically all attempts at perfusion flow measurement have used either a tracer method (radio-active dyes, microspheres)<sup>1,2</sup> or a thermal method where the rate of heat clearance from a heated probe is used as a measure of local flow. Tracer methods suffer from the fact that they give essentially a single measurement of flow and this only after tissue has been removed and analysed. Thermal methods on the other hand can give a continuous measurement. What is actually being measured in the thermal method is the apparent thermal conductivity of the tissue in the immediate vicinity of the probe. The apparent thermal conductivity increases with flow as heat from the probe is not only conducted away by the surrounding tissue but is also carried away by the perfusing fluid. The way in which local perfusion is related to thermal conductivity and the methods used to measure thermal conductivity have led to criticisms of thermal methods<sup>3,4</sup>.

This work deals with instrumentation to eliminate some sources of error in thermal methods and automate the whole measurement procedure. It also includes a critical review of thermal methods in general and previous work in the field in particular.

## SECTION 1

### 1. Velocity Flow Measurement using Thermal Methods.

Local perfusion flow measurement using thermal methods has much in common with velocity measurement using thermal methods and thus velocity measurement is discussed first.

#### Hot "Wire" Anemometry.

##### 1.1 King's Law.

Hot wire anemometry is a very well established measurement technique used extensively by aeronautical and mechanical engineers. The basic ideas and the theory behind the operation of the hot wire anemometer were developed by King in an elegant paper in 1914<sup>5</sup>. King showed that the power  $P$  necessary to maintain a wire at a temperature  $\Delta T$  higher than that of the fluid flowing past the wire at velocity  $V$  was related to the velocity by the equations :

$$P = (A + BV^{\frac{1}{2}}) \Delta T \quad \dots \quad (\text{high velocities}) \quad \dots \quad 1.11$$

$$P = \frac{C \Delta T}{D - \log \frac{1}{2} V} \quad \dots \quad (\text{low velocities}) \quad \dots \quad 1.12$$

A, B, C, D constants dependent on  
wire and fluid

$$\Delta T = (T_{\text{wire}} - T_{\text{fluid}})$$

Equation 1.11 is commonly called King's Law and is widely accepted<sup>6,7</sup>. (sometimes with slight modifications)<sup>10</sup> both for hot wire and hot thermistor anemometers.

Equation 1.12, on the other hand, is usually conveniently ignored as it is rather more difficult to "curve fit" and applies to extremely slow flows. In practice over a limited range of very slow flows  $P$  seems approximately proportional to  $V$ .

Kramers<sup>8</sup> has derived empirically more accurate equations describing heat transfer in terms of the dimensionless Reynoldt, Prandtl and Nusselt numbers. However, King's law in simple form gives quite a good approximation and is used in the following discussion.

The term  $A\Delta T$  represents power lost by conduction  
and  $BV^{\frac{1}{2}}\Delta T$  the power lost by "forced" convection.

Rewriting 1.11 in terms of the resistance  $R$  of the wire and the current  $I$  which flows through it :

$$P = I^2 R = (A + BV^{\frac{1}{2}}) \Delta T \quad \dots \dots \quad \dots \dots \quad \dots \dots \quad 1.13$$

Notice that  $R$  is a weak function of  $T$  for a metal (wire)

$$(Pt \approx + 0,3\% / ^\circ C)$$

and that  $R$  is a stronger function of  $T$  for a thermistor

$$(\text{typ.} \approx -3 \text{ to } -4\% / ^\circ C).$$

## 1.2 Constant Current Operation.

In this mode of operation  $I$  is maintained constant in equation 1.13. Let  $\Delta T_0$  be the temperature difference at zero flow and, assuming  $T$  fluid remains constant, then for a wire anemometer operated with small  $\Delta T_0$  this approximates to constant power ( $P_1$ ) since  $R$  changes only slightly for a change of  $\Delta T_0$ .

$$\text{Hence } P_1 = (A + BV^{\frac{1}{2}}) \Delta T \quad \text{and} \quad V^{\frac{1}{2}} = \frac{1}{B} \left( \frac{P_1}{\Delta T} - A \right) \quad \dots \dots \quad 1.21$$

Thus  $\Delta T$  varies inversely with velocity.

To measure flow velocity  $\Delta T$  is measured either by looking at the voltage across  $R$  or with a separate temperature sensor. Notice that equation 1.21 indicates that sensitivity decreases rapidly as velocity increases. Also, since the power injected is approximately

constant, if the velocity suddenly decreases, the time taken for the hot wire to reach the new equilibrium temperature is considerably longer than the equilibrium time for a similar increase in velocity. In electrical engineering terms the "slew rate" and settling time are not the same for an increase in flow as for a decrease in flow. This is a result of the fact that heat is injected at a constant rate to establish a particular temperature gradient in the fluid under a decrease in flow, while heat can be transported away rapidly under an increase in flow establishing the new temperature gradient almost immediately.

For a hot thermistor anemometer with a much larger (negative) temperature coefficient the situation is more complicated since the power injected changes substantially with  $\Delta T$ . This improves the sensitivity at higher velocities as the power injected increases somewhat with flow. In practice, since a large  $\Delta T$  cannot be used for physiological probes, the increase in power is not appreciable.

For example, assume  $\Delta T_{\max} = 5^{\circ} \text{C}$ .

Typically temperature coefficient of thermistor  $\approx 4\% / ^{\circ} \text{C}$ .

Then  $\Delta R_{\max} \approx 20\%$ . Hence maximum power increase  $\approx 20\%$ .

A practical problem of constant current operation is possible probe burnout on removal from a high thermal conductivity fluid (the injected power must be quite high for reasonable sensitivity in the fluid).

### 1.3 Operation at Constant-Temperature Difference.

By using suitable circuitry which adjusts the power injected ( $P$ ) the temperature difference ( $\Delta T$ ) (equation 1.11) can be maintained constant.

$$\text{Under this condition } V = \left( \frac{P - A \Delta T}{B \Delta T} \right)^2 \dots\dots \dots 1.31$$

This equation is readily solveable by a simple hard wired analogue computer (fig.1) and is the principle behind most linearisers<sup>6,7</sup>. Since  $\Delta T$  is maintained constant by adjusting the power injected, the settling time for a decrease in flow is considerably faster than it is for constant current operation. Under this condition the probe's frequency response is also improved. For measuring pulsatile flow a wide frequency response is essential. If the frequency response is inadequate, then the probe effectively averages the pulsatile non-linear velocity signal prior to linearization. This makes meaningful linearization impossible. In particular for measuring pulsatile blood flow in some of the major arteries a wide frequency response is essential<sup>9</sup>.

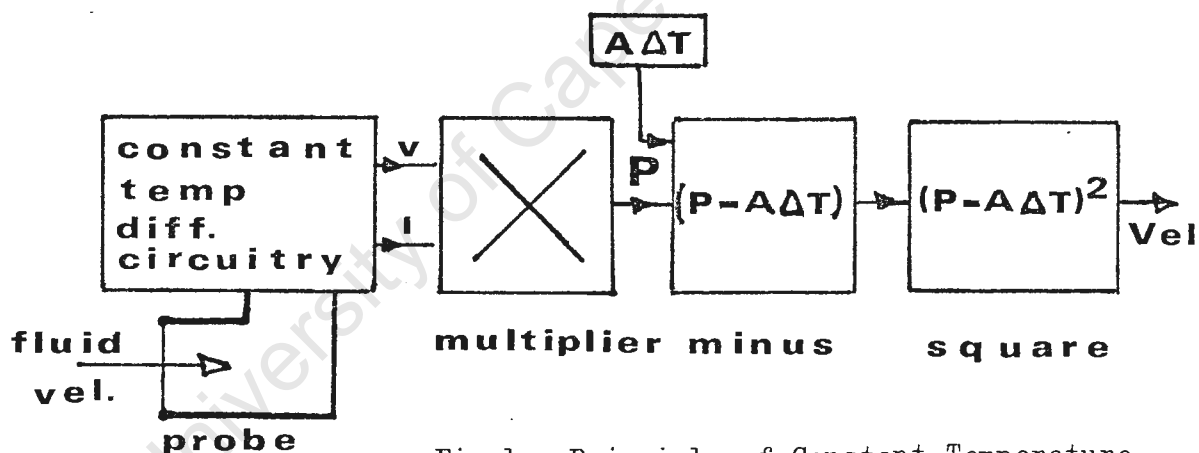


Fig.1. Principle of Constant-Temperature-Difference Linearizer.

Section 1  
Summary

Constant current systems suffer from long settling times, poor frequency response, possible probe burnout and large temperature differences at slow flows. The output is non-linear and difficult to curve fit. Constant-temperature-difference operation yields faster response, faster settling, probe burnout not possible and curve fitting is generally easier. However circuitry is more complicated than with constant current systems. Both systems require compensation for changes in fluid temperature. This is usually accomplished using a separate temperature sensor.

SECTION 22. Thermal Methods for Blood Flow Measurement in Large Vessels.

2.1 The thermostromuhr method for measuring blood flow, first described by Rein in 1928<sup>11,12</sup>, was used extensively for some years, with some modifications<sup>13,14</sup>, until it was totally discredited by a number of critical papers<sup>15,16,17</sup> which showed that gross errors were routinely possible and results could be ambiguous. In this method a high frequency current is passed through electrodes placed on opposite sides of a vessel to heat the blood flowing past. The increase in temperature of the fluid on the downstream side of the electrodes is measured, being some inverse function of flow. Although this method is only of historical interest now, one of the sources of error was due to heat transport by local perfusion. That is local perfusion in tissues surrounding the vessel as well as blood flow in the vessel was being measured!<sup>15</sup>

The modified thermostromuhr method<sup>13,14</sup> is similar to a constant current hot wire anemometer with the hot wire placed externally round the vessel instead of being placed in the blood stream. This introduces a large number of additional sources of error<sup>15</sup>.

2.2 Most flow-measuring systems measure velocity and volume flow rate is then obtained by multiplying by the cross-sectional area of the vessel. Thermal dilution techniques<sup>18,19,20</sup> measure volume flow rate directly. A thermal indicator (usually saline) is introduced into the bloodstream at high velocity to promote complete mixing. The temperature of the blood  $T_b$ , the indicator  $T_i$  and the mixture  $T_m$  must be measured. The volume flow rate of the

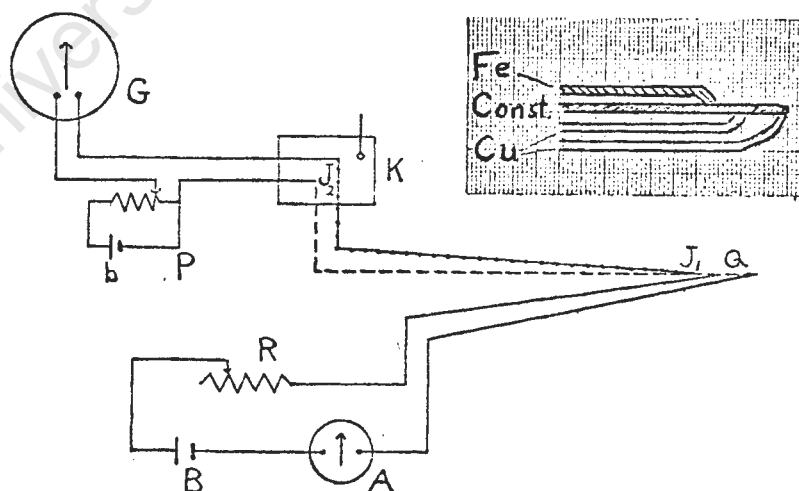
blood  $\dot{Q}_b$  can then be calculated using the equation :

$$\dot{Q}_b = K \dot{Q}_i \frac{(T_m - T_i)}{(T_b - T_m)}$$

where  $\dot{Q}_i$  = volume flow rate of indicator.  
The constant K depends on specific heat and density of both blood and indicator and hence this varies slightly with haematocrit.

The calculation is usually performed using a hard wired analogue computer giving a direct readout<sup>20</sup>. The disadvantage of thermal dilution techniques is that they are single point and cannot be used for continuous measurements.

2.3 A number of papers describing what effectively are constant current hot "wire" anemometers for blood velocity measurement have appeared over the years<sup>21, 22, 23, 24, 25, 26</sup>. In 1933 Gibbs<sup>25</sup> described the first anemometer-type probe which he used for measuring both flow velocity in large vessels and local perfusion in tissue. (See Section 3.) This probe consisted of a constantan wire heater and thermocouple temperature sensor. (See fig. 2.31.)



Wiring diagram of needle blood flow recorder.

Solid line, copper wire; dotted line, iron wire; broken line, constantan wire.  $J_1$  and  $J_2$ , thermojunctions; K, constant temperature box; P, potentiometer with b, source of known E. M. F.; G, galvanometer; Q, length of constantan used as heating element; A, milliammeter; B, battery; R, variable resistance. Insert shows large scale drawing of needle tip.

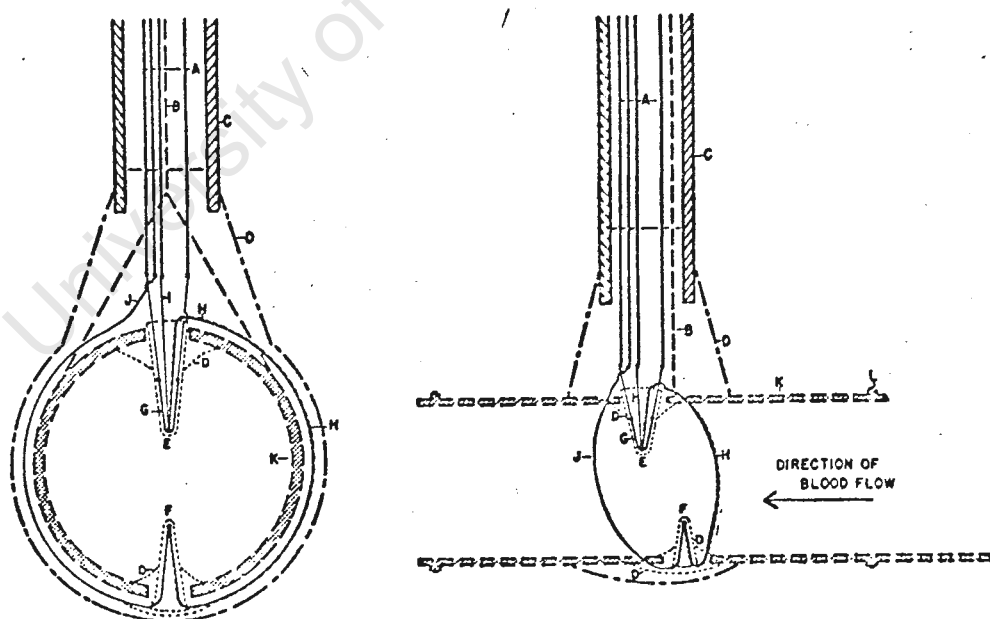
Fig.No. 2.31.

Gibbs alternately measured flow and blood temperature by switching the constantan heater on and off. He could thus test whether flow artifacts were being introduced by slow variations in blood temperature. He also suggested that by placing the reference (cold) thermocouple junction in the same vessel more rapid temperature changes could be automatically compensated for.

In 1944 Bennet and co-workers<sup>21</sup> at Harvard University published an excellent paper on a cannulated constant current hot wire flowmeter. (Fig. No.2.32.) The cannula they used reduces errors due to changes in the caliber of the vessel which Gibbs<sup>25</sup> had mentioned as a possible source of error when probes are calibrated in terms of volume flow instead of velocity. More important, however, it maintained the probes at a fixed position near the centre of the vessel so that the slower blood velocity at the vessel wall was not measured. The major contribution of this paper was not the carefully developed hardware but rather the discussion of most sources of error inherent in thermal methods of determining blood flow, a number of which had not been appreciated by previous workers and some of which do not seem to have been appreciated by subsequent workers. The most important criticisms were :

- (a) "Thermal methods cannot be relied upon to record rapid phasic changes in fluids involving phases of very slow flow or of complete stoppage. The thermal lag of fluid surrounding the heated element is such that several seconds may be required for equilibrium to be attained after flow stops."
- (b) "Uneven temperature in various portions of a given blood stream in a vessel may be present" (especially near the junction of two vessels) "to a degree sufficient to cause temperature changes in the heated element, falsely representing flow changes of considerable magnitude."

- (c) "The temperature of the heated element does not bear a linear relationship to flow. Hence, when pulsatile flow changes are present, an integration of voltage or resistance changes by a recording system will not represent a true mean flow."  
(Although not directly stated here by the authors, this also applies to integration inherent in a slow probe response time i.e. poor frequency response.)
- (d) "Fluid moving in either direction cools a heated element equally well, and, hence, phasic back flow will record as forward flow." (This is true but errors tend to cancel at very slow flows as warmed fluid is carried back to probe reducing cooling effect of back flow.)



## LEGEND

A- COPPER LEAD WIRES	E- HOT JUNCTION	I- HOT CHROMEL OR COPPER
B- STAY WIRE	F- COLD JUNCTION	J- COLD CHROMEL OR COPPER
C- PLASTIC TUBING	G- NICHROME HEATER	K- METAL OR PLASTIC CANNULA
D- PLASTIC SEAL	H- CONSTANTAN WIRE	L- BEADS

DIAGRAMMATIC CROSS SECTION AND LONGITUDINAL SECTION OF FLOWMETER CANNULA WITH THERMOCOUPLE TIPS MOUNTED IN POSITION

Fig. No.2.32.

The authors concluded that, even though their equipment was more accurate (accuracy  $\pm 10\%$  in model experiments) than that of previous workers :

"these limitations, when combined with the great difficulty encountered in attempting to free completely the heated element from varying environmental factors, appear to be sufficient to render unlikely the development of a very satisfactory blood flow recording system utilizing the thermal principle."

The above criticisms, although valid, have been overcome or reduced by more modern instrumentation and constant-temperature-difference operation as discussed in section 2.4.

Delaunois<sup>22, 23</sup> has described a number of constant-current probes using two thermistors connected in a bridge circuit for temperature compensation and sensing. His most recent paper (1973) describes a catheterised probe with modern instrumentation to simplify operation. The heater is constantan wire attached to a small silver tube which is partially exposed to the blood. (Fig. No. 2.33.)

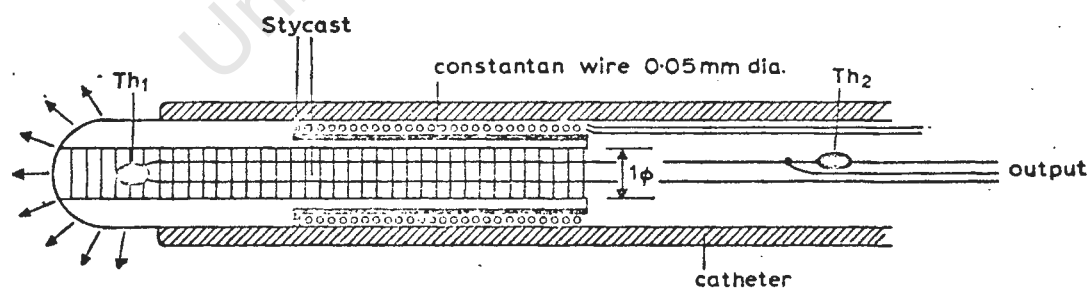


Fig.No. 2.33.

*Construction of flowmeter, showing catheter and thermistors. The arrows show heat loss by convection from the silver tube*

Sources of error, however, are the same as listed by Bennet et al above. In fact, the probe probably has a longer settling time due to the additional thermal capacity of the silver. The injected power at almost  $\frac{1}{4}$  watt also seems excessive (cf. Bennet 20 mW.)

and could cause high probe temperatures at slow flows. Considering these factors this probe seems suitable only for determination of non-pulsatile high velocities.

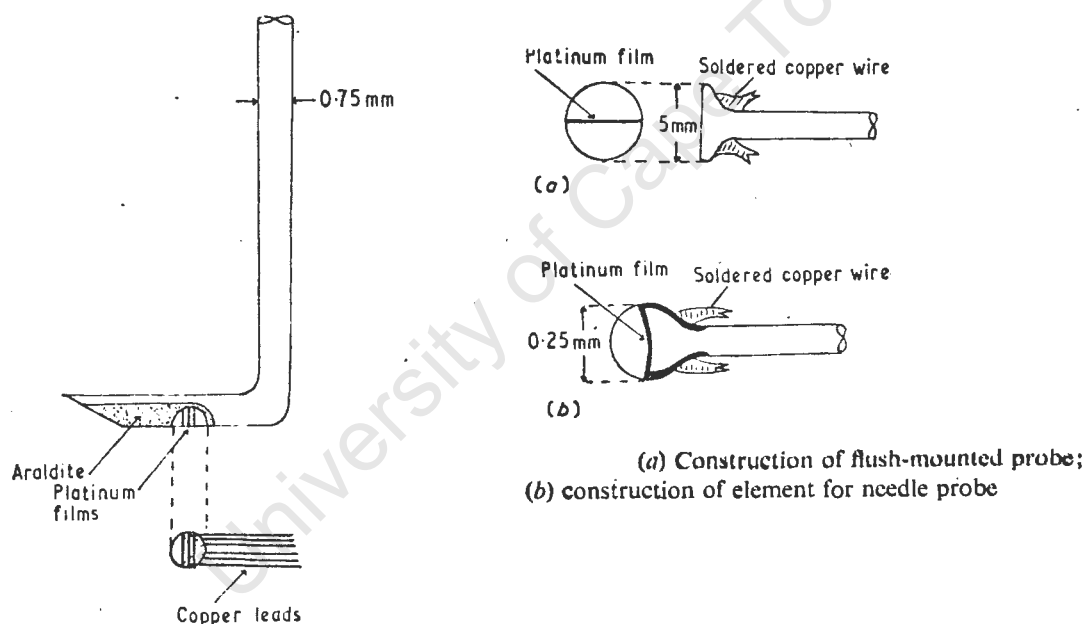
Juhasz<sup>24</sup> designed a hypodermic probe containing two thermistors. In this design the thermistors are connected in a bridge configuration so that self heating of both thermistors occurs. (This is also similar to early work of Delaunois.) One thermistor exposed to flow is cooled by forced convection, while the second thermistor inside the probe is designed to compensate the bridge for slow temperature variations of the blood. The design requirements of not sensing flow by having a large thermal resistance from the second thermistor to the blood and yet sensing temperature changes rapidly seem incompatible. Juhasz claimed only qualitative results for his probe, partly because of the long time constant of his flow sensor. Simple circuitry could operate the two thermistors at different power levels making the design compromise for the temperature sensor unnecessary. However, the problems associated with constant-current operation would still remain.

#### 2.4 Constant-Temperature-Difference Blood Velocity Meters.

Thermal blood flowmeters operating at a constant temperature difference (sometimes called isothermal flowmeters) date from the late nineteen fifties at a time when discrete operational amplifiers were starting to be widely used. Mellander and Rushmer<sup>27</sup> in 1959 described such a flowmeter using a catheterised probe containing a compensated thermistor temperature sensor and constantan wire heater. The voltage supplied to the heater was controlled by feedback from the temperature sensor and power delivered to the heater was measured by squaring the voltage. Accuracy in model experiments was 5% for a decade range of flow rates. Over this range the output was linearly proportional to flow. This is a surprising result since one would expect

King's law to be at least approximately obeyed. One possible explanation is probe construction. With a separate temperature sensor and heater it might be possible that with increased flow a temperature gradient would be established from heater to sensor. Under these conditions the temperature difference from heater to blood established by the feedback would increase with flow tending to linearize the response. This linearization would be critically dependent on mechanical construction of the probe.

Bellhouse and Bellhouse<sup>28</sup> in 1968 described the construction of thin film platinum probes for blood velocity measurement. (Fig. 2.41)



Thin film velocity probe in hypodermic needle  
of 0.75 mm outside diameter

Fig. 2.41.

Since this is a thin film probe it offers a wide frequency response although sensitivity is an order of magnitude lower than that of a thermistor probe. The authors used general purpose Disa(R)<sup>x</sup> anemometry equipment for constant temperature operation and

<sup>x</sup> Disa Elektronika A/S, DK2740 Skovlunde, Denmark.

linearization (King's Law). No temperature compensation was employed to maintain constant temperature difference so large errors could be expected from blood temperature variations. This probe should be capable of high performance with suitable instrumentation.

Grahn et al in 1968<sup>29</sup> described a catheter tip constant-temperature-difference flowmeter using thermistors. This design used a self-balancing bridge in which the thermistor acts as both temperature sensor and heater. With this mode of operation a bandwidth of greater than 100 Hz was achieved. (This is better than most electromagnetic flowmeters which usually have a limited bandwidth to reduce spurious e.m.g., e.c.g. and noise signals!) The empirically obtained non-linear law was found to be of the form:

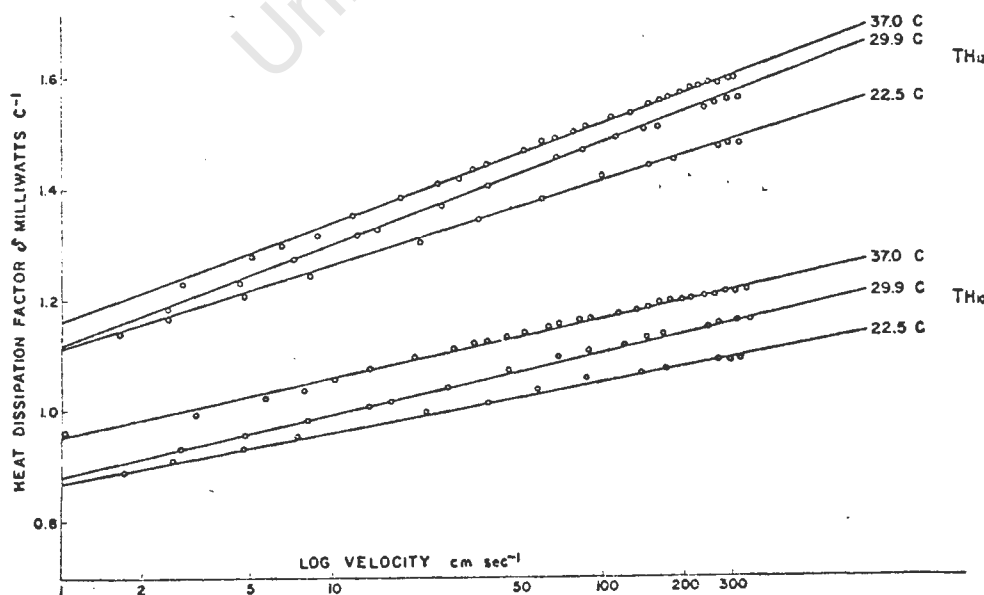
$$P = (E + F \log V) \Delta T \quad \dots \quad 2.41$$

E, F constants

V blood velocity

P power supplied to heater  
(the thermistor)

$\Delta T$  temperature difference  
blood to heater (maintained constant)



Dissipation Factor :  

$$\delta = \frac{P}{\Delta T}$$
 plotted against log velocity for two different thermistors at three different fluid temperatures. Notice dissipation factor is a weak function of temperature.

Fig.No.2.42.

Power was measured using a multiplier with the output using anti-log circuitry. (Fig. No.2.43.)

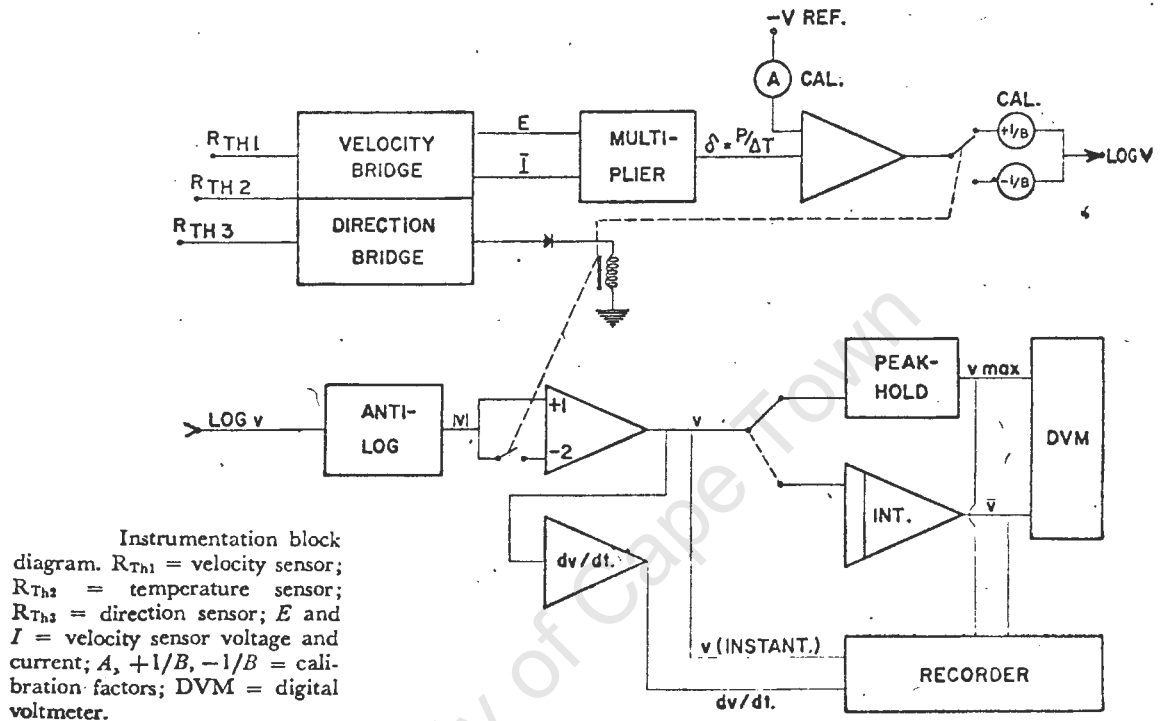


Fig. No.2.43.

The problem of forward and reverse flow both yielding a positive output was overcome by sensing flow direction with an additional thermistor to sense heat transported from the heated thermistor (fig.2.44) The direction signal was used to switch the gain of an amplifier (connected to the linearized velocity signal) between plus or minus one, thus restoring the directional information. (Fig.2.43.)

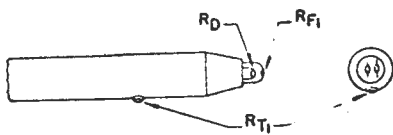


Fig.No.2.44.

Velocity probe used in direction sensing. Heat flow from velocity sensor  $R_{F1}$  detected by direction sensor  $R_D$ . Temperature compensating thermistor  $R_{T1}$ .

The same authors in 1969<sup>30</sup> refined their flow measuring system by using two flow sensing bridge circuits with the probe physically arranged (Fig. No.2.45) so that only one sensor measured forward flow while the second sensor measured only reverse flow. The two signals were then linearised as before and the results subtracted to give an output including directional information.

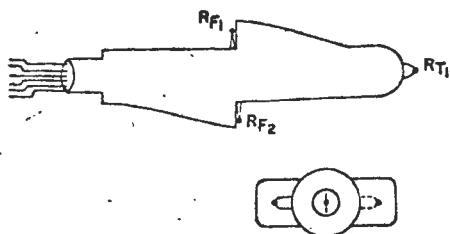


Fig.2.45.

Mounting of velocity sensors  $R_{F1}$  and  $R_{F2}$  provides shielding from flow in one direction for each velocity sensor. With upstream insertion of catheter  $R_{F1}$  is shielded from forward flow. Temperature compensating thermistor  $R_{T1}$  is mounted at tip.

## Section 2

Summary. Blood flow measurements using thermal methods have been refined over the years until results now compare quite favourably with electromagnetic flowmeters, particularly as far as frequency response is concerned. This may be useful for "beat by beat" analysis of pulsatile flow, especially as the catheter is pushed closer to the heart. Almost all the problems encountered by early workers have been eliminated in recent designs. This is the result of :

- (a) constant-temperature-difference operation which offers the same improvements as in conventional anemometry;
- (b) careful probe design;
- (c) instrumentation to permit linearization;
- (d) using a single self-heated thermistor as flow sensor.

The equipment designed by Grahn et al<sup>29,30</sup> probably offers the highest performance of any equipment to date.

### 3. Perfusion Flow Measurement using Thermal Methods.

In this section previous work on perfusion flow measurement using transient and steady state thermal methods is discussed. General problems of thermal methods of perfusion flow measurement are also discussed.

#### 3.1 The Difference between Normal Velocity Measurement and Perfusion Measurement.

In section 2 blood velocity measurement was discussed in the light of conventional hot "wire" anemometry. Blood volume flow rate can be calculated from the velocity if the cross-sectional area of the vessel can be measured (e.g. ultrasonically, X-rays). Velocity is actually measured at a single point and for the volume flow calculation to be correct the velocity profile across the vessel is assumed to be blunt<sup>31</sup>. The thermal ("hot wire") probe strictly measures "apparent" thermal conductivity, not velocity. However, under forced convection (flow) the rate of local heat clearance changes with velocity increasing the apparent thermal conductivity. In a similar manner local perfusion measurement using heated probes measures the apparent local thermal conductivity of the tissue-bed through which fluid is perfusing. The perfusion probe heats a small volume of tissue containing a matrix of vessels. Fluid perfusing through the vessels increases the rate of heat clearance from the matrix and hence from the probe. The temperature gradient in the immediate vicinity of the probe will thus also change with flow. Notice that the measurement takes place within a volume of tissue and the radiation resistance from the heat source to the fluid depends on the physical properties and construction of the matrix within this volume. Notice also that the thermal capacity of the tissue in the sphere of influence of the probe increases the time taken to establish a new temperature gradient when a change in flow occurs. This aggravates the problem of slow settling time mentioned previously. (Section 2.)

The units of local perfusion flow are conventionally quoted in the literature as millilitres per 100 grams of tissue per minute (ml/100g/min) or cubic centimetres per hundred cubic centimetres of tissue per minute (cc/100cc/min). These quantities are somewhat

ill-defined when one considers that under flow conditions the volume of the tissue-bed will change depending on blood pressure, degree of local vasodilation or whether blood is being stored in, or discharged from, the organ.<sup>x</sup> If the tissue volume is measured when the tissue has been well drained of fluid, then the volume will depend on the rigidity of the tissue matrix. The measurement of "well-drained" mass would appear the most repeatable measurement.

### 3.2 Problems of Perfusion Flow Measurement.

Bill<sup>3</sup> in 1962 performed a number of model experiments to show under what conditions thermal methods of perfusion flow measurement could be expected to give reliable results. In these experiments Bill investigated the flow through polyethylene tubes embedded in blocks of gelatine. His perfusion probe was a constant-current thermocouple system similar to that of Gibbs<sup>25</sup>.

From Bill's first experiment summarised in fig.3.21 it can be seen that probe sensitivity is reduced with increasing vessel wall thickness and that at faster flow rates the change in apparent thermal conductivity ( $\Delta K$ ) approaches a constant value. Bill defined the flow rate  $F_{50}$  as that flow rate (for a particular diameter tube) at which the thermal conductivity increment ( $\Delta K$ ) was 50% of its maximum value. This enabled him to define an "arbitrary acceptable flow range" for a particular diameter tube - that is the flow range from 0 to twice  $F_{50}$  over which changes of flow give reasonable changes in  $\Delta K$  compared to the maximum change in  $\Delta K$ . It should also be pointed out that over this arbitrary acceptable flow range  $\Delta K$  varies approximately linearly with flow.

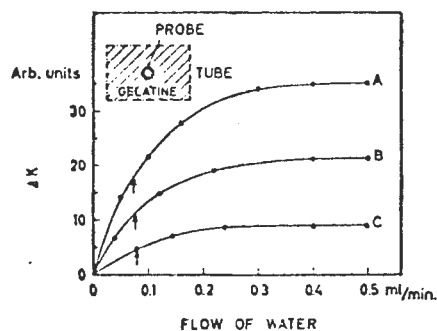


Fig. 3.21

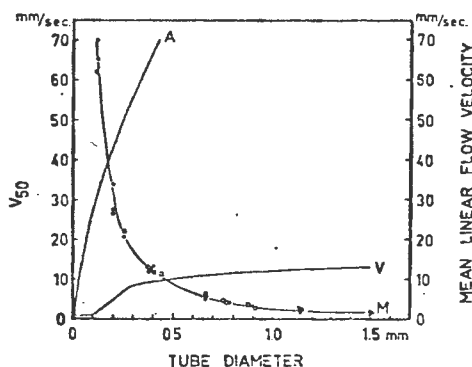
The relationship between  $\Delta K$  and flow of water. The model used is shown inset in the figure. The probe was placed close to and in parallel with the polyethylene tube, which had an inner diameter of 0.36 mm, wall thickness 0.20 mm. Curve A was obtained when there was no extra layer of polyethylene added to the tube, curve B when one extra layer, thickness 0.20 mm, had been added to the tube wall, and C when two extra layers had been added. Arrows at value  $F_{50}$ .

x(For example it has been suggested by Herrick et al<sup>34</sup> that periodic filling and "emptying" of the liver occurs. Unfortunately their paper is based on measurements made using the not very reliable thermostromuhr!)

For convenience Bill then defined the fluid velocity  $V_{50}$  corresponding to  $F_{50}$  for a particular diameter tube.

$$V_{50} = \frac{F_{50}}{\pi r^2} \quad (r = \text{radius of tube})$$

Curve M on fig. 3.22 shows  $V_{50}$  varies inversely with tube diameter.



The relationship between  $V_{50}$  and the inner diameter of the tube in the model experiments. Solid circles represent values obtained with flow of water through polyethylene tubes embedded in 20 % gelatin. Curve M connects these values. Solid squares represent values obtained with flow of water through tubes in 10 or 30 % gelatin, open circles values obtained with flow of blood in polyethylene tubes embedded in 20% gelatin, open squares values obtained with flow of water through channels in 20 % gelatin. Approximate values for the mean linear flow velocities in tissue vessels are plotted against the corresponding diameters. Curve A gives the values for the arterial side, curve V those for the venous side.

Fig.No.3.22

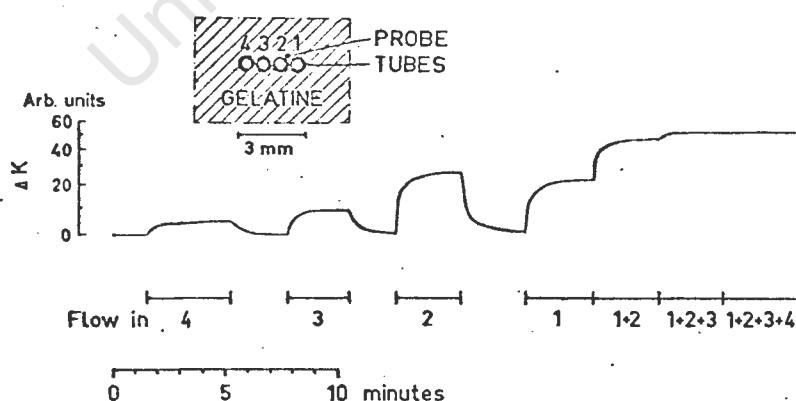
On the same graph are approximate values of arterial and venous mean blood velocities for the corresponding tube diameters<sup>32</sup>.

From the graph it can be seen that a much wider range of flow velocities falls within the arbitrary acceptable range of flows for very fine tubes. Also, if the blood velocity exceeds mean values by at most 100 %, the maximum-sized arterial side vessel diameter for which the probe is suitable is  $\approx 0,18 \text{ mm } \emptyset \text{ max.}$  and for the venous side  $\approx 0,5 \text{ mm } \emptyset \text{ max.}$  If the average flow velocities are rarely exceeded the limits should then be 0,23 mm max. for arteries and 0,65 mm max. for veins. The thermal conductivity of polyethylene is in the same range as that of human tissues (see fig.3.23) and from fig.3.21  $V_{50}$  is essentially constant independent of the tube wall thickness. Hence these experiments should represent fairly accurately conditions in human tissue. One possible difference in tissue would be changes in vessel diameter as flow or other conditions vary.

Substance	Temp. °C	Thermal conductivity $\times 10^{-4} \cdot \text{cal} \cdot \text{cm}^{-1} \cdot \text{sec}^{-1} \cdot \text{C}^{-1}$	Source
10% gelatin .....	37	12.2	GRAYSON (1952)
20% gelatin .....	37	11.5	GRAYSON (1952)
30% gelatin .....	37	11.0	GRAYSON (1952)
Polyethylene .....	—	8.0-11.0	FRITZ (1957)
Water .....	20	14.2	HODGEMAN (1958)
Liver, rat .....	37	11.8	GRAYSON (1952)
Liver, dog .....	37	11.9-12.0	GRAF et al. (1957)
Kidney, rabbit .....	37	12.0	GRAYSON (1952)
Muscle, human .....	about 32	11.7	HENSEL et al. (1954)
Blood, human .....	36.8-39.4	12.1	SPELLS (1960)
Steel .....	18	115.0	HODGEMAN (1958)
Ethyl alcohol.....	20	4.0	HODGEMAN (1958)

Fig. 3.23.

Bill's other experiments (figs. 3.24 and 3.25) show that fluid flowing through vessels in the immediate vicinity of the probe almost totally screens the effects of fluid flowing in other vessels. On the other hand the effect of vessels not screened is approximately the sum of the effects of the vessels acting separately. (Fig. No. 3.26.) As would be expected when screening does not exist vessels more distant from the probe have less effect. (Fig. 3.24.)



The influence of flow through distant tubes on the probe, when there is not, respectively is, flow through tubes placed in between the distant tubes and the probe. The model used is shown inset in the figure. The probe was sited close to one of 4 parallel tubes placed deep in gelatin. Inner diameter of the tubes 0.36 mm, wall thickness 0.20 mm. The flow rate in each tube was zero or 0.4 ml per minute.

Fig. No. 3.24.

The relationship between the  $\Delta K$  and the flow when the probe was influenced by flow through two tubes. The model used is shown inset in the figure. The probe was placed close to one of two polyethylene tubes, inner diameters 0.36 mm, wall thickness 0.20 mm, placed in parallel. Curve A was obtained when there was flow only through tube 1, curve B when there was flow only through tube 2. (The tube without flow was filled with water.) Curve C was obtained when there was the same flow through both the tubes. The abscissa gives the flow through each tube. Arrows at value  $F_{50}$ .

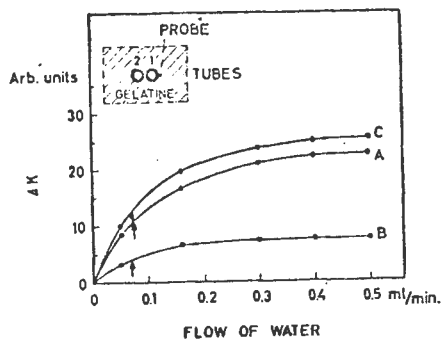


Fig. No.3.25.

The relationship between  $\Delta K$  and the flow when the probe was influenced by the flow in two tubes. The model used is shown inset in the figure. The probe was placed close to one of two polyethylene tubes, inner diameter 0.36 mm, wall thickness 0.20 mm, the other being sited at some distance from the probe, but not screened by the closest tube. Curve A was obtained with flow only through tube 1, curve B with flow only through tube 2 and curve C with flow through the two tubes at the same time. The abscissa gives the flow through each tube. When there was flow only through one tube the other was filled with water. Arrows at value  $F_{50}$ .

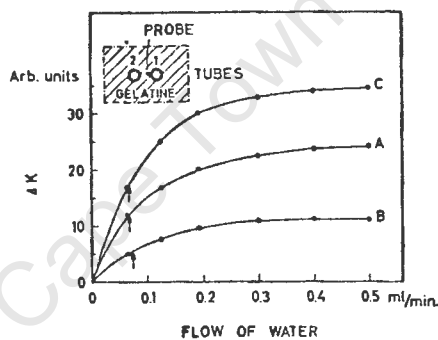


Fig. No.3.26.

Bill's experiments show that the ideal conditions for placing a heated perfusion probe exist in homogenous tissue containing a large number of very fine vessels. The worst conditions exist where the probe is placed near a single large diameter vessel. Under this condition even qualitative results will be poor since  $V_{50}$  will probably be exceeded and large changes in flow will give only a small change in output. Under this condition sources of error may give larger changes in output than the measured quantity. For this reason curve fitting is not practical and the only useful output occurs if flow in the tube almost completely ceases!

Bill also showed that the screening effect of the tubes nearest the probe was such that the effective sphere of influence with flow through these tubes was of the order 1.5 mm. While Grayson<sup>33</sup> showed that under zero flow conditions the sphere of influence was about 4 to 5 mm. It was pointed out earlier that

tissue beds may vary in fluid content at different times. This may result in variations in thermal conductivity which bear no relation to flow. This becomes a serious problem if the fluid has a very different thermal conductivity from that of the tissue. Fortunately blood has a thermal conductivity very much the same as that of a number of different types of tissue. Tissue containing a high fat content, however, has an appreciably lower conductivity.

Human blood	$11.4 \times 10^{-4}$	cal/cm / sec/°C	(Graf et al) <sup>4</sup>
Human fat	$4.77 \times 10^{-4}$	-do-	(Spells)

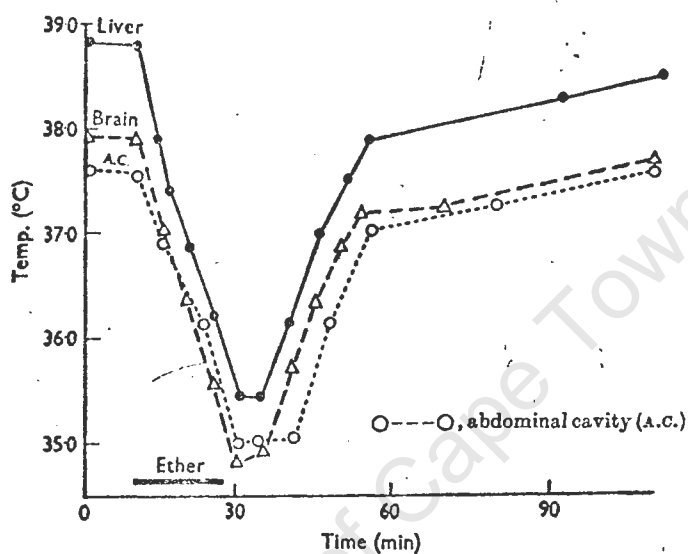
See also fig. 3.23.

Notice that a probe placed in tissue containing an appreciable amount of fat may give erratic results due to variable amounts of fat from site to site.

Another source of thermal conductivity variation which is not related to flow is the variation of thermal conductivity of blood and tissue with temperature. This variation for blood only can be seen from the changes of dissipation factor at different temperatures shown in the graphs of fig. 2.42. Notice that this complicates complete temperature compensation unless the working temperature range is restricted, a factor which does not seem to have been generally appreciated.

Errors induced by temperature variations are probably amongst the worst kind in thermal flow-measuring systems because they are likely to introduce the errors when changes in flow occur making these errors more difficult to detect or guard against. Apart from the thermal conductivity variation already mentioned (which is a second-order effect for a small temperature range) errors arise from steady-state temperature gradients and transient temperature gradients. Transient temperature gradients are likely to occur under changes in flow since the blood's cooling effect<sup>38</sup> on local metabolic heat sources changes with flow. This applies particularly to major sources of heat in the body such as the liver

and the brain. Birnie and Grayson<sup>37</sup>, in experiments on rats, showed that not only do changes of flow occur in these organs following the administration of pharmacological preparations but also rapid temperature changes which are probably the result of changes of local metabolic heat production. (Fig.No.3.27.)



The effect of ether on temperature distribution in the rat.

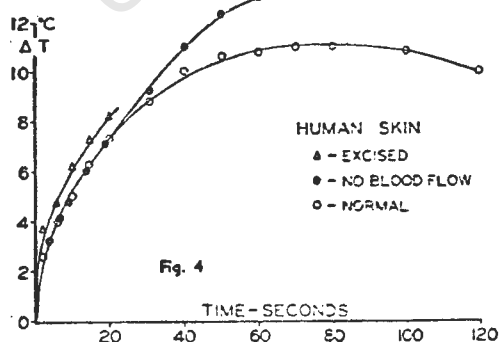
Fig.No.3.27.

Temperature gradient problems are particularly serious in the brain according to Newell and Powers who report<sup>38</sup> spatial gradients in cat brains in excess of  $0,1^{\circ}\text{C}/\text{mm}$  over a 5 mm range and transient temperature changes of up to  $0,2^{\circ}\text{C}/\text{min}$  after the injection of epinephrine.<sup>x</sup> Errors due to temperature gradient effects result from the fact that in both constant-current and constant-temperature-difference probes the difference between heated probe temperature and "ambient" tissue temperature must be sensed normally requiring two spatially separated sensors which are then prone to temperature gradient errors. (Ways of overcoming this problem and detecting artifacts are discussed in later sections of this thesis.)

x This disagrees with the work of Schmidt and Pierson<sup>39</sup> who claimed that only flow changes occurred in the medulla of cats after administration of chemical agents or after changes in chemical composition of the blood. However they performed only very limited temperature tests.

One source of possible error using heated probes that has not been thoroughly investigated is the possibility that the elevated temperature in the immediate vicinity of the probe may itself change the flow rate. Stow and Schieve<sup>40</sup> in measurements of blood flow in human skin measured the mean temperature coefficient of flow as  $+ 39 \%/^{\circ} \text{C}$ . However, the range was  $- 57\%$  to  $+ 81\%/^{\circ} \text{C}$ . Lipkin and Hardy<sup>41</sup> using an infra red source and a radiometer measured the inertia for surface heating ( $K\rho C$ ) of a number of human tissues including in vivo tests on human skin. ( $K$  - thermal conductivity.  $\rho$  - density.  $C$  - thermal capacity.)

From fig. 3.28 it can be seen the thermal conductivity increases slowly with temperature as the skin heats up until eventually skin temperature actually drops slightly. These authors suggested that the large increase in  $K\rho C$  with temperature was a result of the local passive dilation of the peripheral vessels in the skin area being heated.<sup>x</sup> Whether the same phenomenon occurs for other types of tissue for the very much smaller quantities of heat injected by heated perfusion probes does not seem to have been thoroughly investigated, although some data which show the effect is negligible in dog livers and human muscle are presented later.



Increase in surface temperature of excised human skin, living human skin with blood flow occluded and normal human skin irradiated with  $0.055 \text{ cal/sec/cm}^2$ .

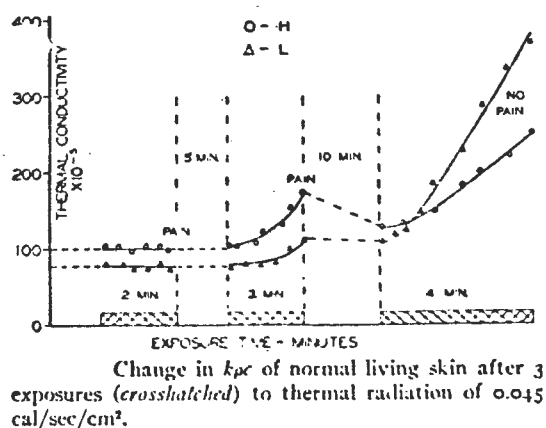


Fig. 3.28.

x (although this could also be due to perspiration.)

One possible source of error which is difficult to assess is that arising from local trauma after probe insertion which could change the flow pattern near the probe. This applies particularly to chronic implantation. Some of Grayson's experiments on rats gave results which seemed consistent over a period of some days. (Fig.3.29.)

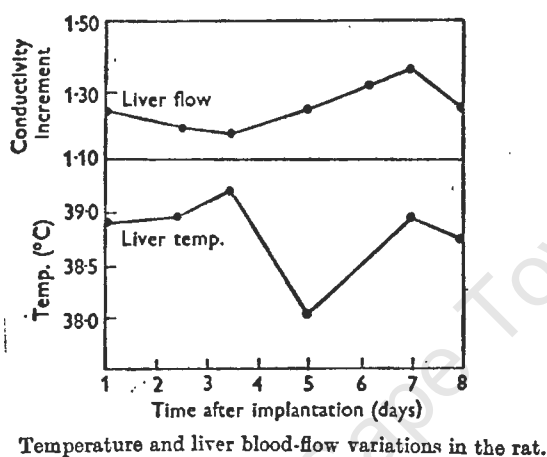


Fig.3.29.

3.3 Previous Work on Perfusion Flow Measurement can be conveniently divided up into three sections: constant current, constant-temperature difference (these are "steady state" methods) and transient methods. It is interesting to point out at this stage that an exact current flow - heat flow analogy can be used to predict temperature distribution in the vicinity of a heated probe. This is useful to the electrical engineer as the problems become more familiar and, more important, by using an approximate lumped-parameter equivalent circuit problems can be solved using simple network analysis. Bill's results quoted above, for example, could have been obtained qualitatively very simply using this analogy. Electrical engineers commonly use this heat flow - current flow lumped-parameter analysis for designing heat sinking<sup>42</sup>.

Steady state methods measure either the final temperature of a heated probe under conditions of constant-power injection

or the power required to maintain a constant-temperature difference (probe to tissue) once a stationary temperature distribution around the probe has been established. Transient methods, on the other hand, either measure the initial rate of heating of a probe under conditions of constant power injection or the rate of heating under flow conditions and with flow to the region stopped. The latter method involves a complicated calculation to compensate for local metabolic heat production - this is conveniently performed with a minicomputer.

The first perfusion probe was that described by Gibbs<sup>25</sup> in 1933. (See section 2.3.) This was a constant-current system<sup>x</sup> which he used for measuring both blood velocity and perfusion flow. Gibbs commented that "standardisation" (i.e. calibration) even if carried out for each experiment was not very reliable and suggested that the probe should be used only for qualitative assessment of flow.

Since Gibbs's work a number of workers have built constant-current systems. In 1959 Mowbray<sup>50</sup> described a hypodermic-mounted system virtually identical with that of Gibbs for which he claimed high linearity, results repeatable to better than 10 per cent and calibration in glass wool placed in water such that the thermal conductivity was the same as that of tissue at zero flow. Considering Gibbs's work and Bill's model experiments these claims seem very dubious and no other workers have been able to obtain similar results. See also Bill's comments<sup>3</sup> on Mowbray's work.

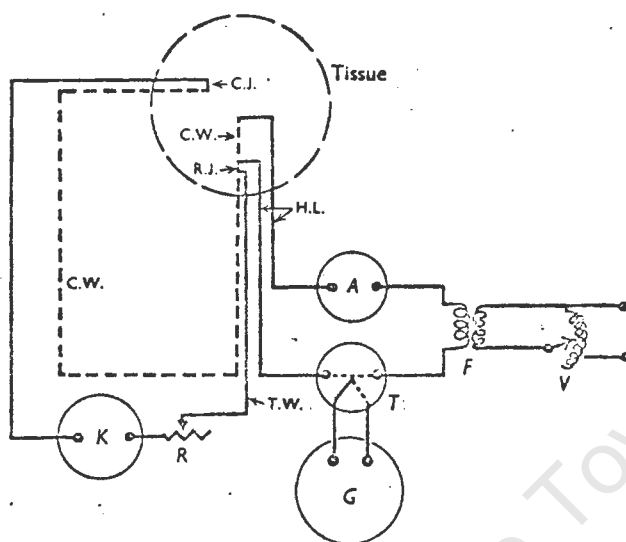
Juhasz<sup>24</sup>, Hancock<sup>43</sup> have described what are effectively constant-current bridge circuits using self-heated thermistors. (See previous comments on Juhasz's probe. Section 3.2) Hancock used two hypodermic probes, one flow sensor and one temperature-compensating sensor. However in vivo his equipment was awkward to use requiring frequent balancing. Hancock also

x (As pointed out earlier this approximates to constant-power injection.)

showed theoretically that for the flow conditions in vessels King's Law is correct. Other workers (Linzell<sup>35</sup>, Graf et al<sup>4</sup>) have shown experimentally that this law is only approximately correct, while Grahn et al<sup>30</sup> as mentioned earlier have shown experimentally that a logarithmic relationship fits the curve more accurately. A number of workers have used probes similar to that of Gibbs for measuring blood flow in bones. Shaw<sup>46</sup>, for example, used a Gibbs probe with a chopper-stabilised amplifier to measure the thermocouple voltage to obtain qualitative measurements.

An interesting variation of Gibbs's probe was described by Schmidt and Pierson<sup>39</sup>. They used a silver rod placed in a vacuum flask containing ice. The other end of the rod with a thermocouple attached was used to measure local perfusion flow in the brain. Perfusing blood warmed the probe instead of cooling it. The equilibrium temperature measured by the thermocouple depended on flowrate. Using a cooled probe enabled a larger temperature difference to be used ( $\Delta T \approx 10^\circ\text{C}$ ). Unfortunately the probe was rather unwieldy and the results obtained are suspect since no temperature correction was employed. (A careful comparison with the work of Grayson<sup>37</sup> seems to indicate that some of the results are definitely artifacts introduced by uncorrected temperature changes.)

The first constant-temperature-difference perfusion measurement system was that used by Grayson (1951) who called his method of measurement internal calorimetry<sup>33</sup>. Grayson used a heated thermocouple flow sensor with the temperature-compensating (cold) couple placed nearby in the same tissue. (Fig. No. 3.31.)



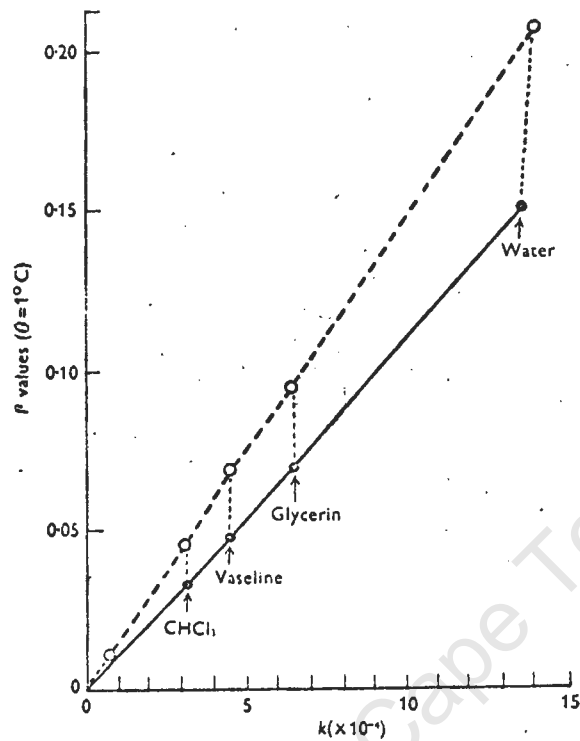
Internal calorimetry. General circuit. Interrupted lines, constantan wire; continuous lines, copper wire.

Fig. 3.31 illustrates the essentials of the apparatus. The recording instrument consists of a constantan wire (c.w.), with two fine gauge copper wires, the heater leads (H.L.), soldered to it, one at the tip and the other 2 mm below. A further copper wire, the thermocouple lead (T.W.), is soldered to it 0.5 mm further back. The constantan wire and the thermocouple lead together form the recording junction (R.J.). With the instrument embedded in animal tissue the galvanometer (K) calibrated by means of the resistance (R) records the tissue temperature in relation to the cold junction (C.J.), which may be inserted in a Dewar flask or alternatively embedded in a different part of the animal. Heating current may be supplied either from a source of d.c. such as a storage battery, or from the a.c. mains. In the present work the a.c. mains have been preferred. The mains voltage is stepped down first by means of a Variac autotransformer (V) which enables the output to be delicately and accurately varied from 0 to 240 V. The Variac output is fed through a fixed transformer (F), input 220 V, output 6 V. The adjustable head of the Variac thus enables a very fine control of output voltages over the range 0 to 6 V. An ammeter (A) records the current in the heating circuit.

The square of the current is also recorded directly, using a Cambridge Vacuo junction (T). This instrument consists of a thermojunction attached to a vacuum-mounted filament heated by the current to be measured. The current generated in the secondary thermoelectric circuit is thus linearly related to the square of the primary current.

By manually adjusting the current to the heater Grayson maintained a constant-temperature difference probe to tissue of  $1^{\circ}\text{C}$ . Under these conditions the power injected is directly related to the thermal conductivity of the tissue in which it is placed.

(See fig. No.3.32. Power  $\propto I^2$ )



The relation between  $I^2$  and thermal conductivity ( $k$ ). Interrupted line, needle recorder; continuous line, standard recorder as used for implantation.

Fig.3.32.

Grayson showed that over the range of flows measured in isolated perfused organs the apparent change in thermal conductivity with flow was linearly related to flow rate and did not vary appreciably from site to site in the same organ. From his experiments he suggested tentatively that by multiplying this thermal conductivity increment (in cal/cm/sec/°C) by 12.5 the flow rate in ml/ml tissue/sec could be obtained.

Unfortunately since Grayson's initial work subsequent investigators have shown that this linear relationship between flowrate and  $\Delta K$  is true only under certain conditions and for a limited range of flowrates depending on the tissue and probe placement.

Linzell<sup>35</sup> investigated Grayson's work and in model experiments in glass tubes showed that the conductivity increment was approximately proportional to flow only at low flow rates, King's Law being approximately true at moderate flow rates while at high flow rates no further change in conductivity occurred. The electrical insulation on the heater probably also acted as a thermal insulator at high flow rates causing this final reduction in sensitivity. Linzell was critical of Grayson's work and claimed that his own results showed a very much larger spread. In experiments on goat udder perfusions his results could not be used even qualitatively although he tried connecting a number of thermocouples in parallel to obtain an average for a number of sites. (This seems a very dubious method of summing thermocouple signals. It is also prone to gross errors from temperature gradients.) Linzell also claimed that d.c. heating introduced errors due to the Peltier effect at the heater's copper-constantan junctions and suggested that only a.c. heating should be used.

Hensel and co-workers<sup>4,44</sup> used Grayson's method of internal calorimetry but constructed their constant-temperature-difference probe in the form of a needle containing the heated thermocouple at the tip and the reference (cold) junction a short distance from the tip. (Fig. 3.33) Hensel produced far more repeatable results than those of Linzell but showed that a linear relationship between conductivity increment and flow occurred only under certain conditions of probe placement and suggested the probe was generally best suited for qualitative assessments of flow.

Schematisierter Längs- und Querschnitt durch die Sondenspitze.

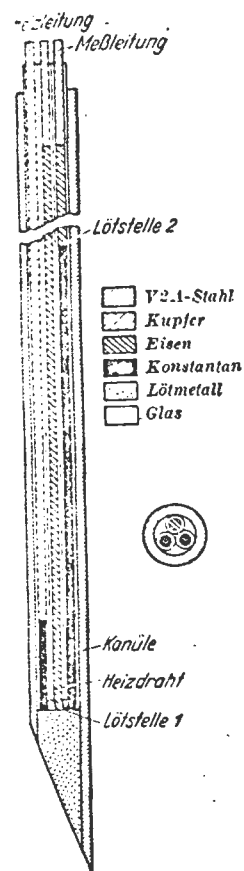


Fig. 3.33.

Recently Kopaniky and Gann (1971)<sup>45</sup> described initial work on a constant-temperature-difference probe using a heated thermistor. These authors used a probe consisting of two thermistors in close thermal contact mounted at the tip of a glass rod. One thermistor acted as temperature sensor while the other acted as heater. Feedback from the temperature sensor to the heater maintained the probe at constant temperature. A second unheated probe compensated for changes in local temperature, thus maintaining the probe at a constant 2.5°C above tissue temperature. It should be pointed out that glass is a poor probe material because of its large thermal capacity. This criticism applies to Hensel's probe as well. Initial tests using this probe showed a linear relation between flow rate and conductivity increment (power injected) in isolated thyroid glands.

Even more recently Newell and Powers (1974)<sup>38</sup> have reported testing a similar probe for measuring flow in cat brains with very variable results which they claimed were a result of large local temperature gradients. Using a separate heater and sensor in the flow probe has the disadvantage, compared to a single self-heated sensor, of an additional lag in the feedback loop as well as a doubling in thermal capacity of the sensor.

A detailed discussion of transient methods of perfusion flow measurement is beyond the scope of this review but results and methods are discussed heuristically here. In reading some of the literature on transient methods it should be borne in mind that a number of criticisms levelled at steady state methods apply only to constant-current probes similar to that of Gibbs. On the other hand transient methods overcome some problems of steady state methods but introduce new problems.

Linzell tried a semi-transient flow measuring method in his investigations of Grayson's work. He measured the temperature reached 30 seconds after switching on the heating current.

This approximates to measuring the rate of heating of the probe under conditions of constant-power injection.

Dolan and Lee<sup>49</sup> instrumentated essentially the same technique using a thermistor heated by a constant  $180 \times 10^{-6}$  joules in an 18 m.sec pulse every 144 m.sec. Feedback during the off period was used to measure probe resistance and hence maintain power injection constant during the on period. Voltage across the thermistor during the on period was differentiated to measure the rate of heating. Under an increase in flow the rate of heating decreases due to heat transport (i.e. apparent increase in thermal conductivity). It can be shown that because the slope of the resistance-temperature characteristic changes with temperature, this compensation is not perfect but is probably adequate for a limited temperature range. The big difference between this measurement and a steady-state one is that the sphere of influence of the probe is reduced to the tissue in immediate contact with the probe. This reduces the chance of errors due to large vessels in the vicinity of the probe. Temperature gradient errors are eliminated due to constant power injection. On the other hand local variations in tissue could give large errors due to the small volume sampled and the lower sensitivity. This applies particularly at faster flow rates.

Perl and Cucinell<sup>47</sup> proposed introducing a blood-flow change and measuring the transient change in rate of heating of the probe. In theory this also reduces the sphere of influence of the probe since after the blood supply has been occluded temperature, and thus temperature gradient, cannot change instantaneously in the vicinity of the probe. From this the relative rate of change of temperature prior to occlusion and post occlusion gives a measure of local perfusion very close to the probe. Perl suggested the probe could give an absolute measurement of perfusion flow (F) according to the equation -

$$F = K(\dot{U}_2 - \dot{U}_1)/U$$

$$K = (\text{density} \times \text{specific heat of tissue}) / (\text{density} \times \text{specific heat of blood})$$

$U$  = temperature increment

$\dot{U}_1$  = time derivative of  $U$  prior to occlusion

$\dot{U}_2$  = time derivative of  $U$  post occlusion

Stow and Schieve<sup>40</sup> suggested a similar method involving two occlusions, one with and one without the heater of the probe connected. (Fig.3.34.)

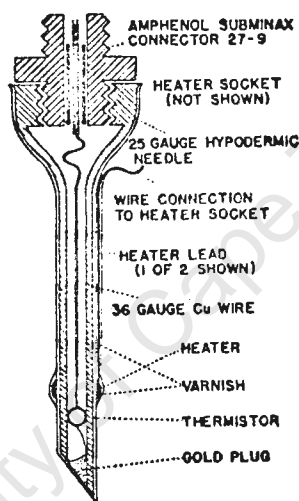


Fig.3.34.

These authors proposed an alternative version of the equation of Perl et al above which would give an absolute measurement of flow. Unfortunately, the time taken to perform a single complete measurement is two to three minutes and, since two occlusions are performed, the flowrate itself may change due to local vasodilation after occlusion<sup>49</sup>. Stow and Schieve also discuss the various assumptions on which this technique is based, some of which may not be valid and are virtually impossible to assess. In vivo results were repeatable but no test calibrations

were performed. It would seem that both of these occlusion methods have a limited range of application due to the fact that a rapid occlusion of the total blood supply to the region must be performed. In addition the measurement is very slow (two to three minutes) and computational requirements higher.

### Summary of Section 3.

Sources of error of thermal-perfusion-flow measuring systems may be broadly listed as :

- (a) Variations of thermal conductivity of tissue from place to place and with temperature.
- (b) Temperature gradients, steady state and transient.
- (c) Inhomogeneity of tissue causing wide variations of radiation resistance. In particular, the presence of single large vessels ( $\phi > 0,18$  to  $0,5$  mm) within 5 mm of probe.
- (d) Changes of blood vessel diameter affecting radiation resistance.
- (e) Temperature coefficient of flow (Injected heat may change flowrate in vicinity of probe.)
- (f) Velocity flowrates in excess of twice  $V_{50}$  giving poor qualitative results.
- (g) Long settling time giving incorrect results under rapid changes of flow.

Different techniques of perfusion-flow measurement can briefly be summarised as measurements of :

- (1) the final temperature of the probe under conditions of constant-power injection ("constant-current systems");
- (2) the power injected to maintain probe at constant-temperature-difference probe to tissue;
- (3) the initial rate of change of temperature under conditions of constant-power-injection when power is first applied to the probe; (A variation of this measures the rate of change of temperature when the heater is switched off.)<sup>38</sup>
- (4) the change in the rate of change of temperature with constant-power injection when flow abruptly ceases. (Requires simultaneous occlusion of all sources of blood supply to the region.)

## SECTION 4

### 4. Minimizing Sources of Error

In this section some of the sources of error discussed in Section 3 are assessed and methods of overcoming them are suggested. This leads to the ideas behind the design of the equipment in this thesis. The effect of the different sources of error discussed in Section 3 will depend largely on the physical properties and homogeneity of the tissue into which the probe is introduced.

Variation of thermal conductivity of the tissue beds into which the probe is introduced will change the power conducted away at zero flow and thus the zero setting will vary. The obvious way of overcoming this problem is to occlude the blood flow to the region to establish the zero condition. In many situations this is not possible since the blood supply to the region may not be simply occluded or stopping the flow may cause damage. e.g. in the brain. Notice that, if an occlusion is performed, the change in conductivity measured is then due only to the blood flow, not to other fluids which are perfusing independently in the vicinity of the probe (e.g. bile, lymph).

If no occlusion is performed how much variation in thermal conductivity can be expected? It was pointed out earlier that fatty tissue was likely to cause a large variation and this is borne out by Hensel's results. (Fig.4.11.)

Wärmeleitahlen von undurchblutung  
normalen Lebern des Menschen

Wärmeleitahlen von undurchblutetem pathologisch verändertem Leber- und  
Uterusgewebe des Menschen

Leber Nr.	$\lambda$ $10^{-4} \text{ cal} \cdot \text{cm}^{-1} \cdot \text{s}^{-1} \cdot ^\circ\text{C}^{-1}$	Pathologisch-anatomischer Befund (makroskopisch)	$\lambda$ $10^{-4} \text{ cal} \cdot \text{cm}^{-1} \cdot \text{s}^{-1} \cdot ^\circ\text{C}^{-1}$	Zahl der Messungen
1	10,9	Stauungsleber . . . . .	11,5	6
	10,7	Stauungsleber . . . . .	11,4	4
	11,1	Stauungsleber mit brauner Leberatrophie . . . . .	11,2	8
	11,3	Stauungsleber mit brauner Leberatrophie . . . . .	11,3	2
	10,8	Vereinzelt Carcinom-Metastasen in sonst normalem Lebergewebe . . . . .	11,2	6
2	11,1	Lebercirrhose (Laennee) . . . . .	11,6	6
	10,9	Lebercirrhose (Laennee) . . . . .	11,2	8
	11,1	Lebercirrhose (Laennee) . . . . .	11,1	7
	11,2	Stauungsleber mit geringgradiger Verfettung . . . . .	11,5	5
	11,4	Diffuse Leberverfettung bei allgemeiner Adipositas . . . . .	10,1	7
	11,0	Diffuse Leberverfettung . . . . .	9,6	6
3	10,8	Stauungsleber mit diffuser Verfettung . . . . .	9,1	5
	11,6	Fibrös verändertes Uterusgewebe . . . . .	11,6	3
	11,7	Fibrös verändertes Uterusgewebe . . . . .	12,2	4
	11,9	Fibrös verändertes Uterusgewebe . . . . .	11,3	6
	11,4			
4	11,9			
	11,4			
	11,3			
	11,6			
5	11,5			
	11,8			
	11,3			
	11,8			
	11,7			

Fig.4.11.

These results also show that where pathological changes have occurred in the liver the variation in thermal conductivity is small except in the case where fatty tissue is present. Another source of conductivity variation depends on the quantity of blood present in the tissue and the relative thermal conductivity of blood and tissue. Fortunately in many cases the tissue has virtually the same conductivity as that of blood (see fig.3.23). Conductivity variation for changes of blood content of the liver are shown in fig.4.12. (Graf et al<sup>4</sup>)

Wärmeleitahlen von Hundelebern bei unterschiedlicher Blutfülle.  
Die Tab. enthält die Ergebnisse aus Messungen an 4 Hundelebern.  
Jeder  $\lambda$ -Wert ist der Mittelwert aus 4–6 Einzelmessungen an verschiedenen Orten  
des untersuchten Leberlappens

Blutreiche Leber		Entblutete Leber		Blutgehalts- abnahme in Prozent	Änderung der Wärme- leitahl bei Entblutung in Prozent
Blutgehalt $\text{ml} \cdot \text{g}^{-1}$	$\lambda$ $10^{-4} \text{ cal} \cdot \text{cm}^{-1} \cdot \text{s}^{-1} \cdot ^\circ\text{C}^{-1}$	Blutgehalt $\text{ml} \cdot \text{g}^{-1}$	$\lambda$ $10^{-4} \text{ cal} \cdot \text{cm}^{-1} \cdot \text{s}^{-1} \cdot ^\circ\text{C}^{-1}$		
0,160	11,5	0,080	11,3	20	-1,8
0,183	12,0	0,095	12,0	48	0,0
0,196	12,5	0,099	12,6	50	+0,8
0,258	12,1	0,132	11,8	49	-2,5
Mittelwerte: 0,199	12,0	0,102	11,9	49	-0,9

Fig.4.12

Apart from temperature variations, which are generally random errors, the largest source of systematic error in thermal-perfusion measuring systems arises from the non-homogeneity of the tissue beds. This changes the radiation resistance from the heated probe to the blood and means that absolute measurements can be made only if the tissue beds are uniform from site to site. As pointed out earlier from Bill's work, if the probe is placed near a single large vessel, errors are particularly large. The probe will correctly<sup>x</sup> indicate a large flow in the region but will not indicate qualitative changes in flow. The homogeneity of the tissue beds in which the probe is placed will determine whether an absolute measurement is possible or not. If the person using the probe could always place the probe so that it is not influenced by "large" vessels, then quantitative results should be possible for tissue containing many small vessels. Where the probe is introduced into tissue containing some larger vessels qualitative results should be good provided the blood velocities do not exceed about twice  $V_{50}$ . (See Section 3.) This means that experiments on small animals will tend to give much better results than on larger animals, as vessel size will generally be smaller in the small animals. This helps explain why so many conflicting reports of the relationship between apparent thermal conductivity and flowrate exist.

In sites where relatively few blood vessels exist the change in local thermal conductivity may be so small that errors due to temperature changes, fluid content of tissue etc effectively set a noise level which obscures the desired signal. In this situation the average of a number of measurements should give

x It appears to this author that many criticisms of perfusion-measuring systems stem from the fact that people would like an average measurement for a whole organ or region from a measuring system which inherently makes a measurement in a very small prescribed region. The fact that a perfusion probe indicates a larger flow when placed near a large vessel is in a sense a correct indication.

more reproduceable results.

Tab. 1 bringt eine größere Zahl von Messungen der Wärmeleitfähigkeit des *M. gastrocnemius* bei verschiedenen Versuchspersonen. Die Werte stimmen mit den mittels anderer Methodik gewonnenen Ergebnissen von HENRIQUES u. MORITZ<sup>12</sup> (toter Schweinemuskel,  $\lambda = 0,0011$ ) und unseren eigenen Messungen am Rindermuskel ( $\lambda = 0,00115$ ) sehr gut überein. Die mittlere Streuung der einzelnen Wärmeleitfähigkeiten bei Ruhedurchblutung beträgt nur  $\pm 3,9\%$ . Bei Unterbrechung des

Tab. 1. Wärmeleitfähigkeiten im *M. gastrocnemius* des Menschen *in situ* bei verschiedenen Versuchspersonen.

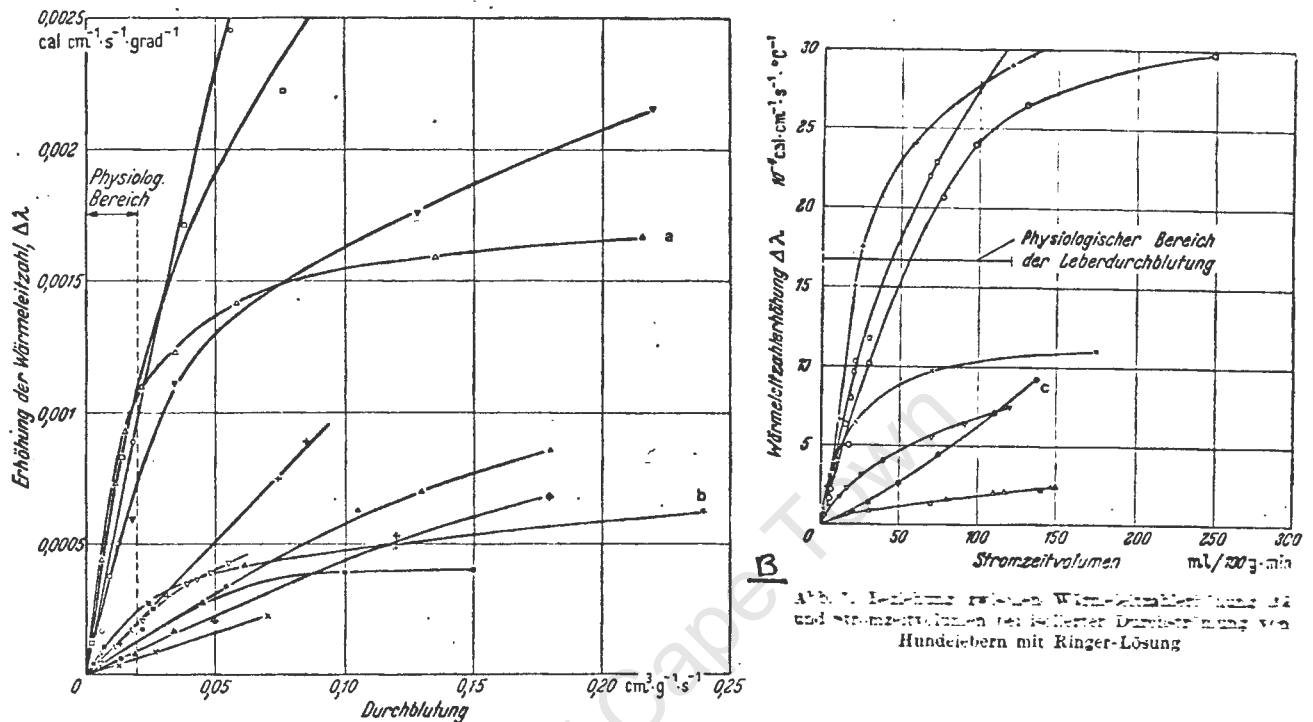
Ruhedurchblutung $\lambda$ $\text{cal}\cdot\text{cm}^{-1}\cdot\text{s}^{-1}\cdot\text{Grad}^{-1}$	Blutstrom unterbrochen $\lambda$	Reaktive Hyperämie $\lambda$	Differenz zwischen nicht durchblutetem und hyperämisiertem Muskel $\Delta \lambda$
0,00124	0,00110	0,00129	0,00019
0,00123	0,00121	0,00127	0,00006
0,00118	0,00117	0,00122	0,00016
0,00119	0,00118	0,00122	0,00004
0,00107	0,00106	0,00123	0,00017
0,00121	0,00118	0,00129	0,00011
0,00124	0,00122	0,00141	0,00019
0,00119	0,00114	0,00162	0,00048
0,00123	0,00121	0,00127	0,00005
0,00125	0,00122	0,00136	0,00014
0,00128	0,00119	0,00132	0,00013
0,00117	0,00113	0,00124	0,00011
0,00119	0,00117	0,00130	0,00013
0,00119	0,00112	0,00137	0,00025
0,00127	0,00125	0,00130	0,00005
0,00123	0,00119	0,00129	0,00010
M = 0,00121	M = 0,00117	M = 0,00132	M = 0,00015
$\sigma = \pm 3,9\%$			
$\sigma_M = \pm 1\%$			

Fig. 4.13

Blutstromes findet man eine durchschnittliche Abnahme von  $\lambda$  um 0,00004, während die Zunahme der Wärmeleitfähigkeit auf dem Höhepunkt der reaktiven Hyperämie durchschnittlich 0,00015 erreicht. Da man in diesem Bereich eine annähernd lineare Beziehung zwischen Stromzeitvolumen und  $\lambda$  voraussetzen kann, würde also die Muskeldurchblutung bei reaktiver Hyperämie durchschnittlich 400% der Ruhedurchblutung erreichen. Dies stimmt mit Versuchen von MURPHY und Mitarb.<sup>14</sup> gut überein, die mittels venöser Verschlussplethysmographie am menschlichen Unterschenkel bei reaktiver Hyperämie Zunahmen von 400—500% fanden.

Fig. 4.13 (Hensel<sup>44</sup>) indicates such a situation (human, gastrocnemius muscle) where the thermal conductivity increment is small as can be seen by comparing the first two columns.

The effect of  $2 \times V_{50}$  being exceeded in different tissue sites is illustrated by the results of fig. 4.14. (Hensel et al<sup>44</sup>, Graf et al<sup>4</sup>).



**A** Durchströmung isolierter Schafsmilzen mit RINGER-Lösung. Erhöhung der Wärmeleitfähigkeit  $\Delta\lambda$  als Funktion des Stromzeitvolumens.

**B** Erhöhung relativer Wärmeleitfähigkeit  $\Delta\lambda$  und Stromzeitvolumen bei isolierter Durchströmung von Hundelebern mit Ringer-Lösung

Fig. 4.14.

It can be seen that in the case of the isolated sheep's spleen (fig.4.14A) over the range of expected physiological flowrates the relationship between conductivity increment and flowrate is linear indicating qualitatively results should be very good. It is interesting to note from this figure that measurements tend to fall into two groups, one with a much steeper slope. There are two possible explanations: the first being that the curves accurately represent flow and that some areas normally have much higher flowrates than others; the second explanation using Bill's results indicate that the steeper set of curves are for probe placements near large vessels. This tends to be supported by the curves I have marked a and b which seem to have the same values of  $V_{50}$  i.e. the probe is influenced in each case by the same diameter vessels but in

the case of curve b the vessel is further from the probe reducing the sensitivity. A number of the other curves are quite close together and may actually indicate slight differences in local perfusion rate rather than variations in vessel size. From Fig.4.14B it can be seen that qualitative results from the dog liver will not be as good as those from Fig.4.14A since over the physiological range  $2 V_{50}$  can sometimes be exceeded. The likelihood of poor probe placement (i.e. near a vessel where  $2 V_{50}$  is exceeded) can be assessed from the results of Fig.4.15b.

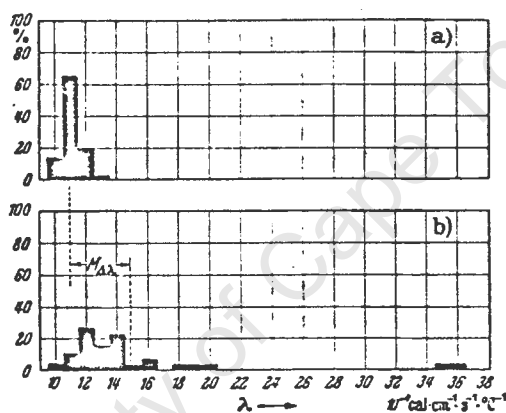


Fig. 4.15.

Abb. 3. Häufigkeitsverteilung der Wärmeleitfähigkeit  $\lambda$  in der Hundeleber in Prozent. a) 37 Messungen bei undurchbluteter Leber; b) 32 Messungen bei unbeeinflusster Leberdurchblutung.  $M_{AA}$  bezeichnet die mittlere Wärmeleitfähigkeit bei Ruhedurchblutung der Leber gegenüber dem undurchbluteten Zustand.

This result could be interpreted by saying that probe placements fall into three categories: the first in an area where flow is small, representing most measurements of  $11 \times 10^{-4}$  and below; those measurements around  $14 \times 10^{-4}$  where the probe was influenced by a large number of small vessels; and those measurements above this where the probe was influenced by both small and large vessels. In the case of the results at  $35 \times 10^{-4}$  the probe might actually be placed in a large vessel. Hensel's results on rat livers appear similar to those on the dog liver despite the smaller animal. (Fig.4.16).

Tabelle 4. Wärmeleitahlen in der Rattenleber

Vers. Nr.	Sondenlage Nr.	$10^{-4} \text{ cal} \cdot \text{cm}^{-1} \cdot \text{s}^{-1} \cdot \text{C}^{-1}$	
		Ruhelurchblutung	Durchblutung 0
1	1	16,4	
		23,1	
	2	13,5	
	3	12,2	
2	4	14,6	11,0
	1	20,3	
	2	33,8	11,2
3	1	31,3	
	2	17,3	
	3	18,0	12,3
4	1	20,7	
	2	24,2	12,0
Mittelwert:		20,4	11,6

Fig. 4.16.

Bill suggested that local dilation of vessels with changes of flow might actually help linearise the flowrate-conductivity relationship. (See fig.4.17.)

The effect of distension of the vessel on the relationship between  $\Delta K$  and flow. Unbroken lines, hypothetical curves showing the relationship between  $\Delta K$  and flow in a vessel at three different states of distension. Broken line, the same relationship when the vessel is permitted to dilate in a continuous fashion.

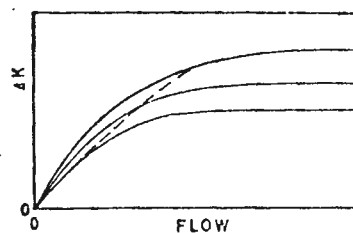


Fig. 4.17.

I have marked one unusual curve C (fig.4.14B) which might tend to support this idea.

A possible method of discrimination between a "poor" probe placement and a "good" one is to reject readings from a probe if they exceed the average value by more than a small margin. Although not guaranteeing good placement, this should generally give very much better qualitative results. It should be noted that qualitatively for an increase in flow the probe never overestimates.

The problem of determining whether local heating caused by

It is interesting to compare these results with those of Grayson<sup>37</sup> whose experiments on rats showed normal in vivo conductivity of about  $16 \times 10^{-4}$ . Grayson's probe was much more fragile than the needle probe of Hensel et al so that a placement in a large vessel was probably less likely, which might explain the difference in their results.

the probe changes the flowrate can be investigated by seeing whether the conductivity increases with temperature increment. Such an experiment is shown in fig.4.18

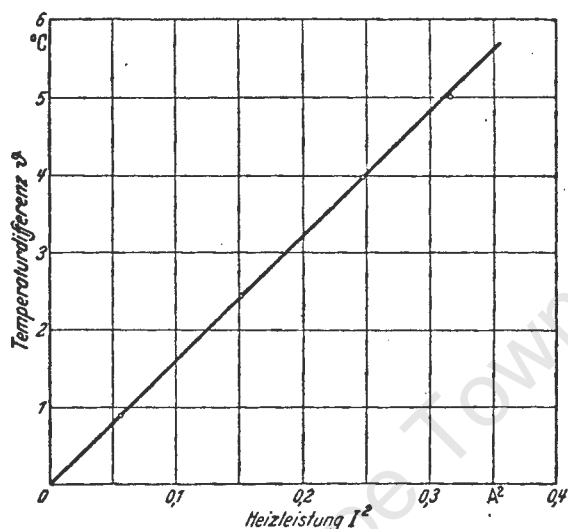


Abb. 7.  
Versuch am M. gastrocnemius des Menschen. Temperaturdifferenz  $\Delta$  der Lötstellen als Funktion der Heizleistung  $I^2$ .

Fig. 4.18.

This indicates the thermal conductivity does not change and hence the injected heat has no effect.

Settling time is another problem of steady-state flow-measuring systems. The difference in settling time between constant-current and constant-temperature-difference systems for identical conditions is illustrated in fig.4.19. (Grayson). It can be seen that settling time is improved by a factor of five for constant-temperature-difference operation.

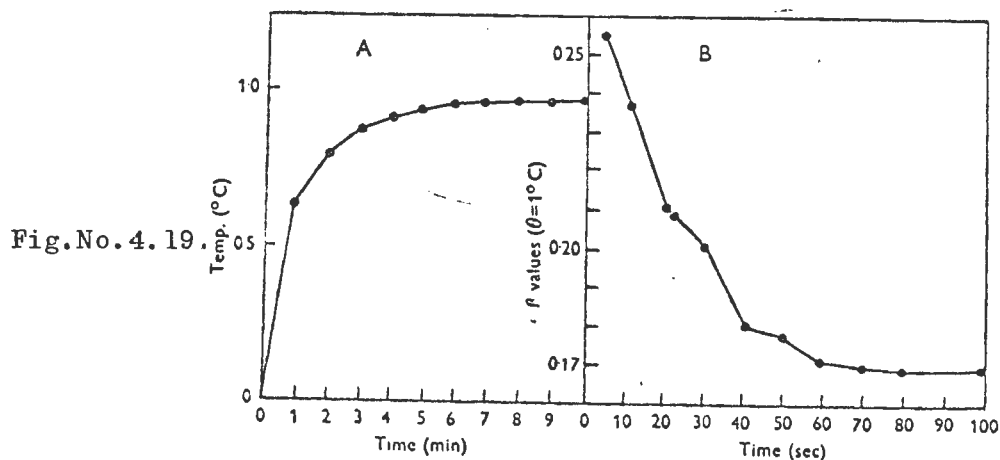


Fig.No. 4.19.

The time taken to establish equilibrium. Recorder in gel (10% gelatin in water). A, current kept constant (shows slow rise of  $\theta$  to equilibrium); B,  $\theta$  raised quickly to 1°C by applying excess current which was then reduced to counter tendency to upward temperature drift.

The settling time depends somewhat on probe material, size and construction. The difference in slew rate and settling time for an increase compared to a decrease in flow is illustrated in fig.4.110. (Hancock<sup>43</sup>) x

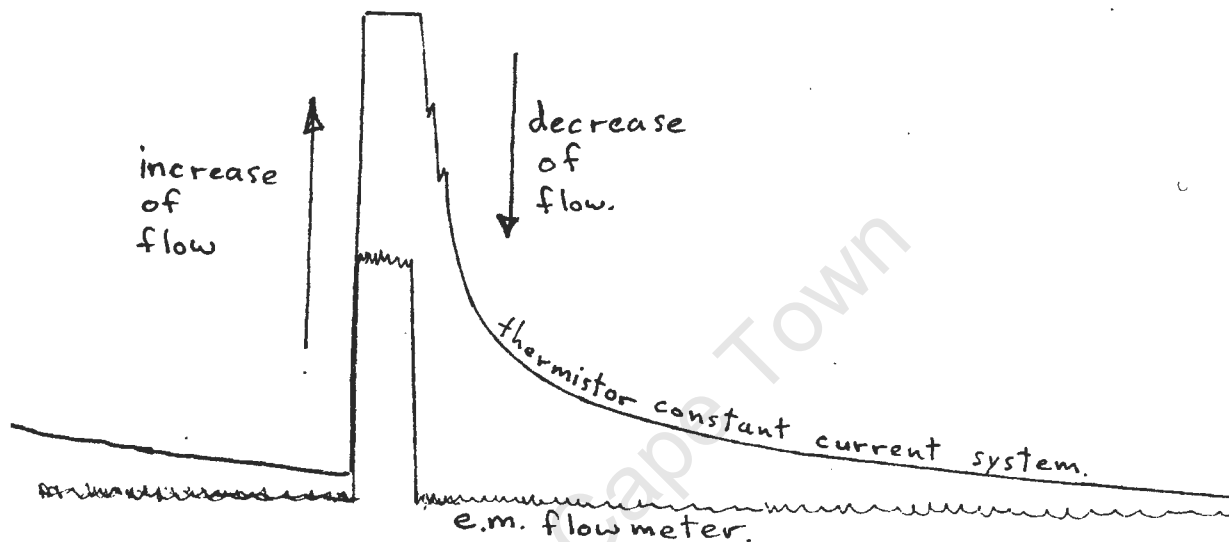


Fig.4.110.

Errors due to temperature changes have already been discussed in detail in section 3 and will not be repeated here.

- x Hancock's results seem peculiar at first until one realises that he must have recorded the results with the galvanometers of the U.V. recorder connected the wrong way round, since otherwise his results would indicate that the thermistor probe starts indicating changes of flow sometime before they actually occur. The results shown in the diagram above have been inverted so that they are correct.

SECTION 5

It was felt that considering all the different requirements a constant-temperature-difference probe offered the best sensitivity with a reduction of many of the problems of constant-current systems. (See Section 3 for comparison.) Transient electrical systems might offer certain advantages, although of lower sensitivity, but were not investigated further.

In the equipment developed a hypodermic-mounted thermistor acts as both temperature sensor and heating element in a self-balancing bridge circuit. Feedback around the bridge adjusts the power fed to the thermistor to maintain its temperature constant. This eliminates the problems associated with having a separate heater and temperature sensor and simplifies probe construction. Instead of using a second probe to compensate for tissue temperature changes so that  $\Delta T$  can be kept constant, the same thermistor probe is used to sense temperature and flow alternately. A sample-and-hold circuit holds the last measured temperature and feeds this into the bridge circuit so that  $\Delta T$  is kept constant during flow measurement. This minimises trauma (one probe) and, more important, means that matched thermistors are unnecessary and thermistor ageing has no effect on the circuit. Errors due to temperature gradients (See section 3.) which affect a two-sensor system are also eliminated. The final design is not a true steady-state system. The probe takes about 40 secs to finally settle to equilibrium (at zero flow) after a temperature measurement. To eliminate this long period the digital display holds the value measured after settling for 16 secs. This value is displayed for the duration of the next temperature measurement. Since the measurement always occurs after the same period of time, it is repeatable despite the fact that final equilibrium has not been achieved.

Block diagram of the system is shown in fig.5.01.

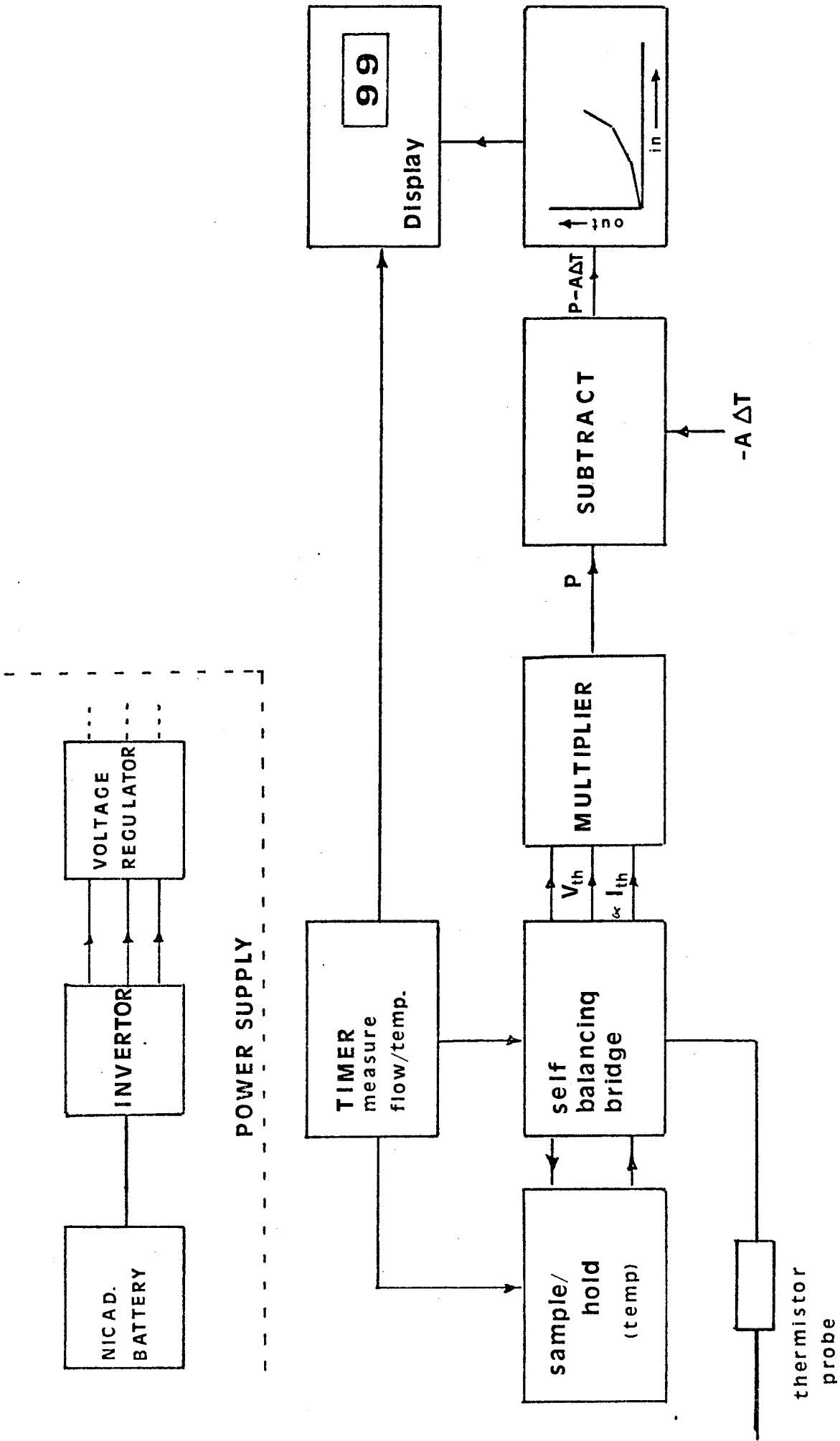


FIG 5.01 PERFUSION FLOWMETER

## Circuitry and Design Features.

### 5.1 Precision Multiplier

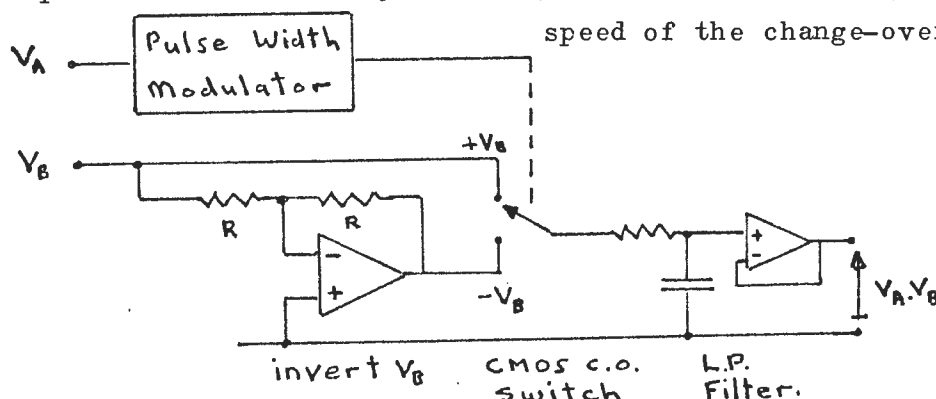
Various techniques can be used for multiplication - transconductance multipliers (using transistors), quarter square multipliers (using F.E.T.'s diode networks or thermistors), triangle averaging multipliers, time-division multipliers, Hall-effect multipliers, magneto resistive multipliers, photo conductive multipliers, stochastic multipliers and digital multipliers (requiring A/D convertors).

At present commercial analogue multipliers are most commonly transconductance devices with an accuracy of from  $\frac{1}{4}$  to 2 % of F.S.D. depending on price. Temperature drift of these devices may introduce still larger errors. Time-division multipliers are used in higher precision applications but cost considerably more than the R60 to R100 + price of the transconductance devices.

A low-cost time-division multiplier was designed with an accuracy of about  $\pm 0,07$  % of F.S.D. However the current consumption was excessive for battery operation. A careful redesign increased complexity slightly but reduced current consumption by a factor of four and reduced errors to about 5 mV maximum in any quadrant (0,05% of F.S.D.)

It is necessary to achieve a fairly high performance in the multiplier since a constant is subtracted from the multiplier's output by the curve fitting circuitry and multiplier errors are then a much larger percentage of the difference.

Errors of time-division multipliers (See simplified diagram) depend on the linearity of the pulse width modulator, the switching speed of the change-over switch and

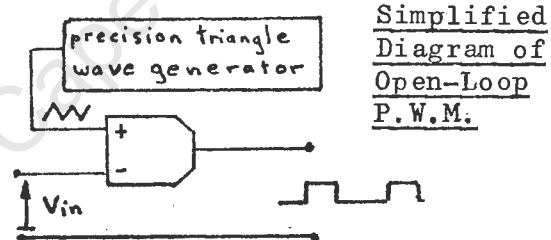


switching noise introduced by switch feed through. A number of circuit configurations for switching the gain of an amplifier between plus or minus one are possible but the passive change-over switch configuration used here introduces less switching noise and does not suffer from amplifier slew-rate errors. The simple low-pass filter is also better than many active systems which tend to pass switching noise to the output and usually require wide-bandwidth operational amplifiers which have large bias currents making long filter time-constants difficult to achieve.

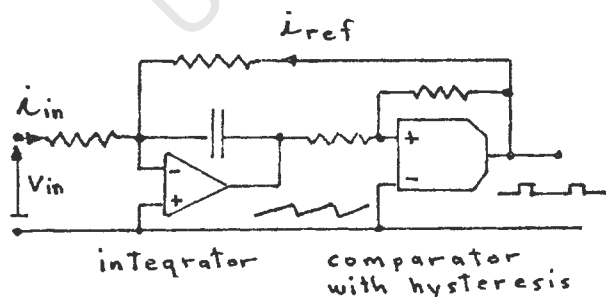
Pulse-width modulators can be divided into two types : feedback systems and open-loop systems.

#### Open-loop systems

require very high speed comparators and a precision triangular wave generator. The linearity of this type of pulse-width modulator depends on the linearity of the triangle wave generator. Finite comparator response time introduces errors.



Feedback systems correct for finite switching-time errors and thus tend to have higher accuracy than open-loop systems.



One disadvantage of feedback pulse-width modulators is that the carrier frequency decreases with increasing input signal. This means that the maximum input signal should be limited so that the carrier frequency is not too low.

The practical pulse-width modulator (fig. 5.11) uses parallel CMOS gates to buffer the comparator output and provide a precise switched reference source. The reference source of a 723 regulator provides the positive reference to the gates while its internal amplifier with a level shifted discrete transistor (2N2907A) provides the negative reference source. The 311 comparator has a constant-current F.E.T. load which is buffered from the positive reference by a BC109 transistor. This eliminates the loading on the positive reference.

The 5 pF feedback capacitance around the 311 provides a positive switching action eliminating parasitic oscillation when switching occurs. A feedforward compensated 301 operational amplifier is used as a fast integrator for the pulse-width modulator. CD4016 CMOS transmission gates are used for the change over switch in the multiplier. Stray capacitance at the junction of the two switches and on the control lines to the switches should be minimised.

The maximum output signals from the 308 amplifiers feeding the CMOS switches are clamped to the CMOS reference voltages so that possible latch conditions in the CMOS switches can not occur. For high accuracy the outputs from these amplifiers should not exceed about 6 volts. Similarly the maximum input current signal to the integrator of the pulse-width modulator should not exceed about 200  $\mu$  A as otherwise the carrier frequency will drop to less than half of its value at zero input.

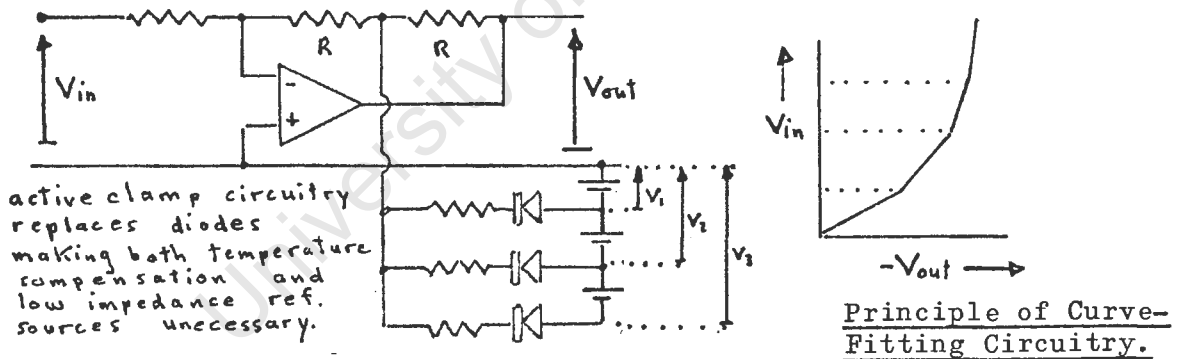
The 308 amplifier used for the inverter feeding the CMOS switches as well as the output buffer amplifier should have low input offset voltage ( $< 0,5$  mV) or should be nulled (using external null components) to achieve errors of less than 10 m.V.

The symmetry control is adjusted so that the output under conditions of zero input to the P.W.M. and plus or minus maximum signal to the other input is zero.



### Curve-Fitting Circuitry

Various circuits using diodes, zener diodes or transistors are commonly used for curve fitting. Careful design is normally required to eliminate break-point drift due to temperature changes. Temperature compensation generally requires matched components mounted in close proximity. Some systems also have interactive slope and breakpoint controls which make setting up a difficult procedure requiring a number of iterations. Some advantages of these simple systems are fast response and a very smooth change from one slope to the next provided by the logarithmic diode characteristics. The curve-fitting circuit designed here is based on the fact that low-cost low-power consumption quad operational amplifiers are now available, which means that a single op-amp per breakpoint is no longer an extravagance and does not increase layout complexity. The principle of the curve-fitting circuitry is shown in the following simplified diagram :



The feedback factor decreases when the voltage at the junction of the two feedback resistors (R) exceeds the reference voltage. The diodes shown are actually "perfect" diodes created by connecting a diode in the feedback path of an operational amplifier. (See fig.5.21) This configuration eliminates temperature drift and, provided setting up is carried out starting from the lowest voltage breakpoint, no interaction occurs. In the final circuit a pre-set zero control is also provided to subtract a quantity representing the power conducted away from the probe under zero flow conditions.

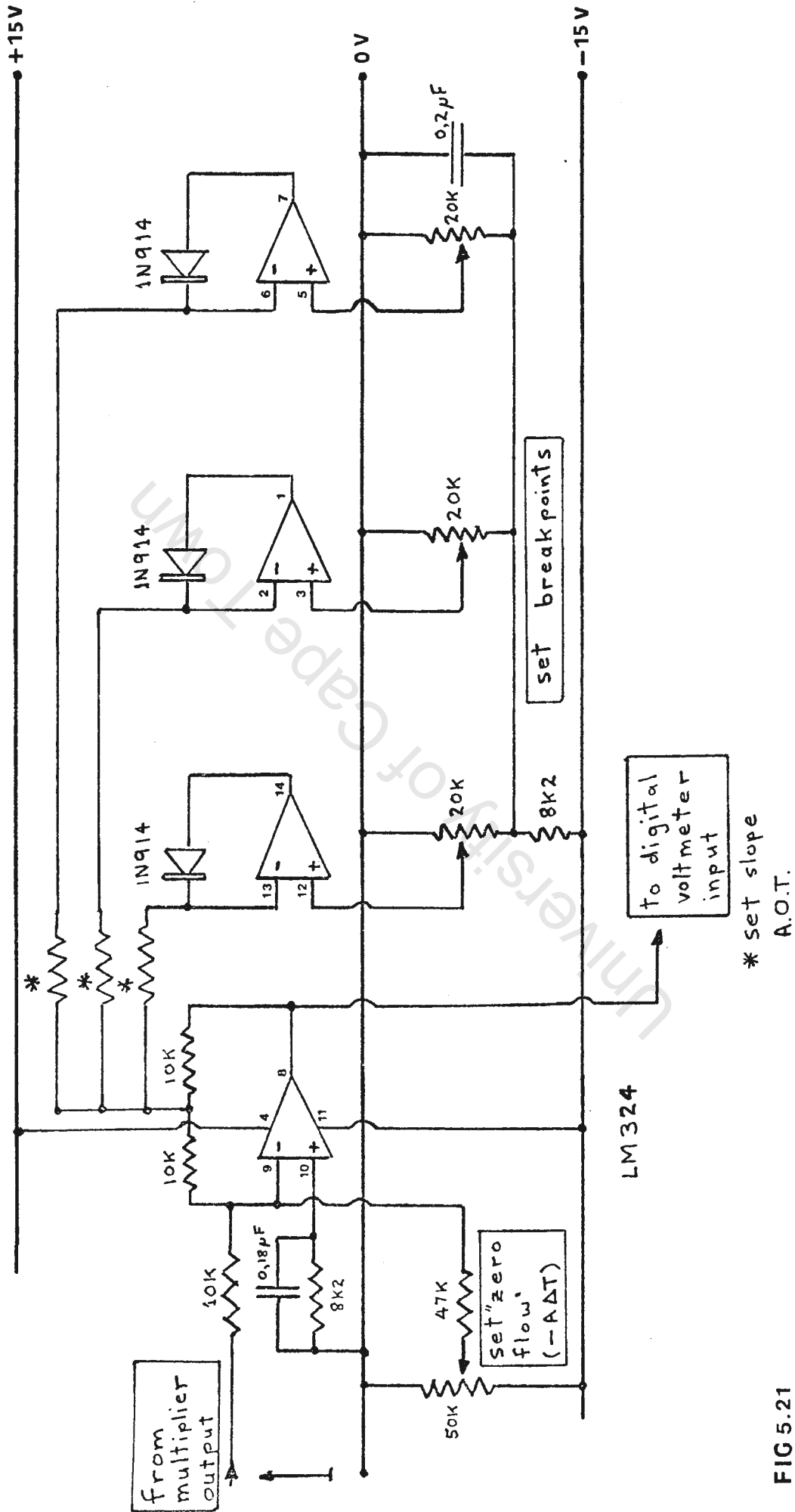


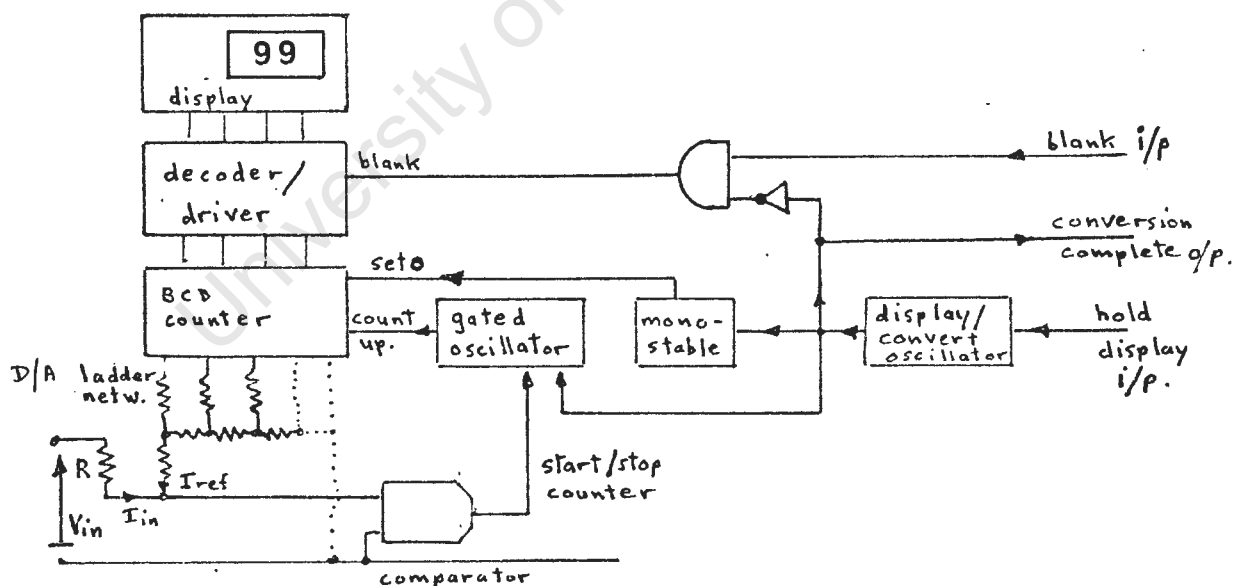
FIG 5.21  
 CURVE  
 FITTING  
 CIRCUITRY

## 5.3

A/D Converter.

The precision expected from thermal flow measuring techniques is unlikely to be better than 5 per cent. Hence a two-digit display (1 per cent) would seem to offer adequate accuracy while at the same time minimizing power consumption. An extra digit would also encourage operators to read the display to a meaningless accuracy.

The display/convert oscillator supplies 1,3 m.sec. conversion pulses to the A/D converter every 600 m.sec. A single conversion is completed in under 1,3 m.sec. No sample and hold is used ahead of the A/D converter since conversion is fast enough for the output signal from the multiplier to be considered stationary (multiplier l.p. filter cut off frequency  $\approx 0,7$  Hz). The display is blanked during the conversion time to eliminate segment flicker but since the conversion time is short the display appears continuous.



The A/D converter itself is a digital-ramp system using low cost CMOS counters which perform as counters, "display latches" and D/A ladder network drivers. A convert pulse starts a conversion cycle by triggering the monostable and presetting 0 in the counter. (Using the preset input rather than the reset input reduces gate

count by eliminating an inverter.) The convert signal also enables the gated clock which is counted by the cascaded binary coded decimal and binary counters. When the output current from the D.A. convertor ( $I_{ref}$ ) equals the input current signal ( $I_{in} = V_{in}/R$ ) the comparator gates the oscillator off stopping the counter.

A binary rather than a b.c.d. counter is used for the most significant digit to allow the convertor to over-range without giving an erroneous output. The gated oscillator operates at a frequency of about 100 K Hz. Hence the 1,3 m.sec. wide conversion pulse gates the oscillator off on an over-range signal limiting the maximum count to about 130, which is below 159 where the counter would start from zero once more.

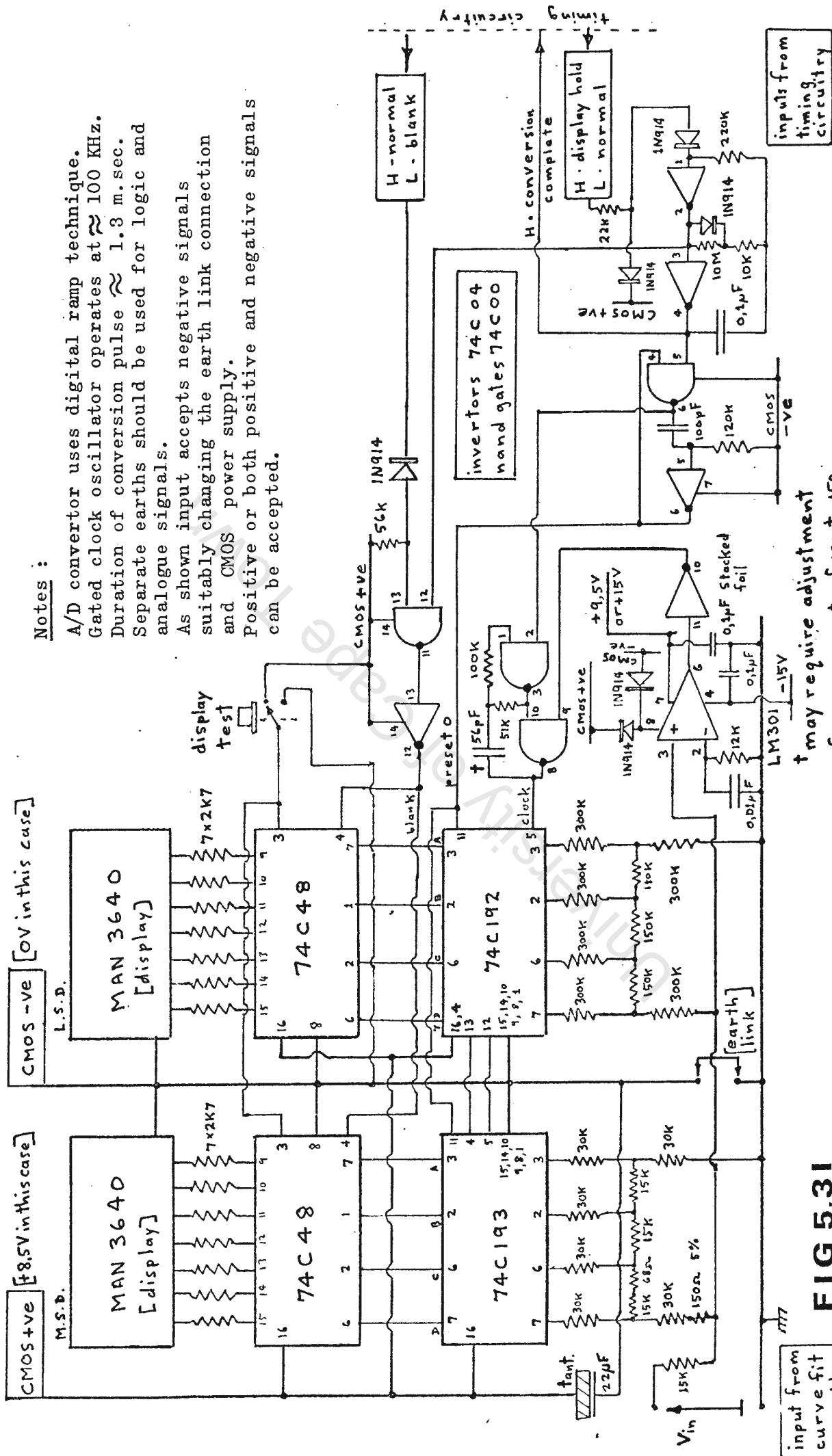
The 74C48 decoder uniquely decodes outputs above 99 although these outputs look unusual on the display. Unlike the equivalent 74 TTL decoder this decoder has on chip transistor drivers for l.e.d. displays. The displays used are recently introduced low-current orange l.e.d. displays which give adequate brightness at 3 mA/segment.

The counters have "standard" 74C output characteristics which, from measurements done on a number of different gates and counters, means initial slope resistances of about  $200\ \Omega$  for p channel transistors and  $120\ \Omega$  for n channel transistors (measured at  $V_{cc} = 15\ V$  and  $T_a \approx 20^\circ C$ ). These resistances introduce errors into the ladder network making 40 K loads about the minimum for an 8-bit accuracy. (load = 40 K,  $R = 15\ K$   $2R = 30\ K$ ) The ladder network has two additional resistances ( $150\ \Omega$  and  $68\ \Omega$ ) to reduce errors from this source. (See fig.5.31)

The ratio matching required in the resistors of the two most significant bits of the ladder network is about 0,1% with ratio accuracy required decreasing by a factor of two for each successive bit.

The A/D convertor should strictly have its comparator's zero input offset by  $\frac{1}{2}$  L.S.B. This would be easy to do with one additional resistor but this was not actually incorporated since the curve-fit circuitry has a variable offset control (set zero flow).

Measured linearity of the convertor was better than  $1/3$  L.S.B. over full range of inputs. A 301 op-amp without compensation was used as comparator since this has low power consumption and permits easy output clamping to the CMOS logic levels. Separate earth rails for logic and analogue signals are used with a shorting-link connecting the earths at only one point. This is useful if the A/D convertor is to be connected for positive inputs or for plus or minus inputs (offset coding) which can be easily implemented by changing the analogue signal earth and the regulated CMOS power supplies. (See fig. 5.31)



**Notes :**

- A/D convertor uses digital ramp technique.
- Gated clock oscillator operates at  $\approx 100$  KHz.
- Duration of conversion pulse  $\approx 1.3$  m.sec.
- Separate earths should be used for logic and analogue signals.
- As shown input accepts negative signals suitably changing the earth link connection and CMOS power supply.
- Positive or both positive and negative signals can be accepted.

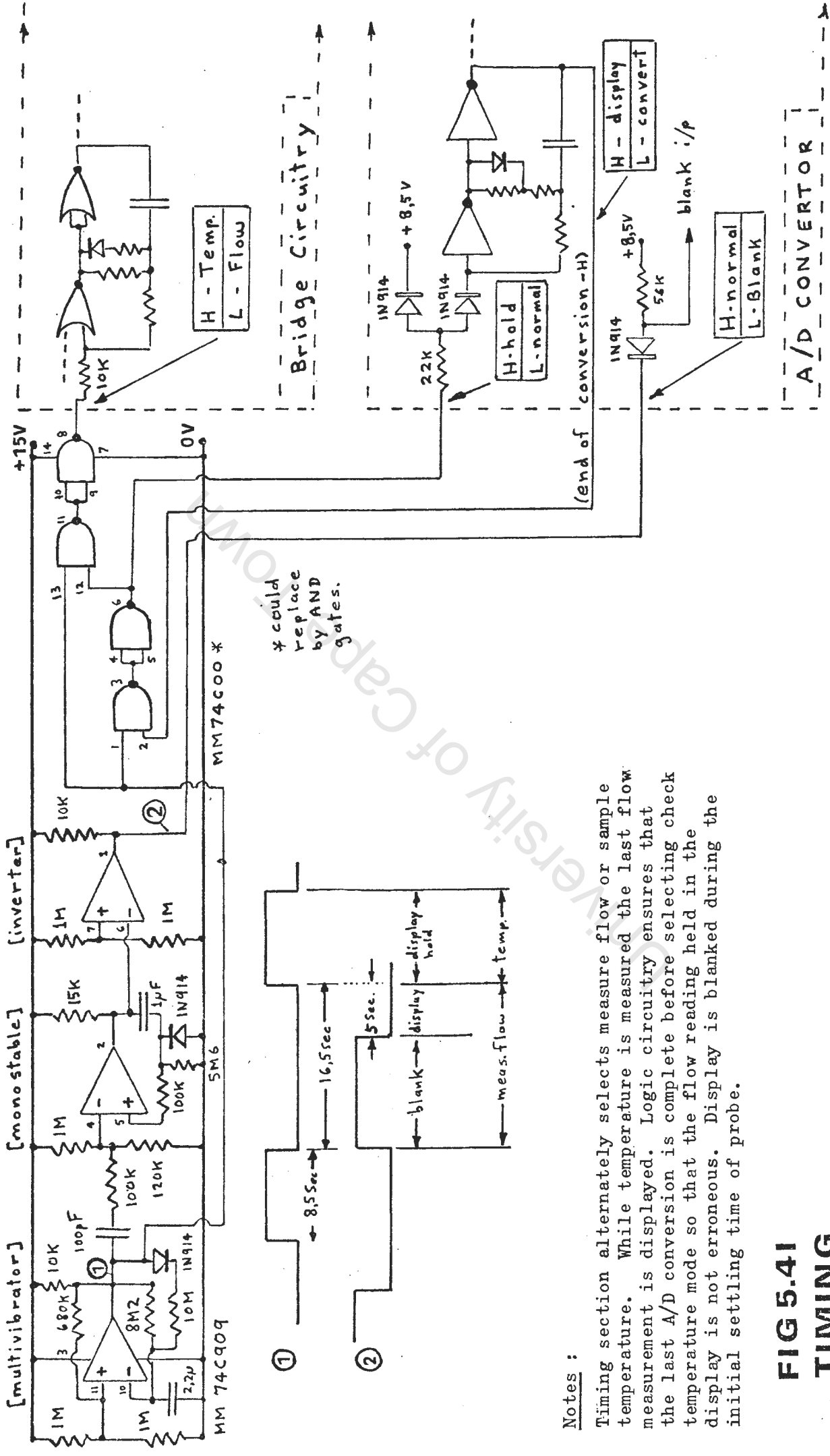
† may require adjustment for max count of 120 to 150 on over-range signal.

**FIG 5.31**  
**A/D CONVERTOR (d.v.m.)**

## 5.4

### Timing Circuitry

The timing circuitry used for controlling the measurement sequence could have used purpose-designed timers (555, 3905 etc) or CMOS gates but a low-cost quad comparator package was used instead. This has the advantages of lower power consumption and a single package. Spare comparators can be used for other functions such as indicating low battery voltage. Time intervals are generated using an astable multivibrator with unequal mark-space ratio. A monostable and gating logic then ensure the correct sequence of operations for the rest of the circuitry. This logic circuitry ensures that an A/D conversion is complete before switching to the hold-display/measure-temperature mode. The circuitry latches the A/D convertor's oscillator in the hold-display condition via a diode gate to the oscillator's input. (See fig. 5.4). NAND gates are used instead of AND gates to reduce the variety of integrated circuits used. (Package count is the same for either case.) Resistor diode networks are used to clamp the logic signals at the 15 volt level to the 8.5 volt level of the A/D convertor. The timing circuit disables the internal oscillator of the bridge circuit. The internal oscillator is meant for test purposes when no external timing connection is made to the board.



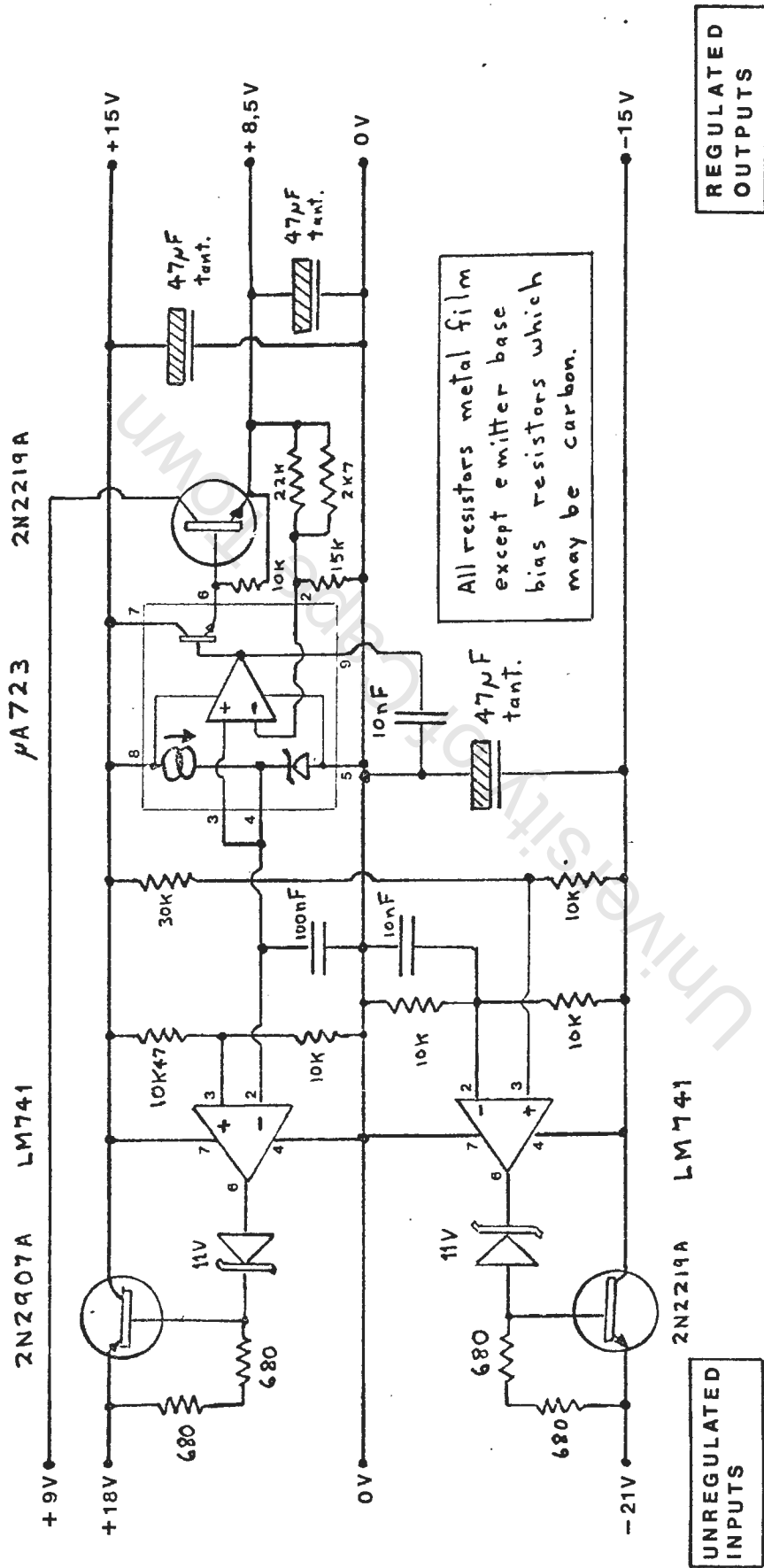
**FIG 5.41**  
**TIMING**  
**CIRCUITRY**

**Notes :**  
Timing section alternately selects measure flow or sample temperature. While temperature is measured the last flow measurement is displayed. Logic circuitry ensures that the last A/D conversion is complete before selecting check temperature mode so that the flow reading held in the display is not erroneous. Display is blanked during the initial settling time of probe.



of about 200 mV at 60 mA compared to about 1 volt minimum if the regulator's own transistor had been used in this position.

The decoupling capacitors at various points in the circuit and at the outputs are necessary for stability.

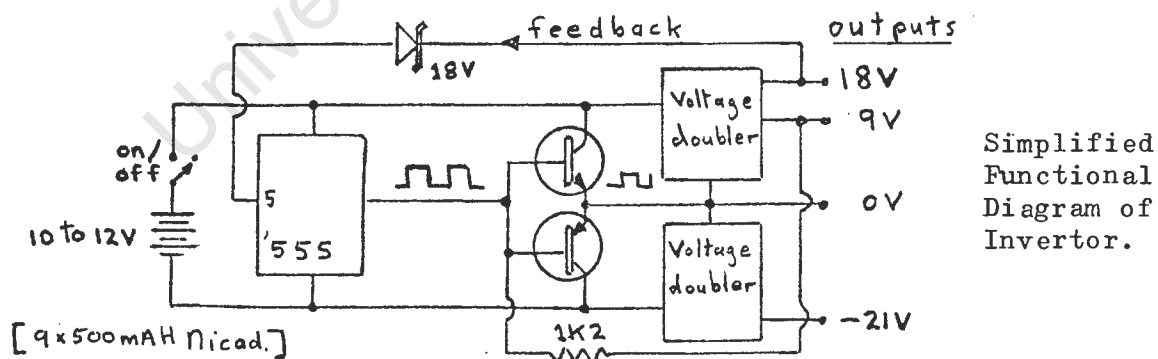


Notes : Semi-discrete regulator circuitry and common emitter output stage improves battery life by enabling operation down to 200 mV input-output differential. This is considerably better than any monolithic regulator. 723 acts as voltage reference for all three outputs and regulates the lower voltage output via a discrete transistor for improved performance.

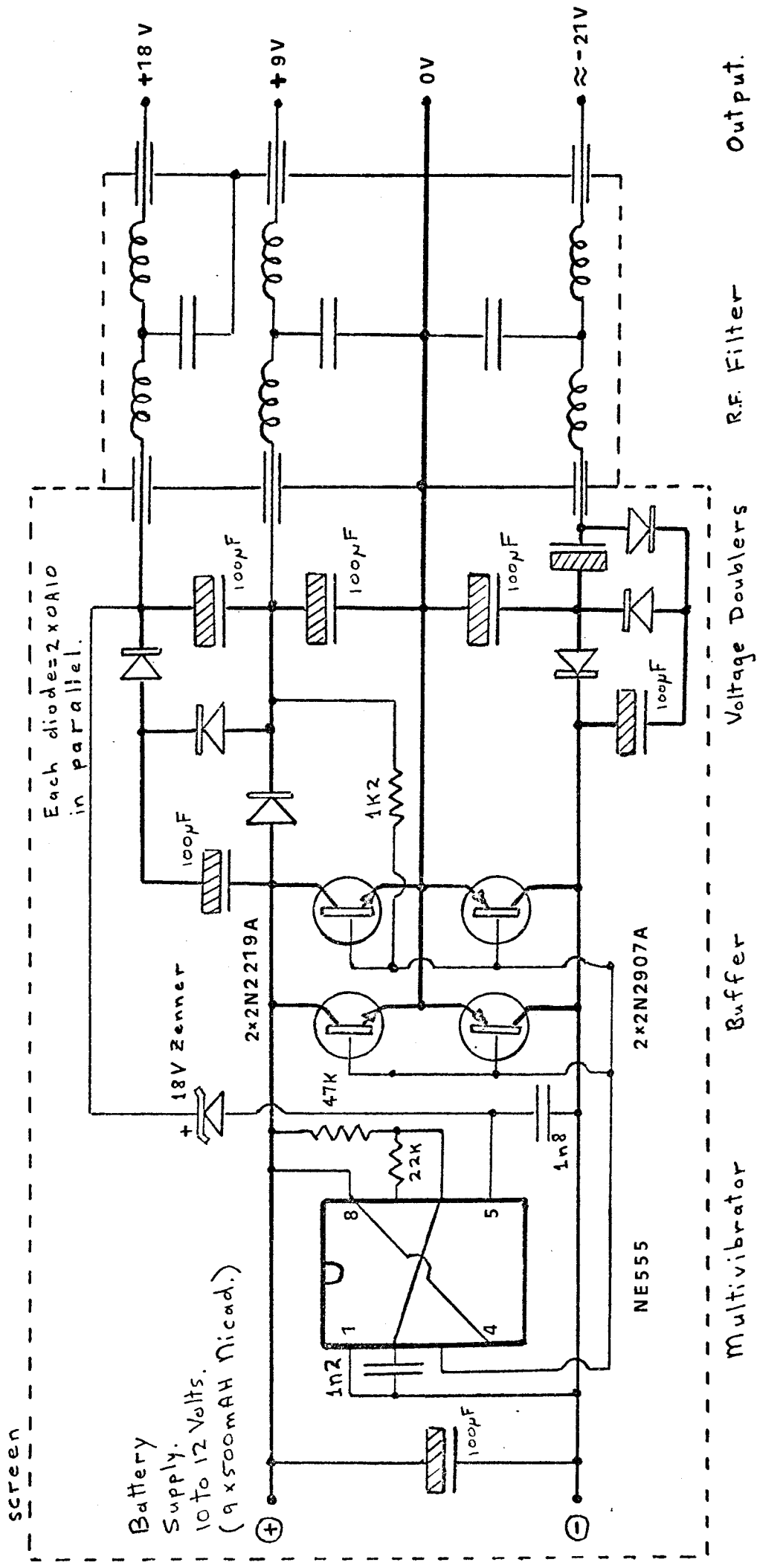
FIG 5.51  
TRACKING  
VOLTAGE  
REGULATORS

5.6Transformerless Inverter

A rechargeable battery supply is used to eliminate any possibility of micro shock due to earth leakage or earth loops. A 555 timer connected as a multivibrator drives a high current buffer feeding two voltage doublers. Feedback from the output of one of the voltage doublers adjusts the mark-space ratio of the multivibrator to preregulate both positive outputs. This extends the battery life. The negative output is not preregulated as this would complicate the design unnecessarily as the power drawn from the negative supply is less than that drawn from the positive supply. To improve efficiency high current gold bonded germanium junction diodes are used in the voltage doubler as they offer a much lower forward voltage drop than silicon diodes. Low resistance wiring in the voltage doublers and low E.S.R. capacitors are necessary to charge the capacitors rapidly and reduce losses due to large peak currents. The output saturation characteristics of the 555 timer are poor near the positive supply rail. To improve the situation the "bootstrapped" 1K2 resistor is added enabling the emitters of the 2N2219A transistors to be driven much closer to the positive supply rail.



The lower voltage positive tap is used for driving the light-emitting diode display and analogue-to-digital converter. This reduces the power consumed by the display by a half but means a small amount of clamping circuitry is necessary to level shift logic signals at 15 V to 8.5 V. Inverter efficiency (depending on load) is between 60 and 80 % .

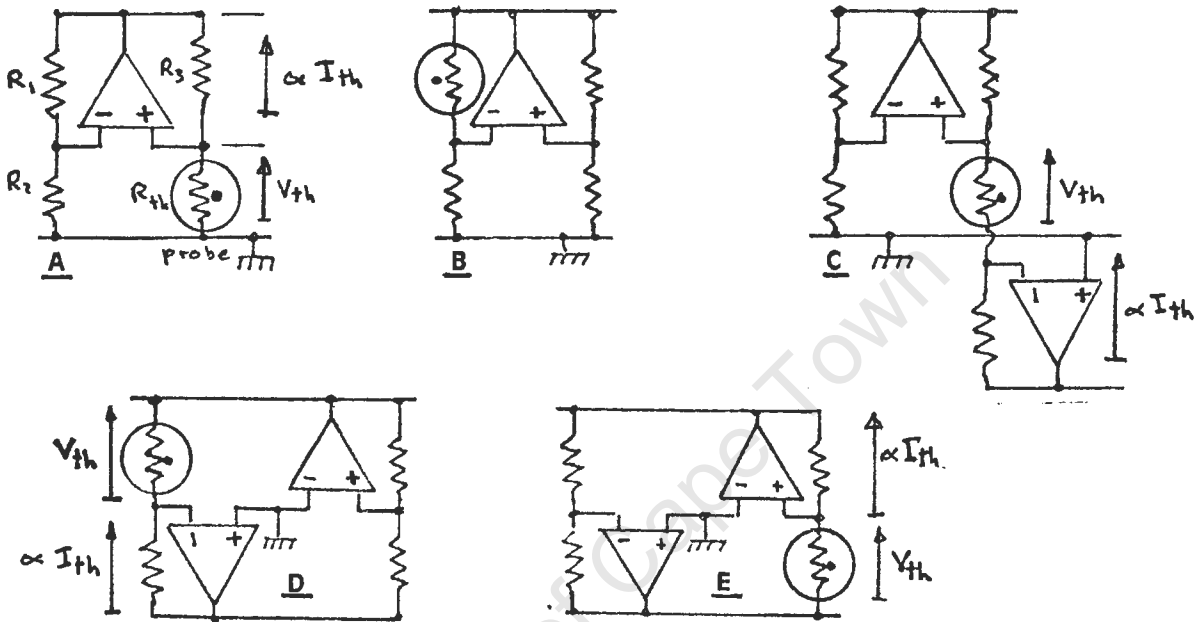


**FIG5.61**  
**TRANSFORMERLESS**  
**INVERTER**

Notes : Feedback via the 18 V zener adjusts the mark-space ratio of the multivibrator to stabilize the positive output. The 1K2 resistor bootstraps the drive to the buffer transistors improving efficiency by driving the 2N2219's further into saturation. A short circuit from any output to earth will destroy 2 of the transistors.

Bridge Circuitry

Different configurations for self-balancing constant-temperature bridge circuits are possible :-



In these circuits with zero output from the operational amplifiers, the positive feedback exceeds the negative feedback. Under these conditions the output from the amplifier rises until the thermistor's resistance drops<sup>x</sup> sufficiently for the negative feedback to equal the positive feedback i.e.

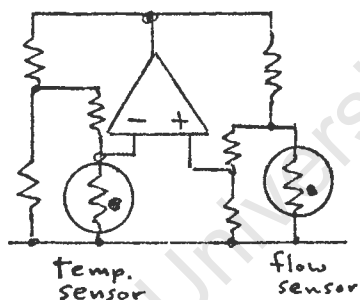
$$R_{th} = \frac{R_2 R_3}{R_1}$$

The thermistor is maintained at constant resistance and hence at constant temperature.

Circuit A has the advantage that one side of the thermistor is grounded making probe construction simpler and reducing noise problems. However, circuits C and D and E offer ground referred signals for the multiplier. Circuits D and E also make lower demands on the C.M.R.R. of the amplifiers. One problem with the dual-amplifier bridge circuits D and E is that the saturation<sup>x</sup> due to self dissipation

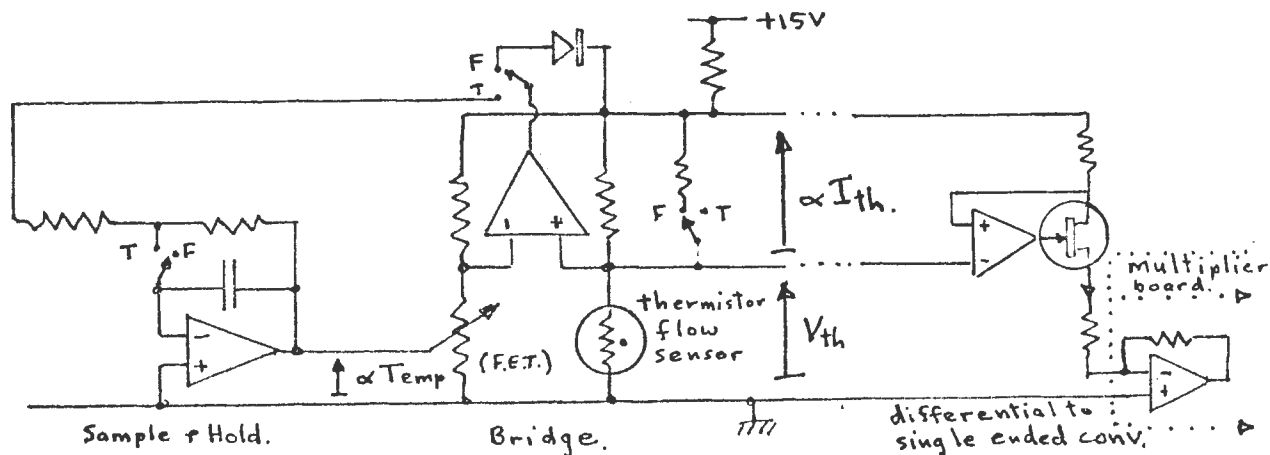
characteristics of the amplifiers do not match on negative and positive outputs and, depending on the choice of resistance values, latch conditions at switch-on are likely to occur unless clamping circuitry is added. After constructing both dual and single amplifier designs, circuit A was finally used because of the advantages of having one side of the thermistor grounded.

Temperature-compensating the bridge so that a constant-temperature-difference is maintained requires an additional thermistor probe. The simplest way of achieving this is to use a thermistor for  $R_2$  with a very much larger resistance than the flow sensor so that self dissipation is small and the second sensor does not sense flow. This requires a thermistor with exactly the same incremental temperature coefficient as the flow sensor but with at least 100 times the resistance. Obtaining such thermistors is a problem. A better method is to use two similar thermistors with the voltage to the temperature sensor reduced by a resistive divider. It can be shown that the temperature compensation



offered by these methods is not complete because of the thermistor's resistance-temperature characteristics. The compensation is adequate for a restricted temperature range.

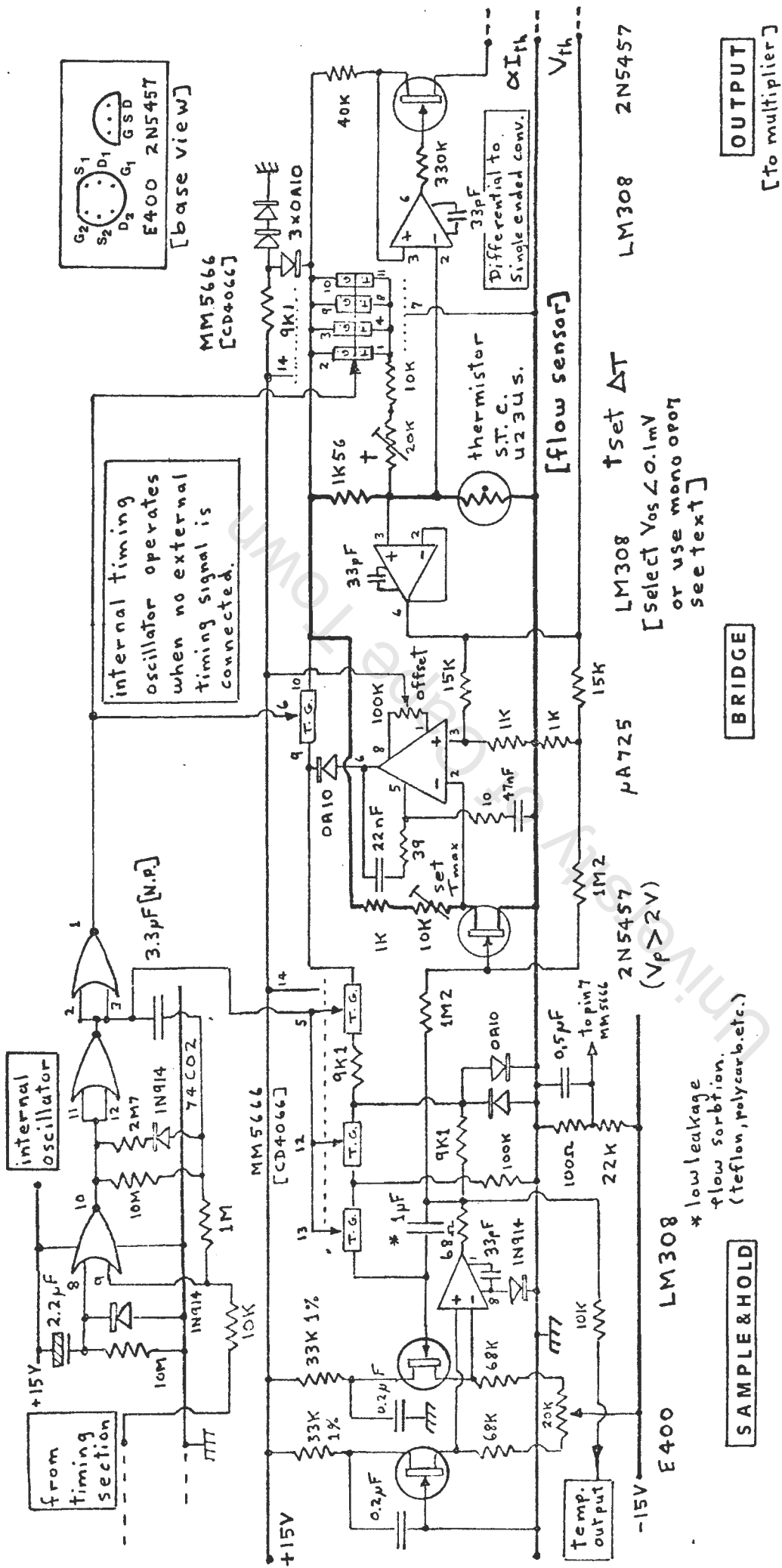
The final circuit (fig. No.5.71) designed does not use two sensors but a single sensor which is alternately used to measure temperature and flow. A field effect transistor is used as voltage-controlled resistance replacing the temperature-sensing thermistor. A grossly simplified diagram is shown here :-



In the temperature measure mode the voltage across the thermistor is small minimizing self heating. (Current to the bridge under this condition comes from the positive rail.) The output from the bridge amplifier is connected via the sample/hold to the F.E.T.'s gate adjusting the F.E.T.'s resistance until the bridge balances. In the flow measure mode the voltage at the gate of the F.E.T. is maintained constant by the sample/hold and the bridge is unbalanced by switching in a resistance in parallel with one of the bridge resistors. Feedback round the op-amp then maintains the temperature of the thermistor constant. The diode shown in the diagram is necessary to ensure the amplifier output is always positive after switch-on since the circuit has two possible stable states with either a positive or a negative output depending on transient conditions at switch-on. The original design used a cadmium sulphide photo-cell and L.E.D. for the temperature-compensating voltage controlled resistance. This was found totally unsatisfactory due to the self dissipation of the photo-cell changing its resistance. The F.E.T. voltage-controlled resistance finally used was "linearised" by reducing maximum voltage across the F.E.T. with a resistive divider and applying feedback from the drain to gate. This introduced problems because the voltage across the bridge is very small in the temperature mode and the voltage to the op-amp input is then attenuated by a factor of fifteen. Thus a very low drift low offset op-amp is required. A carefully nulled 725 op-amp was used in this position but a better choice would be the laser-trimmed monolithic precision mono OP-07. The 308 used in the bridge as a buffer should also be selected with an offset of less than 0,5 mV (or a mono OP-07 could be used here  $V_{os} < 27 \mu V$ ). The attenuation could probably be reduced since the final linearity of the F.E.T.-resistance was found to be extremely good. ( $\Delta R < 1\%$  for  $V_{ds}$  from 0 to 1,6 Volt.) The F.E.T. used in this position should have as large a value of  $V_p$  as possible combined with as high an  $R_{ds(on)}$  as possible (i.e. a low  $I_{dss}$ ). Unfortunately the joint distribution of  $I_{dss}$  and  $V_p$  for FETS usually results in high  $V_p$  devices

having low  $R_{ds(on)}$  (high  $I_{dss}$ ). The F.E.T. specified has a fairly accurate square law characteristic making linearisation reasonably accurate despite the low value of  $V_p$ . Feedback from the drain to gate was applied between a point at the same potential as the drain to avoid upsetting bridge balance at very low voltages. (See fig.5.71.)

The sample-and-hold circuitry (fig.5.71) achieves a low drift rate of 3 mV/minute at room temperature. To achieve this figure low leakage capacitors, teflon standoff insulators and F.E.T. buffered op-amp were used. The drain-gate leakage of the F.E.T. buffer is substantially reduced by operating with a low drain to gate voltage (See Siliconix data book, 1974.) Low resistance quad CMOS switches are used for switching. The 100 K resistive "clamp" to ground between two of the switches reduces the voltage across the CMOS switch minimising leakage to the hold capacitor. A number of clamp diodes around the CMOS switches are necessary to avoid latch conditions which occur at switch on.

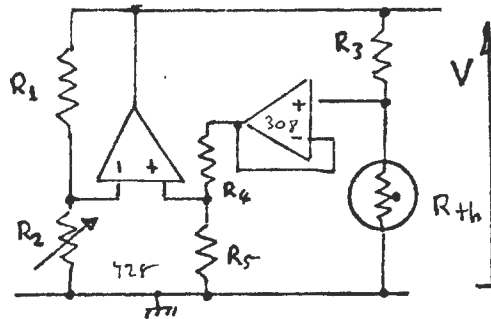


**FIG 5.71  
BRIDGE  
CIRCUITRY**

## SECTION 6

6. Temperature Compensation Calculations

Consider the simplified bridge circuit shown :-



At balance the inputs to the 725 are equal.

Hence -

$$V \left( \frac{R_2}{R_1 + R_2} \right) = V \left( \frac{R_{th}}{R_3 + R_{th}} \right) \left( \frac{R_5}{R_4 + R_5} \right)$$

and rearranging -

$$R_{th} = \frac{R_3 R_2 (R_4 + R_5)}{R_5 (R_1 + R_2) - R_2 (R_4 + R_5)} \quad \dots\dots 6.11$$

Now, if the bridge is first balanced with  $R_2$  (i.e. in temperature mode) and a resistance is switched in parallel with  $R_3$  (i.e. in flow mode) so that  $R_3$  becomes  $R_3'$ , then  $R_{th}$  changes to  $R_{th}'$  due to self heating and rebalances the bridge.

Rewriting the balanced condition equation (6.11) for the second case and then combining the equations :

$$\frac{R_{th}'}{R_{th}} = \frac{R_3'}{R_3} \quad \dots\dots \quad \dots\dots 6.12$$

This equation shows the temperature compensation is perfect if the incremental resistance/temperature characteristic of the thermistor is a linear function of temperature.

The thermistor resistance/temperature characteristic can be approximated by the equation :

$$R_{th} = A e^{B/T} \quad \begin{array}{l} A, B \text{ constants} \\ T \text{ temperature in } ^\circ K \end{array} \quad \dots \dots 6.13$$

Measurements on the S.T.C. thermistor (U 23US) from 22°C to 42°C showed that this law was obeyed within the accuracy of the measuring equipment ( $\approx 0,2\%$ ). The constant A depends on the particular thermistor used (tolerance is of the order of 10% for unselected thermistors) while B is quoted as 2900 for this thermistor.

Since the thermistor law is not linear temperature compensation will not be perfect. We can calculate the errors introduced into measuring the power injected if we calculate the change in temperature difference probe to tissue set up by this temperature compensation system for a range of temperatures. Power injected will vary directly with  $\Delta T$ .

Assume the tissue temperature is  $T_2$  and probe temperature  $T_1$  ( $T_1 > T_2$ ) and at another tissue temperature  $T_4$  probe temperature is  $T_3$  ( $T_3 > T_4$ ).

Corresponding thermistor resistances are  $R_{T_2}$ ,  $R_{T_1}$ ,  $R_{T_4}$ ,  $R_{T_3}$  respectively.

From 6.12 and 6.13

$$\frac{R'_{th}}{R_{th}} = \frac{R_{T_1}}{R_{T_2}} = \frac{R_{T_3}}{R_{T_4}}$$

and  $\frac{Ae^{B/T_1}}{Ae^{B/T_2}} = \frac{Ae^{B/T_3}}{Ae^{B/T_4}}$  which simplifies to

$$\frac{1}{T_1} - \frac{1}{T_2} = \frac{1}{T_3} - \frac{1}{T_4} \quad \dots \dots 6.14$$

or  $\frac{T_1 T_2}{T_1 - T_2} = \frac{T_3 T_4}{T_3 - T_4}$

(Notice that the temperature compensation is independent of the actual resistance value of the thermistor and is hence unaffected

by thermistor ageing which can be a serious problem with microbead thermistors.)

Using equation 6.14 the percentage change in  $\Delta T$  was calculated for a range of temperatures around  $37^{\circ}\text{C}$ . (Table 6.11)

$T_1$	$\Delta T$	% change in $\Delta T$ from value at $37^{\circ}\text{C}$
42	2.582	3.26
41	2.566	2.60
40	2.549	1.95
39	2.532	1.30
38	2.516	0.64
→ 37	2.5	-
36	2.48	- 0.65
35	2.47	- 1.29
34	2.452	- 1.93
33	2.436	- 2.57
32	2.420	- 3.21

Table 6.11

It appears that the error introduced by the temperature compensation system is small for a limited range of temperatures. However, it should be noted that the error is larger than this since it is the change in thermal conductivity which is measured. If the probe is placed in a position where the percentage change in injected power (i.e. thermal conductivity increment) is small, the error will be very much larger.

In the liver for an "average" placement the actual error might be two to three times that indicated in the table. <sup>x</sup> Slightly better temperature compensation can be obtained by switching yet another resistance into the bridge circuit (in series with the F.E.T.'s drain - fig.5.71). A better way would probably be to record the sample and hold output simultaneously with the multiplier output and apply a small correction factor later if precise results are required.

x (based on Hensel's results)

Summary The temperature compensation used in the equipment designed provides temperature compensation independent of the thermistor's actual resistance, eliminating errors due to thermistor ageing and making different probes electrically interchangeable. Thermistor ageing appears to be a fairly serious problem with other systems since one of the leading suppliers of precision thermistors (Yellow Springs Instruments) will not at present supply hypodermic-mounted thermistors because of the difficulty of manufacturing microbead thermistors with a good long-term drift performance. Temperature compensation is adequate provided the thermal conductivity increment to be measured is not too small. Other temperature-compensation schemes for thermistor bridge circuits will have inherent errors of the same order of magnitude.

SECTION 77. Experimental Work

Experimental work reported here is fairly limited and is largely of a qualitative nature. This was due both to lack of time and to my lack of knowledge of physiology which meant I was not able to set up in vitro experiments for calibration tests on isolated organs.

Tests were carried out at the University of Cape Town's Medical School with facilities kindly organised by Dr Rosemary Hickman. The first tests performed were to assess practical problems in using the equipment. The probe was used on a number of rats under deep ether anaesthesia. The probe was introduced either into the kidney or the liver. The probe was found to be unsatisfactory for use on the kidneys due to the small size of the kidneys used (A number of the rats were not fully grown) and a smaller probe needle would be an improvement. In the liver the probe produced much more reproduceable results although again a smaller probe would have been much easier to use.

Where the probe was used a number of times in the same liver readings were similar from site to site although bleeding due to probe damage soon caused this to drop off. Temperature changes did sometimes cause artifacts especially at death when the temperature dropped rapidly to room temperature. The equipment at this stage had a time from one temperature check to the next of about 40 secs and this was subsequently shortened to 16 secs to reduce artifacts due to rapid temperature changes.

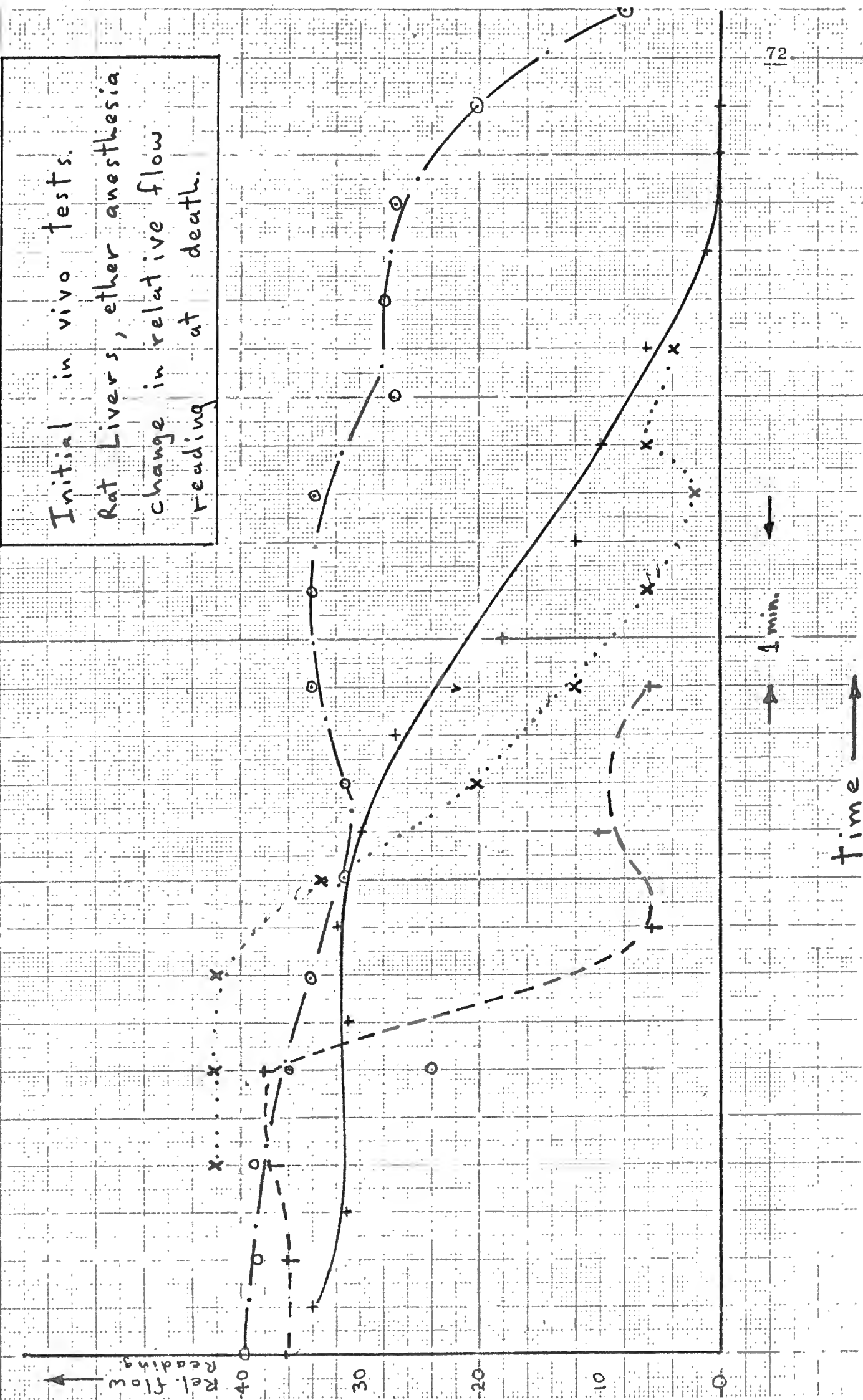
Results of these tests (Graph 7.11) show how the thermal conductivity increment changes at death for a number of different rats. According to Grayson's findings ether anaesthesia causes a large reduction in flowrate through the liver.<sup>37</sup>

A single experiment subsequently produced results with more spread which showed a large fluctuation in flowrate over a period

of about six minutes with a similar final reduction of flowrate at death.

Another experiment was performed on a pig where the probe was placed in the kidney. Blood flow was stopped by occluding the renal artery. Results were poor with only small changes of thermal conductivity indicated by the flowmeter. Artifacts could be introduced when a blower heater was used to warm the operating table. (The experiment was carried out using the 40 sec. period between temperature corrections, so this should be less of a problem with the 16 sec period subsequently used.) Grayson also reported worse results using his probe in the kidney. A rough measurement of the blood flow through the renal artery at the end of the experiment was obtained by briefly bleeding the animal. The indicated flowrate was found to be rather slow at about 75 ml/min. This corresponds to a perfusion rate of about 1.1 ml/gm tissue per minute. A practical problem encountered was that R.F. from the cauterizing equipment caused small changes in the displayed output.

Initial in vivo tests.  
 Rat Livers, ether anesthesia  
 change in relative flow  
 reading at death.



ACKNOWLEDGMENTS

The author would like to acknowledge :

Professor L. Besseling,  
Department of Electrical Engineering,  
University of Cape Town,

and

Dr Rosemary Hickman,  
Liver Research Unit,  
Department of Medicine,  
Groote Schuur Hospital,  
Cape Town,

for help and advice and

the Research Committee,  
University of Cape Town,

for financial assistance.

Also my mother for typing  
this manuscript.

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