DISCUSSION

The Sixth Symposium on Underwater Physiology (1978) acknowledged the importance of inert gas exchange in shortening decompression time by devoting an entire section of the proceedings to this topic, entitled "Inert Gas Transport: Reduction of Decompression Time". Of the numerous procedures attempted by various investigators (Bond et al., 1978; Cabarrou et al., 1978) the most successful in enhancing inert gas exchange and reducing decompression time was noted by Fife et al. (1978). These authors designed decompression schedules with deeper initial decompression stops (smaller initial pressure reduction step) and obtained shortened overall decompression time. They recognized that the presence of bubbles would impair inert gas elimination, and postulated that the absence of bubbles as a result of the deeper first decompression stop in their experiments with the pig, would be facilitatory to inert gas elimination. Consequently, decompression time decreased.

Inert gas exchange at the tissues and clearance from the lungs (Jones, 1951; Katy, 1951; Farhi, 1967) are principally perfusion limited processes. Therefore, alterations in cardiac output and/or its regional distribution should markedly affect inert gas elimination from the body. Balldin (1970) and Balldin and Lundgren (1972) have observed increased nitrogen clearance from the lung in men exposed to increased ambient temperature and head-out water immersion. Bove et al. (1978) have demonstrated an increased lung clearance of Xe-133 during general body heating of the rabbit.
These increases in gas elimination have been attributed to specific hemodynamic changes, principally cardiac output. Benefits from such maneuvers were evidenced by Balldin (1973b) when he showed that men who had breathed oxygen for 25 minutes at 1 ATA while immersed in warm water had a lower incidence of bends when exposed to 0.2 ATA in an altitude chamber than if they breathed oxygen for 25 minutes when sitting in a neutral air temperature of 25°C. Application and/or benefit from such maneuvers during decompression after hyperbaric exposures are unknown at present.

In addition to an increased clearance of inert gas from the lung during heating, transcutaneous diffusion of inert gas across the skin also increases (Benhke and Willmon, 1941; Klocke et al., 1963; Sejrsen, 1968). Transcutaneous transfer of inert gas is a diffusion-limited process, however, it is subject to modification by changes in blood flow. Increased blood flow, such as by increasing ambient temperature, facilitates the diffusion by enlarging the capillary surface area for diffusion, and by reducing the diffusion path as more capillaries open up, the latter being more important since the ultimate limiting surface is the skin, which is not changing, and not the capillary surface area (Monash and Blank, 1958; Matoltsy et al., 1962; Sejrsen, 1968). Cutaneous transfer of inert gas, though small, nevertheless is important in some special applications, such as nitrogen washout procedures. Since inward diffusion of nitrogen can exceed the washout rate from the "slow compartment", breathing oxygen alone without regard to the
ambient gas compositions cannot achieve a complete washout (Groom et al., 1974). This property of inert gas exchange is currently under-utilized in decompression procedures.

As previous investigators have indicated, enhancement of inert gas elimination and subsequent reduction in decompression time could be accomplished by an increased cardiovascular activity. The results of this study, as illustrated in Figure 21, demonstrate that whole body inert gas elimination in the rat is linearly correlated with cardiac output. The washout of inert gas from individual tissue compartments, slow ($k_1$) and intermediate ($k_2$), were also linearly related to cardiac output (Figures 24 and 25). In addition, the rate of cutaneous diffusion of inert gases, rose exponentially with increases in skin blood flow (Figure 31). In effect, total body inert gas elimination, respiratory and transcutaneous, was markedly enhanced under conditions of increased blood flow.

I. Functional Relationship Between Inert Gas Elimination and Cardiac Output

The functional relationship between nitrogen elimination and cardiac output can be described by the regression coefficient (slope) of the calculated regression line (Figure 21). From the design of these experiments, cardiac output can be defined as the independent variable while inert gas exchange represents the dependent variable. However, since both $Q$ and $V_{N2}$ are subject to experimental error, the estimates of the slope of this relation are
biased when general linear regression procedures are utilized (Sokal and Rohlf, 1981). Statistical strategies for showing the optimal functional relationship of two variables under these conditions are unclear, however, various methods are available. Of the available procedures, the method of calculating a geometric mean square regression (or reduced major axis) equation has been preferred on both theoretical and empirical grounds by Richer (1973). However, the regression lines calculated by both simple linear and geometric mean regression procedures are very similar when the correlation coefficient (r) of the relationship exceeds 0.800 (Sokal and Rohlf, 1981).

Linear regression analysis of the $V_{N2}$ versus $Q$ produced an r value of 0.573, therefore, geometric mean procedures were used to describe the functional relationship. Figure 37 compares the relationship between $V_{N2}$ and $Q$ as described by both simple linear and geometric mean regression procedures. This plot illustrates that $V_{N2}$ increased 2.5 ml/kg·2 hrs for every 100 ml/min·kg increment in $Q$. More simply, for a 40% increase in $Q$ (300 to 420 ml/min·kg) $V_{N2}$ will increase 40% (7.8 to 10.9 ml/kg·2 hrs). This relationship fits well into the theoretical analysis presented by Farhi (1967) and Kety (1951) and supports the concept that promotion of inert gas elimination is primarily dependent on perfusion processes.

In a perfusion limited system, whole body nitrogen washout represents the weighted average of gas elimination from the various
Figure 37

Functional relationship between cardiac output ($Q$) and the volume of nitrogen eliminated ($V_{N2}$) from the rat in 2 hours of $O_2$ breathing, as described by simple linear regression analysis (---) and by mean geometric regression procedures (----).

These relationships are expressed as follows:

Linear $V_{N2} = 5.230 + 0.0142Q$, $n=40$, $r=0.573$, $p<0.01$

Geometric $V_{N2} = 0.317 + 0.0250Q$, $n=40$, $r=0.569$, $p<0.01$
NITROGEN ELIMINATION, ml/kg in 2 hrs.

\[ \dot{Q}, \text{ml/min} \cdot \text{kg} \]
tissues. The fundamental equation describing gas exchange at the tissue level states that the gas tension \( (P_t) \) within the tissue is proportional to the gas tension in the blood \( (P_b) \) as shown below:

\[
P_t = P_b (1 - e^{-kt})
\]

And:

\[
k = \frac{(a_b \times F_t)/(a_t \times V_t)}{}
\]

where \( a_b \) and \( a_t \) are the solubilities of inert gas in the blood and tissue, respectively; \( F_t \) is the blood perfusion rate to the tissue and; \( V_t \) is the volume of the tissue. Consequently, factors which influence \( k \) will alter tissue washout of inert gases. If \( a_b \), \( a_t \) and \( V_t \) are assumed to be constant then the limiting factor for inert gas exchange becomes blood flow.

In analysis of the kinetics of whole body inert gas exchange, the process can be described by 3 major compartments, the slow \( (k_1) \), intermediate \( (k_2) \) and fast \( (k_3) \). Each compartment rate constant represents that group of tissues whose mean \( k \) value is equal to the measured rate constant for that compartment. Whole body inert gas exchange can be described as the sum of the washout from each of these compartments, as given below:

\[
V_{N2} = A_1 (1-e^{-k_1t}) + A_2 (1-e^{-k_2t}) + A_3 (1-e^{-k_3t})
\]

In this equation, it is important to note that \( V_{N2} \) represents the capacity of the system, while the rate constant \( (k_1) \) reflects the rate of desaturation at any given time. \( A_1 \) is the total inert gas store for the respective compartment, as defined by multiplying the tissue volume by the inert gas solubility \( (a) \). Since each
compartment may consist of a number of different tissues, the value for the compartment inert gas storage capacity becomes the weighted average of all the tissue volumes and their respective inert gas solubilities. Each compartment can then be described by an "apparent" compartment volume and/or inert gas solubility coefficient; "apparent" referring to the fact that this value is not constant for a given compartment but is dependent on the composition of the tissues comprising that compartment. A change in the composition of the compartment may occur as the result of a redistribution of cardiac output away from or towards that particular compartment.

The composition of the compartments as described by the classical exponential stripping analysis has not been clearly identified by previous investigators (Jones, 1951; Pearl et al., 1965; Groom et al., 1974). However, based upon the characteristics of tissue blood flows and the solubility coefficients the following general distinction can be made for each compartment, during normothermic conditions. The slowest compartment should represent the most homogeneous compartment containing mainly adipose tissue (Jones, 1951) but may contain some a vascular tissue, such as tendon, cartilage, or vitreous body of the eye (Hempleman, 1982). The intermediate compartment is most likely a combination of poorly perfused lean tissue (resting skeletal muscle and skin) and highly perfused fatty tissue (Pearl et al., 1965). The fast compartment consists mainly of highly perfused lean tissue (viscera).

Using equation 9, with the rate constants set based upon
compartment blood flow and the apparent tissue volume and solubility coefficients held constant, then whole body inert gas elimination can be calculated as a function of the total cardiac output and the percentage flow to the slow compartment (Figure 38). As Figure 38 illustrates, if total flow is increased from 100 to 150 ml/min, but the slow compartment flow decreases from 4 to 2% of the total cardiac output, then the total volume of inert gas eliminated at the lungs will decrease. This analysis illustrates the importance of shifts in regional blood flow distribution on the process of whole body inert gas washout.

This type of analysis may be taken one step further to illustrate the effect of changes in blood flow and apparent tissue volume on the measured rate constants. From Figure 24, $k_1$ can be set at a value of 0.0031 when cardiac output is 200 ml/min·kg. In Figure 39, if apparent tissue volume is held constant ($V_t = 1.0$) and blood flow allowed to increase as a constant fraction of cardiac output, then the $k$ value would reach a level of 0.0077 at a cardiac output of 500 ml/min·kg. This predicted value was not significantly different from the $k$ value of 0.009 actually observed (Figure 24). However, under similar blood flow conditions, if the apparent tissue volume is allowed to vary in either direction, the predicted value for $k_1$ is markedly affected by the change in compartment volume (Figure 39). The measured $k$ value as described in equation 8 is, therefore, not only affected by changes in blood flow but also by alterations in apparent compartment tissue volumes and/or inert gas solubility coefficients.
Figure 38
The influence of changes in cardiac output (Q) and slow compartment blood flow, as a percentage of $Q$, on the volume of nitrogen eliminated over a 2 period of $O_2$ breathing.
Calculations are based upon equations 8 and 9 on page 154 of the text, with compartment tissue volumes and inert gas solubilities held constant.
Figure 39

The interaction of changes in cardiac output ($\dot{Q}$) and apparent compartment volume ($V_t$) on the measured slow compartment rate constant, $k_1$. Compartment volumes are given relative to the control condition ($V_t=1.0$) where $V_t$ was held constant while $\dot{Q}$ was allowed to increase. Calculations are based upon equation 8 within the text while the initial conditions ($k_1=0.0031$ at $\dot{Q}=200$ ml/min/kg) were derived from the regression line in Figure 24 relating $k_1$ to $\dot{Q}$. 
Groom et al (1974) clearly illustrated that the effect of anesthesia on nitrogen washout in the dog was to decrease the slow compartment rate constant by 21%; however, the blood flow to that compartment was increased 68%. In this case the estimated slow compartment volume had doubled in the anesthetized dog as presumably the result of a redistribution of blood flow. In effect, blood flow to the slow compartment was greater for the anesthetized animal yet the respective rate constant was slower. These data follow the analysis presented in Figure 39. Such dramatic shifts in blood flow are not expected to occur under the present experimental conditions. However, a characteristic redistribution of cardiac output should accompany each treatment.

Considering all experimental conditions, the rate of inert gas washout from the slow compartment was linearly correlated with \( Q \) (Figure 24). This relationship was predictable based upon the blood-tissue inert gas exchange equation (Equation 8), when all factors except blood flow were held constant. The intermediate compartment washout rate constant demonstrated a similar linear relationship with measured \( Q \) (Figure 25). In general, increased cardiac activity enhanced inert gas clearance from the lung and more importantly from the intermediate and slow tissues of the rat. Promotion of inert gas exchange in this manner should lead to a reduction in decompression time. The effect of the various treatments on the slope of the \( k-Q \) relationship are discussed later in their respective sections.
II. Functional Relationship Between Skin Blood Flow and Cutaneous Diffusion

Cutaneous transfer of inert gas, though small, was modified markedly by changes in skin blood flow (Figure 31). In a cool environment where blood flow was low, the conductance was about 30 ml of helium or nitrogen /hr/m²/atm. This was doubled when cutaneous perfusion increased from 15 ml/min/100 ml of tissue to near 40. This means that at a moderate ambient temperature (37°C) the total body store of nitrogen can be exchanged in about 15 hours just through the skin surface alone (Table 15). The rate of exchange is retarded to about 27 hours at lower ambient temperature (Table 15). In comparison, Groom and Farhi (1967) reported 24 hours for total replacement of the entire body nitrogen store for anesthetized dogs weighing between 15 and 33 kg. Helium stores are considerably smaller than the N₂ stores (Table 16) and the replacement time, via cutaneous diffusion, at a skin temperature of 31°C, is only 6.0 hrs. This time decreases to 4.2 hrs. during exposure to high ambient temperatures.

Elevation of skin temperature and thus the skin blood flow appears to be an effective and simple means of promoting elimination of inert gases through the skin. Doubling the rate of gas elimination is possible simply by increasing blood flow. During a prolonged decompression procedure favorable results may be derived by promoting gas exchange through the skin.
Table 15

Estimate of total replacement time for the body nitrogen stores

<table>
<thead>
<tr>
<th>Measurements &amp; Estimates</th>
<th>31</th>
<th>33</th>
<th>35</th>
<th>37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow, ml/min/100 cc</td>
<td>11.8</td>
<td>16.3</td>
<td>22.5</td>
<td>31.1</td>
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<tr>
<td>Conductance, ml STPD/hr/m²/atm</td>
<td>29.1</td>
<td>33.8</td>
<td>40.3</td>
<td>51.5</td>
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<td>Total diffusion, ml STPD/hr/atm</td>
<td>51.8</td>
<td>60.1</td>
<td>71.7</td>
<td>91.7</td>
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<tr>
<td>N₂ Store, 22 ml/kg/atm</td>
<td>1,386</td>
<td>1,386</td>
<td>1,386</td>
<td>1,386</td>
</tr>
<tr>
<td>Total Replacement Time, hr</td>
<td>26.8</td>
<td>23.1</td>
<td>19.3</td>
<td>15.1</td>
</tr>
</tbody>
</table>

Skin temperature in °C, body surface area = 1.780 m², body weight = 63 kg.
Table 16
Estimate of total replacement time for the body helium stores

<table>
<thead>
<tr>
<th>Measurements &amp; Estimates</th>
<th>Skin Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31</td>
</tr>
<tr>
<td>Blood flow, ml/min/100 cc</td>
<td>14.1</td>
</tr>
<tr>
<td>Conductance, ml STPD/hr/m²/atm</td>
<td>31.7</td>
</tr>
<tr>
<td>Total diffusion, ml STPD/hr/atm</td>
<td>56.4</td>
</tr>
<tr>
<td>He Store, 5.4 ml/kg/atm</td>
<td>341</td>
</tr>
<tr>
<td>Total Replacement Time, hr</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Skin temperature in °C, body surface area = 1.780 m², body weight = 63 kg.
III. Effect of Isoproterenol on Inert Gas Exchange

Isoproterenol infusion increased cardiac output as a result of its direct action on the heart. This could be seen by the increase both in HR rate and SV resulting in the observed 30% increase in cardiac output (Table 6). The potent $\beta_1$ and $\beta_2$ agonist activity of isoproterenol should also result in a generalized vasodilation in both the skeletal muscle and adipose tissue (Lans et al., 1967; Rosell, 1979). A generalized vasodilation was demonstrated by the large decrease in TPR (37%) during isoproterenol infusion (Figure 17). The combination of increased total flow and vasodilation should result in increased flows to both of these regions. Goldman (1966) has previously demonstrated that in unanesthetized rats the fraction of total cardiac output perfusing muscle and adipose tissue was unchanged during infusion of low doses of epinephrine (0.5 ug/kg). Wickler et al. (1984), using anesthetized rats, found large increases in brown adipose tissue blood flow in response to an isoproterenol infusion of 12.5 ng·g$^{-0.74}$·min$^{-1}$. This represents a dose of 0.173 ug/kg/min for a 350 g rat. Because of the presence of anesthesia these distribution data may not represent that seen in the awake rat. Therefore, it is most likely the regional blood flow to muscle and adipose tissue is expected to increase in proportion to cardiac output as predicted from Goldman's data (1966).

The present investigation studied inert gas elimination while breathing 100% O$_2$. Breathing oxygen at 1 ATA under normothermic
conditions produces a reduction in HR and Q (Daly and Bondurant, 1962; Kenmure et al., 1972; Kioschos et al., 1970; Whitahorn, Edelman, and Hitchcock, 1946). Also reported is vasoconstriction, leading to increased systemic and regional vascular resistance (Cassuto and Farhi, 1979; Daly and Bondurant, 1962; Egger et al., 1962). Breathing oxygen at 1 ATA has been observed to result in a reduction of flow to many tissues, including kidney, muscle, and fat (Hansen and Madsen, 1973; Reich et al., 1970). Contrary to this, Plewes and Farhi (1983) have demonstrated quite clearly using radiolabelled microspheres that during acute hyperoxic exposures blood flow to skeletal muscle and adipose tissue of the anesthetized dog is unchanged.

The magnitude of the increase in tissue blood flow seen during isoproterenol infusion, therefore, will be the net result of the regional interaction of isoproterenol and hyperoxia. Flow to muscle and adipose tissue, under the present experimental conditions, should not be greatly effected by the presence of hyperoxia and should increase in proportion to the cardiac output as predicted by Goldman's (1966) data.

Under the assumptions of a perfusion limited model for inert gas exchange, the volume of nitrogen cleared from the tissues and the lung should increase in response to elevated blood flow. Isoproterenol increased total flow to the lung by 32% but this resulted in only a 10% increase in the volume of nitrogen eliminated over the two hour washout with 100% O₂. This volume, although
significantly greater \( p < 0.01 \) than for the normothermic-control group, was smaller than anticipated. The fact that only a modest increase in \( VN_2 \) (10%) was associated with a 30% increase in cardiac output suggests an overperfusion of tissues with short half-times and low \( N_2 \) content. As illustrated in Figure 20, the total volume of inert gas eliminated over a two hour washout period was independent of \( Q \) for the isoproterenol infused rats. Considering the analysis presented earlier for Figure 38 this result would have been expected for high flow conditions (cardiac output between 150 and 200 ml/min) when blood flow to the slow compartment is in excess of 2% of the total cardiac output. During isoproterenol infusion similar blood flow conditions should exist and contribute greatly to the observed relationship between \( V_{N2} \) and \( Q \) in Figure 21.

The method utilized for analysis of inert gas exchange provided for the compartmentalization of whole body inert gas washout into three components. In these experiments the observed increase in the mean compartment rate constants, \( k_1 \) and \( k_2 \), in response to isoproterenol infusion were similar to those predicted by the tissue gas exchange equation (Equation 2). As illustrated in Figures 24 and 25, \( k_1 \) and \( k_2 \) demonstrated a significant linear correlation with the measured flow. The \( k_2 - Q \) relationship (Figure 25) contained more scatter in the data than did the \( k_1 - Q \) relationship (Figure 24). This may be due to the non-homogeneity of the intermediate compartment leading to an interaction of changes in
both $Q$ and $\alpha_r$ during isoproterenol infusion. Interestingly, Jones (1951) demonstrated a similar finding in man when attempting to enhance inert gas washout with the use of exercise. In his experiments, exercise, which is known to increase skeletal muscle blood flow by 20-30 fold, could only produce a maximal 3 fold increase in the rate constant.

Isoproterenol infusion increased the rate of inert gas washout from the slow compartment by decreasing the half-time by 27 minutes from 105 to 78 minutes. A small reduction in the intermediate compartment was also seen. The regression coefficient for the $k_1 - Q$ relationship was steepest during isoproterenol infusion. This suggests that a larger fraction of the increase in cardiac output is presented to the slower tissues during infusion of isoproterenol than with the other treatments, representing a more efficient washout. These responses will accelerate inert gas clearance from the body but more importantly the decreased half-time of the slow compartment promotes washout from the slower, more limiting tissues.

IV. Effect of Hypothermia on Inert Gas Exchange

Hypothermia caused a reduction in $Q$ resulting from a decrease in HR (Figure 14, Table 6). During $O_2$ breathing the HR decreased further, but a compensatory increase in SV occurred (Figure 12) minimizing the drop in $Q$ (Table 9). The reduction in HR during hypothermia was 23 b/min/°C (Figure 12) which compares well with the 19 b/min/°C obtained by Bullard (1959). Popovic and Kent...
(1965) observed increases in SV of rats during the first 2 hours of induced hypothermia during oxygen breathing. Bullard (1959) demonstrated a small increase in SV during hypothermia in unanesthetized rats while breathing air. Because of the increase in SV during oxygen breathing and hypothermia, the difference in $Q$ between normothermic and hypothermic rats was minimized. Cardiac output was decreased minimally in the hypothermic group, but $V_{N2}$ was reduced significantly (Table 14). This apparent discrepancy may be the result of a redistribution of blood flow.

In a perfusion limited system, whole body nitrogen washout represents the weighted average of gas elimination from various body tissues. The regional blood flow represents the weighting factor. Consequently, factors which effect regional blood flow may also alter the whole body washout curve. Hypothermia, in the rat, causes a redistribution of blood flow away from the periphery and towards the core (Bullard et al., 1962). Many visceral tissues decrease flow in proportion to the cardiac output while tail skin, limb skin and limb musculature demonstrate significantly greater reductions (Bullard et al., 1962). Reduction in blood flow to subcutaneous fat and a subsequent decrease in $N_2$ washout are expected. During hypothermic conditions the volume of $N_2$ eliminated decreased 30% while mean $Q$ dropped only 8%. A marked reduction in muscle and subcutaneous fat blood flow could account for this response.

Hypothermia, with a marked reduction in total volume of inert gas eliminated showed no decrease in the slow compartment rate
constant. Alterations in the size and composition of the compartment as the result of the previously described changes in regional blood flow may have influenced the measured $k$ value. As shown in Figure 39, a reduction in flow in combination with a decrease in the apparent compartment volume results in no change in the calculated rate constant. In this case, the measured slow compartment rate constants during hypothermia were not significantly different from normothermic rats. The regression coefficient (slope) for the $k_1 - \dot{Q}$ relationship was greatest during isoproterenol infusion and least in the hypothermic rats (Figures 22-23). The slope of this relationship for the hypothermic rats reflects that for a given increment in $\dot{Q}$ a smaller portion of the cardiac output is available for desaturating the slower tissues. This probably the result of a reduction in subcutaneous fat blood flow during hypothermia.

Individual relationships for the intermediate compartment and cardiac output were not found to demonstrate any linear relationships (Figures 26-27). However, the pooled data (Figure 25) shows a significant linear correlation with $\dot{Q}$. The lack of significance on an individual treatment group level may be due to the non-homogeneous nature of the intermediate compartment leading to an interaction of changes in both $\dot{Q}$ and $\alpha$.

Discrepancies between the expected blood flow distribution and the measured rate constants may also be the result of problems associated with the exponential stripping method and its assumptions. Most importantly, because of the reduced volume of
nitrogen eliminated during hypothermia, 120 minutes of oxygen breathing may not have been sufficient to fully characterize the slowest compartment and therefore lead to an over estimation of $k_1$. Small errors in determination of the slowest rate constant can markedly effect subsequent rate constant determinations. This would result in values for $k_1$ and $k_2$ which would over estimate their true values. If this bias is present in all the measurements made during hypothermic conditions then it should not effect the slope of the $k_1$-$Q$ relationship seen in Figure 27. Therefore, the slope of this relationship still represents the decreased responsiveness of inert gas washout from the slow compartment tissues during increases in cardiac output. This may be a reflection of a reduction in the fraction of total cardiac output perfusing the slower tissues in response to hypothermia.

V. Effect of Hyperthermia on Inert Gas Exchange

Man (Rowell, 1974) and some animals (Hales and Dampney, 1975) respond to moderate hyperthermia (2-3°C above $T_{rec}$) by increasing $Q$ to meet the increased demand for skin blood flow. However, sheep (Hales, 1973) and baboons (Hales, Rowell and King, 1979) do not increase cardiac output in response to thermal stress but simply redistribute the available blood flow. The rat meets the demand of moderate hyperthermia with a small increase in $Q$ (Table 6). This response to elevated internal temperature is to some extent masked by the presence of a marked hyperoxic bradycardia. Heart
rate during air breathing for hyperthermic conditions was greater than for the normothermic conditions. The large bradycardiac response to hyperoxia during hyperthermia resulted in the mean HR for the rats in this treatment group to be less than that for the normothermic rats (Figure 14). Stroke volume increased in response to the oxygen breathing which offset sufficiently the bradycardia causing the mean hyperthermic \( \dot{Q} \) value to exceed the normothermic controls.

Despite these types of changes in HR and SV during oxygen breathing in the rat it is quite clear that a distinct linear relationship exists between \( \dot{Q} \) and rectal temperature during air breathing and oxygen breathing (Figures 7 and 12). The regression coefficient for this relationship, during oxygen breathing, was 12.6 \( \text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \cdot ^{\circ}\text{C}^{-1} \). This value is similar in magnitude but greater than Bullard's value of 8.8 \( \text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \cdot ^{\circ}\text{C}^{-1} \) (Bullard, 1962).

The rat, with a small increase in \( \dot{Q} \), appears to primarily utilize redistribution to meet the demand for increased skin blood flow. In doing so the expected redistribution pattern would be a decrease in renal and splanchnic blood flow (Rowell, 1974; Hales and Dampney, 1973; Hales, 1973; Hales, Rowell and King, 1979), an unchanged or reduced muscle blood flow (Rowell, 1974; Dextrey et al., 1972), and a decreased perirenal adipose tissue flow (Rowell, 1974). However, in the rat, the tail is a primary extremity in the control and regulation of body heat loss or gain (Raman et al., 1983). A large increase in tail blood flow is then expected during
hyperthermia. The decrease in $V_{N_2}$ during hyperthermia may be a result of this type of redistribution.

Alternatively, the $V_{N_2}$ seen during hyperthermia may be biased by the measurement procedures utilized in this study. As described previously in the methods section, the procedure for determination of nitrogen elimination requires an obligatory 5 minute chamber flushing period. During this time the chamber and the rats' lungs are brought into equilibration with the washout gas, 100% oxygen. In man, Jones (1951) has suggested a minimum of 5-10 minutes of normal breathing to rinse the lung spaces with oxygen. Hills (1978) who measured nitrogen washout in guinea pigs utilized a 5 minute flush period. Estimates on the volume of inert gas lost during this period of equilibration range from 30-50% of the total $N_2$ stores depending upon the $Q$ (Hills, 1978; Mack and Lin, 1984). It is expected that the volume missed during the initial 5 minutes during hyperthermic conditions will exceed that of normothermic controls (Mack and Lin, 1984). This bias, present in all measurements, will attenuate the volume of nitrogen eliminated in the hyperthermic rats between 5-120 minutes of $O_2$ breathing. This bias will also be present in all other measurements but the magnitude will vary depending upon the cardiac output.

As Table 14 illustrates, the slow compartment rate constant, $k_1$ during hyperthermia increased. However, it might have been expected that this value would decrease as predicted by the redistribution of blood flow away from the adipose tissue during
heating (Hales, 1973; Hales, Rowell and King, 1979; Rowell, 1974). It is likely that mean blood flow to this compartment has decreased, but in addition the compartment volume has also decreased leading to an increased k value. This would be analogous to Groom's (1968) data looking at anesthetized and unanesthetized dogs. The slope of the $k_1$-$Q$ relationship was similar to that of the normothermic animals, suggesting a similar responsiveness of the slow compartment blood flow and inert gas washout to changes in cardiac output in the two conditions.

VI. Effects of Skin Blood Flow on Diffusion of Inert Gases

Transpiration of gases through the human skin has been known for a long time. Fitzgerald (1956) has reviewed this topic in reference to $CO_2$ and $O_2$. However, cutaneous inert gas transport in either directions has received attention only recently (Benhke and Willmon, 1941; Groom and Farhi, 1974; Klocke, Gurtner and Farhi, 1963). The reason for the inattention was justified by the minute amount of the gas exchange through this route. The total cutaneous gas exchange of man falls within the error ranges in measuring pulmonary gas exchange. Demonstration of cutaneous transport of inert gas of low solubilities requires high resolution capability in detecting the minute gas concentration and the ability to exclude contamination (Groom and Farhi, 1974; Groom et al., 1974). The cutaneous transfer rate of nitrogen through the skin can exceed the washout rate from the slowest tissues after 5 hours of oxygen
breathing in air, in the dog (Groom and Farhi, 1967).

Diffusion limitation for transcutaneous inert gas exchange is apparent by comparing the gas delivered to and that diffused through the skin (Table 17). The relationship between blood flow and the skin temperature is known from this study. The blood flow to the hand ranged from about 3,000 ml/hr at 31°C to 7,000 ml/hr at 37°C. The volume of inert gas delivered to the hand is then computed by the product of blood flow, solubility coefficient, and Pa. The relationship between gas diffusion and the cutaneous blood flow is also known for this study. The volume of gas diffused across the skin amounted to only 2.25 to 3.4% of that delivered to the hand.

The diffusion distance can be estimated by taking the diffusion coefficient of gas in water and divided it by the permeability. The apparent diffusion distance for nitrogen decreased as skin temperature rose (Table 18). The same calculation is obtained for helium (Table 18).

The diffusion distance calculated in this manner may not mean very much. It depends a great deal on the diffusion coefficients assumed. The diffusion coefficients should be much smaller in tissue than that in water. But, by how much is not entirely clear. In any case, the relative changes should stand regardless of the diffusion values assumed.

The results of this study demonstrated a significant facilitation of inert gas diffusion through the human skin at elevated skin temperature and blood flow. Since the amount of gas
Table 17

Diffusion-Limited Gas Transport Through Human Skin

<table>
<thead>
<tr>
<th>Measurements &amp; Estimates</th>
<th>Skin Temperature</th>
</tr>
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<td>31</td>
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<tr>
<td>Blood Flow, ml/min/100 ml</td>
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<td>ml/hr</td>
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<tr>
<td>Gas delivered, ml/hr</td>
<td>26.56</td>
</tr>
<tr>
<td>Gas diffused, ml/hr/m²</td>
<td>21.50</td>
</tr>
<tr>
<td>ml/hr</td>
<td>0.91</td>
</tr>
<tr>
<td>% diffused</td>
<td>3.43</td>
</tr>
</tbody>
</table>

Skin temperatures in °C, hand volume = 392 ml and hand surface area = 0.0422 m².
Table 18
Estimates of Diffusion Distance of Inert Gases Through Human Skin

<table>
<thead>
<tr>
<th>Measurements &amp; Estimates</th>
<th>Skin Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31</td>
</tr>
<tr>
<td>N₂ D/h, cm/hr</td>
<td>0.2287</td>
</tr>
<tr>
<td>D in water, cm²/hr</td>
<td>0.0918</td>
</tr>
<tr>
<td>, cm</td>
<td>0.40</td>
</tr>
<tr>
<td>He D/h, cm/hr</td>
<td>0.3034</td>
</tr>
<tr>
<td>D in water, cm²/hr</td>
<td>0.1621</td>
</tr>
<tr>
<td>, cm</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Skin temperature in °C.
eliminated is much smaller than that which is transported to the skin by the blood flow (Table 17), the facilitation is not related to the increased supply of inert gas to the skin. Rather, the facilitation is most likely a result of increased diffusion areas (capillaries) and reduced diffusion path as more capillaries open up resulting from warming the cutaneous tissue. However, it is the available skin surface area that is limiting the transfer and not the surface at the capillaries (Serjesen, 1978). Therefore, the reduced diffusion length by capillary recruitment is the most important mechanism in facilitating transcutaneous gas transfer. This conclusion is substantiated by the estimates shown in Table 18 in which diffusion coefficients of gas in water were utilized. A much smaller value of diffusion distance should result if D values for cutaneous tissue were used. Such values were not available. However, relative changes in h will not be affected by the values of D assumed.

The calculated permeability (D/h) is positively correlated with skin blood flow. Helium exhibits higher D/h than that of nitrogen at a given blood flow (Figure 32). However, at a given blood flow there are no difference in gas conductance between the two (Fig. 31). A plausible explanation for this is the difference in solubilities between the two gases. Though D/h is higher in helium, α is higher for nitrogen making gas conductances (α)(D/h) similar. The values for D for N₂ and He are only different by 15%, therefore, considering the magnitude of experimental error involved, it is not possible to distinguish between the
conductance-blood flow relationships for He and $N_2$ (Figure 31).

The assumption that changes in finger blood flow during warming, as determined by venous occlusion plethysmography, reflect changes in skin blood flow is justified by results established by Dextry et al. (1972) and Johnson and Rowell (1974). They demonstrated in a resting subject that blood flow to underlying muscle remains constant by either direct or indirect surface heating under a variety of conditions. Warming of a small region of the body surface is not expected to alter core temperature of the body.

At a given internal body temperature, regional skin blood flow increases with skin temperature (Roberts and Wenger, 1979; Wenger et al., 1975). On the other hand, it is clear that forearm flow rises as a function of core temperature even if the skin temperature was clamped at a constant level (Nadel, Mitchell and Stolwijk, 1971; Stolwijk et al., 1977; Wenger et al., 1975). Therefore, blood flow is regulated (to a great extent) by the combined thermal conditions at the core and surface temperature (Wyss et al., 1974; Wyss et al., 1975). This explains why our blood flow values are lower than those reported by Aschoff and Wever (1957).

It is of interest however, that finger blood flow at a given ambient temperature was dependent on the gas mixture breathed (Figure 30). The slope of the BF-Tsk relationship for He was less than that for $N_2$. This could be explained by a lower core temperature associated with breathing He:O$_2$ gas mixture for longer than 30 minutes. Although rectal temperature was not measured in the cutaneous diffusion experiments, the literature predicts a
reduction in rectal temperature of 0.2-0.3°C when breathing heliox at 1 ATA for 60 minutes (Epperson et al., 1966, Rhoades et al., 1967). A decreased core temperature during local heating of the hand will influence the the cutaneous blood flow response to various skin temperatures (Wyss et al., 1974; Wyss et al., 1975).

VII. Body Temperature and Inert Gas Elimination

Rectal temperatures (Tr) during isoproterenol infusion were identical to those in the normothermic rats (Table 6). Exposure to a hot environment elevates body temperature in the rat by 2.9°C. It was depressed by 3.5°C in rats exposed to cold conditions. Skin temperature ranged from 31.2-37.6°C during the skin diffusion experiments. Within this temperature range, 31.2-39.0°C, the solubility of nitrogen would not be altered significantly. For example, nitrogen solubility reduces only 1.3% in olive oil when temperature rises from 15 to 37°C (Vernon, 1907). For a 3°C increase in water temperature (36-39°C), the amount of nitrogen dissolved in water decreased only 3% (Altmer and Ditmer, 1971). Changes of similar magnitude are seen in body temperatures of the rat exposed to cold in this experiment. The diffusion coefficient for nitrogen is expected to decrease only 6-8% over the range of body and/or skin temperatures studied (Altmer and Ditmer, 1971). Thus, the effect of thermal factors on whole body inert gas exchange or transcutaneous diffusion of inert gases will be of minimal importance, in comparison to blood flow. The major effect of
changes in body temperature, therefore, is to alter cardiac output (Figures 7 and 12) and its regional distribution (Figure 30).