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The research summarized in the report was conducted in a new Laboratory for Environmental Physiology, which was set up as a result of a THEMIS award. The document describes:

1) the facility, with its high pressure chamber, submergence basin, and man rated centrifuge;

2) a number of new methods, which were found useful in studying cardiovascular and pulmonary function;

3) results of investigations dealing with alveolar gas exchange, examining various facets of O_2, CO_2, and N_2 exchange, as well as transfer of inert tracer gases;

4) the interaction between convection and diffusion in respiratory gas exchange, with particular emphasis on the problems of diffusion of the inspired gas bolus in the pre-existing alveolar gas;

5) tissue gas exchange, and the effects of some environmental and experimental procedures;

6) resorption of gas bubbles from tissues and from blood;

7) physiology of exercise, including work done on swimmers, on subjects breathing a gas denser than air at sea level;

8) the effects of temperature on acid-base balance;

9) description of a new and exciting physical model, the avian egg shell, admirably suited to the study of gas diffusion in abnormal environments; and

10) the regulation of respiration in animals and man, with specific reference to certain operational factors, such as positive pressures; and

11) overall effects of some environmental factors (hypergravity, submergence, altitude) on integrated cardiopulmonary function.

This report summarizes the most important results of experimental work conducted in the Department of Physiology, State University of New York, under the aegis of the Office of Naval Research, from 1968, the year during which Contract N-00014-68-A-0216 was awarded to 1975 when the contract expired. Because much of the initial effect was channeled into building and equipping a working team rather than in direct support of on-going research (in compliance with the guidelines of the THEMIS program of the Department of Defense), the benefits of this far-sighted support will be felt for years to come; the selected papers reviewed in the following pages should therefore be considered as a minor part of the returns of the ONR investment.

The investigators feel that this report would be incomplete if it did not start with a note of thanks to the ONR monitors, who did not limit themselves to ascertaining that our research fell within the scope of our contract, but provided guidance and encouragement at a time when the future of the project - and perhaps of the whole University - appeared in doubt. Even in the darkest hours, they did not waver, and provided the moral support that helped us persevere in what appeared at times to be a losing battle, and we wish to take this opportunity to express once more our heartfelt gratitude.

1. Description of Facilities

A highly visible outcome of our collaboration with ONR has been the creation of an exceptional laboratory for environmental physiology research. Many universities have similarly named units, but to the best of our knowledge, none of these has the same breadth, or the same function within the present academic unit.

The central working area is devoted to the study of physical exercise (with main emphasis on swimming) and of gravity (1). A unique feature of this new unit is a ring-shaped submergence basin, 8 ft. wide and 8 ft. deep built around the area swept by a man-rated centrifuge. This circular test basin permits a man to swim for long periods of time without having to change direction. The centrifuge motors will operate over a very wide range of precisely controlled or servo-regulated speeds. By connecting a removable platform to the centrifuge capsule we are able to precede, lead, or tow a swimmer at any pre-set speed or to follow him accurately at any speed he maintains on a moment-to-moment basis. The platform is able to carry an observer and apparatus, sampling tubes and the monitoring leads, and thus allows us to use the centrifuge instrumentation and, in effect, the entire laboratory for the experiment. Studies of propulsion, drag, and work in currents have been conducted. The outer basin wall has large transparent sections for observation and photography. Parts of the submergence basin can be isolated for specific purposes such as temperature regulation studies. The outer wall is surrounded by an ample walkway at a level that places the water surface at lab-bench height. The circular walk-way is continuous, with its outer portion banked to provide a running track for use in exercise studies. This concentric arrangement of facilities provides multiple laboratory capability under one roof at very moderate cost.

Another major component of the laboratory is the high pressure chamber (2). Although this is supported by another ONR contract, it was constructed at the same time as the rest of the facility and interfaces with it in several ways: it uses water from the submergence basin, it is connected on-line to our computerized monitoring system, and the extent of intellectual interplay between the hyperbaric physiology group and other members of the environmental physiology laboratory has been considerable. It is only proper to mention here that much of what was achieved was due to the vision of Dr. E. H. Lanphier, who has since left our group. In planning this facility, the main objective was the highest practical working pressure. Configuration and essential dimensions were influenced mainly by the needs of saturation studies and of using stationary fin-swimming as a test-form in underwater exertion. A new concept made the traditional "wet pot" unnecessary for submerged exposures. The vessel consists of a sphere of 7 ft. (2.1 m) inside diameter attached to a cylinder of the same diameter and about 14 ft. (4.3 m) useful internal length. Design according to the latest ASME code provisions

and fabrication with familiar materials and methods yielded 1.0 atm working pressure at moderate cost. Wall thickness of the cylindrical portion is 5 in (12.7 cm). Unusual versatility is ensured by features such as 12 in (30.5 cm) penetrations which accommodate removable pass-through locks, window assemblies, or other interchangeable structures. Simplicity, versatility, innovation, and minimal cost are sought in all systems and adjuncts.

Another important component of the laboratory is our computer facility. The central unit is a PDP 11/20 digital computer with A-to-D and D-to-A converters, tape storage, removable disk, and floating point processor. Additional equipment includes a magnetic tape recorder (7 channels + voice), a six channel pen recorder and an X-Y recorder. Any one of seven stations (the centrifuge area, two hyperbaric chambers, and four standard laboratorians) can communicate with the computer facility, into which it can feed up to seven channels of data, and from which it can receive three channels of calculated values. A control panel allows one to route signals in a number of ways. As an example, it is possible to use experimental data as direct computer input, the output being stored on magnetic tape and/or fed back to the lab for display; it is equally feasible to store the data on magnetic tape, and feed it later into the computer, obtaining a printed output. We can also use the data calculated during a run to influence the protocol; this can be valuable in generating decompression tables and dictating chamber pressure changes.

The environmental physiology laboratory also includes a number of standard cardiopulmonary and exercise laboratories, all properly equipped.

2. Methods

Much of our work required either that we develop new methods, or that we adapt existing methods to specific experimental conditions.

To start with, we have described (3) a simple manometric apparatus for measuring partition coefficients of high soluble gases, that do not combine chemically with the solvent. The method has been tested, using water, saline and blood.

Equilibration between gas and solvent and the solubility measurement itself, are done with the same instrument; no separate analysis of gas concentrations in the gas and liquid phase is required. Only the changes of the chamber pressure need to be measured with a pressure transducer in order to calculate the partition coefficient. The technique is easy to follow, and yields reproducible results for gases having a partition coefficient

between 0.3 and 20. At 37°C the water/gas partition coefficient for ethyl ether was found to be 13.07, for chloroform 4.04, and for nitrous oxide, 0.482. The partition coefficients of ethyl ether was also established in saline, plasma, and dog and human blood for temperatures ranging from 35 to 39°C.

In order to measure residual volume accurately and repeatedly, we have modified the classical technique of Rahn, in which the subject expires maximally and then rebreathes rapidly in a bag containing initially 100% O_2. This method (4) introduces a finite error because the $\dot{V}_{CO_2}$ initially exceeds $\dot{V}_{O_2}$, then falls to nearly zero, while $\dot{V}_{O_2}$ continues relatively unchanged. The resulting lung volume change (R effect) is significant but difficult to quantitate. The problem can be avoided by rebreathing an inert tracer gas mixed with O_2, instead of 100% O_2. Since $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ do not alter the ratio of the inert gases in the mixture, the R effect is circumvented by simultaneous measurement of N_2 and tracer concentrations (FL_{N_2} and Fb_t initially, Fm_{N_2} and Fm_t after mixing) using the following equation:

$$V_L^0 = V_b \frac{Fb_t}{Fm_t} \cdot \frac{Fm_{N_2}}{FL_{N_2}}$$

where V_L^0 is initial lung volume and Vb = bag volume. The method has been used in 42 measurements on six subjects, showing a close correlation with the Rahn technique and good reproducibility (SD = 32 ml). The method appears particularly advantageous for use in unusual environments, as an example in hyperbaric conditions, where safety considerations preclude use of 100% O_2.

We have developed an ether-infusion (5) technique for determining cardiac output in anesthetized animals, which requires very little blood (actually only the amount required to measure ethyl ether solubility (3)).

An ether solution was infused at constant rate into the vena cava or the right atrium. Simultaneously, a rebreathing maneuver was performed, and the alveolar ether tension was monitored. Based on this procedure, two different methods have been established to obtain reliable estimates of the mixed venous ether tension. Once the ether tension is known, the ether concentration in the mixed venous blood, the ether dilution in the blood stream, and the cardiac output can be computed. The accuracy of the ether-dilution method, which does not require blood analysis and which is repeatable within short time intervals, was tested by comparison with the direct Fick method. Good agreement between values obtained simultaneously by the two techniques was found: on an average, the difference was 6%.

Obviously, even this simple approach is often not suitable for use on normal volunteers, since the ether solution has to be prepared and infused without any risks to the subject. We have described a rebreathing technique (6) which we have used in resting and exercising subjects. The data needed are the subject's CO_2 dissociation curve, the initial volume and CO_2 fraction of the rebreathing bag, and a record of CO_2 at the mouth during the maneuver. From these, one can obtain all the values required to solve the Fick equation. The combined error due to inaccuracy in reading the tracings and to the simplifying assumptions was found to be small (mean = 0.5%, SD = 2.5%). Cardiac output values determined with this technique in normal subjects were on the average 2% higher than those obtained simultaneously with an acetylene rebreathing method (n = 49, SD = 11%). Among the advantages of the technique are that it required analysis of a single gas, takes less than thirty seconds per determination, allows one to obtain repeated measurements at rapid intervals, is not affected by the ability of lung tissue to store CO_2 and eliminates many of the assumptions usually made in non-invasive measurements of cardiac output.

We had described earlier a technique for measuring cardiac output in which the subject rebreathed into a bag containing initially a CO_2-N_2 mixture. Mixed venous P_{O_2} was estimated from the plateau value that occurred in mouth P_{O_2} during the rebreathing maneuver. Unfortunately, such a plateau was not found in a large percentage of cases. We have been able to use the information available when an equilibrium value was not found, to measure the O_2 diffusing capacity of the lungs (7).

3. Alveolar Gas Exchange - General

Historically, the exchange of O_2 or CO_2 has been measured in terms of volume of gas per unit time. We have suggested (8) that it may be more appropriate to consider O_2 or CO_2 not as a volume, but as a quantity of substance M, expressed in moles. The transfer rate of gas species ($\dot{M}$) with dimension (quantity of substance) $\cdot$ (time)$^{-1}$ may thereby be clearly distinguished from the volume flow rate ($\dot{V}$) which has the dimension (volume) $\cdot$ (time)$^{-1}$. The concentration (C), defined as quantity of substance per volume, is used for a media (blood, water and gas). For the gas phase, C is proportional to the fractional concentration F, and is dependent on temperature, pressure and water vapor pressure.

For the increment of concentration in liquid or gas phase of a gas species per increment of its partial pressure $\Delta C/\Delta P$, the term "capacitance coefficient" is proposed. In respect to gas transfer, it is a measure of the carrying capacity of a medium for a given gas species. It is usefully applied not only to water and to blood (slope of CO_2 and O_2 dissociation curves) but also to the gas phase, for which it is identical for all ideal gases at a given temperature.

Some basic equations of gas transfer by blood, air and water, by convection and by diffusion have been rewritten according to these concepts.

We have re-examined the CO_2 dissociation curve of lung tissue (9) and estimated its effect on alveolar gas exchange (10). Slope of the dissociation curve and the rate of CO_2 storage in lung tissue were studied at 22°C and at 37°C in 21 isolated, bloodless dog lungs, with a total of 465 separate observations. Results at the two temperatures were similar. The slope of the tissue dissociation curve of lung tissue at a P_{CO_2} of 40 torr was approximately 0.3 ml CO_2 x 100 g wet tissue^{-1} x torr^{-1}. Normally, this storage was 90% complete in about 5 seconds. After carbonic anhydrase inhibition by acetazolamide, the total storage capacity was unchanged, but the rate at which storage occurred decreased significantly so that it took about 25 seconds for 90% of the storage to be completed. CO_2 diffusion across the pleura is approximately 20 times faster than that of O_2, a relationship that is not affected by inhibition of carbonic anhydrase. The role of tissue CO_2 stores in limiting respiratory fluctuations of P_{CO_2} or pH in arterial blood is only minor and may be of significance only in rapid, deep inspiration. CO_2 uptake or release by the stores is out of phase with blood CO_2 exchange. As a consequence, the time course of CO_2 exchange at the mouth during expiration cannot be used to predict alveolar or capillary CO_2 exchange.

It has long been held that the absence of CO_2 exchange across the alveolar membrane indicated that alveolar gas and pulmonary arterial blood had the same P_{CO_2}. In some animal experiments (12), we have found that under such conditions, i.e., no CO_2 exchange, there was a difference between alveolar and mixed venous P_{CO2} (ΔP_{CO_2}), the alveolar being higher. The ΔP_{CO_2} appeared to be related to the H^+ and HCO_3^- concentrations of the mixed venous blood and to the pulmonary blood flow rate. A model is presented involving a negatively charged capillary membrane and coupling of viscous and diffusional flows allowing the reaction $H^+ + HCO_3^- \rightleftarrows H_2CO_3 \rightleftarrows H_2O + CO_2$ to be shifted toward CO_2 and causing the CO_2 tension to be higher in the region of the capillary wall than in the bulk phase of capillary blood. Evidence, in support of the theoretical model, that steady state differences of the undissociated form of the weak acid DMO can occur across the lung and under certain conditions P_{CO_2} differences can occur across the charged artificial membranes, also presented. Our findings have since been confirmed by a number of laboratories, but other workers were unable to reproduce our findings. The reason for this discrepancy is not clear and is the object of lively discussions and of further experiments.

Our early work on the effects of ventilation-perfusion mismatching an arterial-alveolar relationship has been greatly expanded. In a first paper (13), we have compared the "shunt" fraction

calculated on the basis of N_2. The similar shunt ($\dot{Q}s/\dot{Q}t$) equation based on O_2 analyses was compared with a mixing equation used to calculate the fractional flow ($\dot{Q}_0/\dot{Q}t$) to an assumed slow compartment with a $\dot{V}_A/\dot{Q}$ of 0 by using arterial-alveolar nitrogen differences. At F_{IO_2} of 0.209, both methods produced a result that was at least 70% of the actual value of the fraction of cardiac output perfusing a compartment with a $\dot{V}_A/\dot{Q}$ of from 0 to 0.15. At higher F_{IO_2} (0.40) the two methods diverged so that when the $\dot{V}_A/\dot{Q}$ of the slow compartment was as great as 0.15, $\dot{Q}s/\dot{Q}t$ produced a value of only 10%, while $\dot{Q}_0/\dot{Q}t$ was 60% of the actual fraction of cardiac output perfusing the slow compartment. This shorthand method of estimating flow to the slow compartment using arterial-alveolar nitrogen differences and assuming 0 $\dot{V}_A/\dot{Q}$ for the slow compartment yields a reliable result if F_{IO_2} is 0.40 or less and the actual $\dot{V}_A/\dot{Q}$ of the slow compartment is no greater than 0.15.

We then attempted to use data obtained with all three respiratory gases, by incorporating in our measurements a determination of the arterial-alveolar CO_2 difference (14). We attempted to determine the contributions of uneven $\dot{V}_A/\dot{Q}$ distribution and direct shunting to the impairment of gas exchange by alveolar-arterial differences for O_2, CO_2, and N_2 in five surgical patients anesthetized with halothane in 38% O_2 and N_2. $(A\text{-}a)DO_2$ varied from 122 to 146 mm Hg, $(a\text{-}A)DN_2$ from -3 to 55 mm Hg and $(a\text{-}A)DCO_2$ from 1.5 to 9.5 mm Hg. A lung model was constructed for each patient with one low $\dot{V}_A/\dot{Q}$ compartment, one high $\dot{V}_A/\dot{Q}$ compartment and a direct right to left shunt. When the low $\dot{V}_A/\dot{Q}$ compartment had a value less than 0.10, uneven distribution of ventilation and perfusion was the prime cause of the $(A\text{-}a)DO_2$. In two patients whose low $\dot{V}_A/\dot{Q}$ compartments had values greater than 0.20 direct right to left shunting was the predominant cause of impaired gas exchange even though ventilation and perfusion were unevenly distributed. In the fifth patient, direct shunting was the sole cause of the $(A\text{-}a)DO_2$.

Having demonstrated that the triple gas difference was a useful method for assessing the lung pathology in patients, we proceeded to study a wider population (15). In 14 patients breathing an enriched oxygen mixture $A\text{-}aDO_2$'s averaged 183 mm Hg and $a\text{-}ADN_2$'s, 69 mm Hg. In six patients breathing room air the mean $A\text{-}aDO_2$ was 47 mm Hg; three had no $a\text{-}ADN_2$'s; the other three had a mean $A\text{-}ADN_2$ of 19 mm Hg. Hence, 17 of the 20 patients showed evidence of $\dot{V}_A/\dot{Q}$ mismatching. Using a two-compartment model, a mixing equation was derived to calculate the percentage flow ($\dot{Q}_0/\dot{Q}_T$) in a compartment with a $\dot{V}_A/\dot{Q}$ of essentially 0 necessary to produce the measurement of $a\text{-}ADN_2$. This value ranged from 9 to 46 percent of the cardiac output in those patients with $a\text{-}ADN_2$'s. The classic technique of separating the $\dot{V}_A/\dot{Q}$ component of the $A\text{-}aDO_2$ by 100 percent oxygen breathing was found to be misleading in eight of ten cases when compared with the $a\text{-}ADN_2$ method of assessing maldistribution. It appeared that units with low $\dot{V}_A/\dot{Q}$ became atelectatic when 100 percent oxygen was breathed. It was postulated that the areas of low $\dot{V}_A/\dot{Q}$ occur as a result of intermittent airway closure in the most dependent areas of the lung and also in the case of interstitial pulmonary edema with airway narrowing.

Since the classical alveolar gas equations assume that there is no N_2 exchange in the lung during the steady state, they cannot be applied to a condition where N_2 is replaced by a soluble gas. A new set of relationships that is applicable when in addition to O_2 and CO_2 one or more gases are also exchanged, has been derived (16). During N_2O uptake, it is possible to predict that P_{O_2} in some alveoli may be higher than in the inspired gas, because the uptake of nitrous oxide reduces alveolar volume and increases the fraction of oxygen. Conversely, during N_2O elimination some respiratory elements may have an oxygen tension lower than that found in the mixed venous blood. During the steady state, the $\dot{V}_A/\dot{Q}$ line obtained when breathing air differs from that prevailing when inspiring a mixture of 20.9% O_2 in N_2O. All these effects can be analyzed in terms of gas exchange in a system where the rate of gas exchange between alveolar gas and blood is more limited for one species (the "slow" gas) than for others because of its low solubility. At high P_{O_2}, oxygen acts as the slow gas and its tension is dictated by the exchange of other gases.

The effects of soluble inert gases on O_2 and CO_2 tensions during uptake or elimination of those inert gases had long been recognized earlier. There is however no previous evidence for the fact that inert gas exchange affects O_2 and CO_2 in the steady state. We were able to predict that this could occur, and to verify that prediction (17).

In the description of the facilities, we have looked at the digital computer strictly as a data-reduction device. We have been able to use the computer off-line to generate programs that allow one to calculate a large number of blood O_2 and CO_2 values when any two of the following: O_2 concentration, CO_2 concentration, O_2 pressure, CO_2 pressure, or pH are known (18). The advantage of this computer-generated Dill nomogram is that it can be applied to normal or abnormal bloods.

We have also described (19) a digital computer program that will calculate the alveolar and capillary blood gas compositions corresponding to any given set of $\dot{V}_A/\dot{Q}$ values. The program is applicable to subjects having abnormal hemoglobin concentrations or base excess, or both. Dissolved oxygen and inert gas exchange are considered in the calculations. The importance of nitrogen exchange at extremely low $\dot{V}_A/\dot{Q}$ values is also discussed in that paper.

The mammalian lung is charged with the exchange of both respiratory gases, which must therefore influence each other. We were able to learn much about human respiration by studying a primitive lung, which is not of major importance in CO_2 elimination (20). The North American ganoid fish, Lepisosteus osseus, is a faculative air breather, progressing from complete dependence on the gills at low water temperature to utilization of the lung at warm temperatures for extraction of about 70-80% of its total oxygen requirements. CO_2 elimination through the lungs is 0% at

low temperatures, up to 8% at 20-25°C. Total lung volume averages 8-10% of the body weight and expired tidal volume is about 40% of the total lung volume. Expiration is accomplished by hydrostatic pressure while inspiration involves a buccal pump. The estimated pulmonary surface area of 800-1000 $cm^2 \cdot ml\ O_2^{-1} \cdot min^{-1}$ is low when compared to other vertebrates and suggests that the lung is an incompletely developed respiratory organ. Blood pH and P_{CO_2} values indicate that the animal relies strictly on ventilation of gills for O_2 and CO_2 exchange at low temperatures. As the temperature increases, the lung becomes the predominant organ for oxygen extraction; the blood P_{CO_2} increases, plasma bicarbonate does not rise and the plasma pH falls.

4. Interaction of Convection and Diffusion in Respiratory Gas Exchange

Recent evidence that gas diffusion within the respiratory lobule is not as rapid as usually postulated has been reviewed and discussed (21). The idea that at the end of inspiration there exists a measurable concentration gradient from the bronchiolar opening to the alveolar wall is supported by experiments which demonstrate the following three points. First, the slope of the alveolar plateau during a single-breath test cannot be explained on the basis of regional inhomogeneity and sequential emptying. In addition, when the test breath contains tracer gases of different diffusivity, the relative changes in their concentration during expiration can be explained only on the basis of diffusion. Finally, the rapid change in slope of the alveolar plateau must also be due to intralobular diffusion. This process is accompanied by considerable mixing with the gas initially contained in the dead space. The central volume in which the inspired gas mixes by convective movement can be influenced by the physical characteristics of the inspired medium.

This review has prompted us to re-investigate several problems dealing with the role of gas diffusion in respiratory gas transport. Since much of the work has been done on mathematical analogs, we have reviewed several such analyses (22), some of which are based on random walk, or model analysis. We have reviewed the underlying assumptions and pointed out the strengths and weaknesses of each model. We followed this with a more detailed theoretical study of diffusion of inspired gas into the alveolar sacs (23).

One of our major contributions in this area (24) is another theoretical paper in which we pointed out that most previous work was based on the unwarranted use of binary diffusion coefficients, which apply only to a mixture of two species. In nature, one deals with at least three (O_2, CO_2, and water vapor), and usually four. A study of this situation allowed us to define the crucial nature of the inert gas diluent. We demonstrated that the requirement that total gas pressure be maintained throughout the system implied that it was impossible that each component move strictly according to its own diffusivity and pressure gradient. We were able to 1) demonstrate that the rate of diffusion of a component

gas may be zero even though its concentration gradient is not zero (known as "diffusion barrier"), that the rate of diffusion of a component gas may not be zero even though its concentration gradient is zero ("osmotic diffusion"), and that a component gas may diffuse against the gradient of its concentration ("reverse diffusion"); 2) compare the discrepancy between results obtained by binary and ternary laws separately; 3) determine the importance of ternary diffusion at high pressure. The findings from the model study suggested that the effects of ternary diffusion may not be pronounced when air is breathed under normal conditions, but the behavior of helium mixtures deviates significantly from that described by binary diffusion laws.

Having established the role of gas diffusion, we then proceeded to set up the simplified equations governing O_2 and CO_2 exchange in air and water, by convection or diffusion (25), a logical extension of the alveolar gas equations derived thirty years ago. Our next step was to attempt to establish experimentally whether ternary gas diffusion was of any importance, by comparing diffusive gas movement in a two-gas system with that in a three-gas system (26). Gas mixtures of different compositions were placed initially on either side of a removable partition dividing a cylindrical lucite diffusion chamber, filled with 3 mm glass beads. This served to slow diffusion, minimize convective currents generated by removing the partition, and stabilize temperature within the chamber. In two-gas systems, after the partition was removed, oxygen equilibrated between the two parts of the chamber more rapidly in a helium environment than in a nitrogen environment, conforming with predictions based on binary gas laws. Results obtained with a three-gas system differed significantly from those obtained with the binary system. With 21% oxygen in helium initially in one half of the chamber and 21% oxygen in nitrogen in the other, P_{O_2} rose transiently in the $He-O_2$ side of the chamber. Qualitatively, similar results were obtained when the O_2-N_2 mixture was replaced by 100% nitrogen. Pressure in the system remained essentially constant. The possible mechanisms responsible for the P_{O_2} rise were studied using a computer model of the system. This showed that movement of a given gas may be affected significantly by movement of other gases in the system. Hence, application of binary gas diffusion laws to systems containing more than two gases may lead to significant errors.

We were now ready to investigate the interaction of convection and diffusion in pulmonary gas transport (27). Normal human subjects inspired various volumes of a normoxic argon mixture containing low concentrations of several biologically inert tracer gases with markedly different diffusivities (helium, neon, and sulfur hexafluoride). The behavior of Ne, Ar, and SF_6 could be predicted on the basis of axial dispersion due to differences in diffusivity. For example, neon, having the highest diffusivity of the three, was more uniformly distributed within the bronchial tree than either argon or SF_6. The behavior of helium, however, was not consistent with predictions based solely on axial diffusion. Contrary to expectation, the early portion of expiration was helium enriched

while gas assumed to come from the alveolar regions contained relatively less helium than the other gases. Results of this study suggest that radial diffusion during convective bulk flow may play a significant role in intrapulmonary gas transport if relative diffusivity is extremely large. We conclude that diffusion gradients do exist within the bronchial tree during normal quiet breathing and that these gradients become less significant as inspired volume increases. This series of experiments raises the important question of the role of gas diffusion in the transport of O_2 and CO_2, which was investigated next (28).

Arterial blood pH, measured continuously in anesthetized, paralyzed dogs, was used to investigate time-dependent factors in gas exchange. When the ventilatory pump was stopped at the end of inspiration, there was often a rise of pH before the fall brought on by CO_2 accumulation. This rise or "hump" was more pronounced when the animal breathed a helium-oxygen mixture. When the ventilation was changed from the usual end-expiratory-pause pattern to a pattern with end-inspiratory pauses, the hump phenomenon could no longer be elicited by a breathhold, and there was a gradual rise of mean pH of the blood, indicating better clearance of CO_2. Apparently, the effectiveness of a breath, so far as CO_2 exchange is concerned, can be improved upon because of better mixing if the breath remains in the lung for a time, rather than being immediately expelled as in ordinary expiratory-pause breathing.

5. Tissue Gas Exchange

Much of the existing knowledge on CO_2 exchange in the periphery is based on the notion that CO_2 diffuses readily throughout the tissues, and we felt that this point should be established experimentally (29). Diffusion of CO_2 through tissue was studied by a simple technique which avoided error due to unstirred layers in a bathing medium and which accounted for CO_2 production in the tissue. The practice of dividing permeation data by solubility to yield the customary Fick diffusion coefficient (units of $cm^2\ min^{-1}$) is valid only in a homogeneous, isotropic substance, which tissue probably is not. Therefore the results are presented here in terms of the permeation coefficient, or Krogh's diffusion constant (units of $cm^2 \cdot min^{-1} \cdot atm^{-1}$). The value at 25°C was $5.0 \times 10^{-4}\ cm^2 \cdot min^{-1} \cdot atm^{-1}$, and there was no appreciable change when metabolism was depressed after the tissue had been kept for four days in a deep freeze and then thawed.

This information, which confirms the rapid diffusive movement of CO_2 could then be applied to another study (30) in which the scatter of O_2 and CO_2 tensions in tissue was determined, and led us to conclude that the scatter in values was due to local differences in the ratio blood flow/metabolism.

We continue to be interested in the wash-out of nitrogen from body stores. To better evaluate the available data, we have studied (31) the effects of anesthesia on N_2 wash-out from body stores of dogs breathing a nitrogen-free mixture by comparing the rate of N_2 elimination in anesthetized supine dogs and in conscious upright animals. Anesthesia changes considerably the pattern of N_2 wash-out. Whereas the unanesthetized dogs eliminates 50% of its nitrogen store in 15 min, the anesthetized animal requires four times as long. Analysis of the data obtained on anesthetized animals has allowed us to distinguish between the delay caused by an overall decrease in cardiac output (to 58% of control value) and by redistribution of peripheral circulation. The rate constant of the "slow compartment" is essentially the same in both groups of animals, but this "compartment", which includes 36.4% of the N_2 store in conscious animals, represents 74.5% of the tissue N_2 in anesthetized animals.

6. Resorption of Gas Bubbles

Resorption of N_2 bubbles (radius 500-2, 500 μ) was measured in vitro in moving streams of saline, red cells suspended in saline, plasma or whole blood (32). The absolute volume of the bubble was determined every 4 min by a compression technique. The diffusion characteristics are described in terms of the mass transfer coefficient which decreased from 0.0059 to 0.0022 cm/sec as the viscosity of the perfusing liquid increased from 1 to 8 centistokes. The results are also interpreted in terms of generalized parameters which allow comparison of these results to those of other investigators using different systems. For a bubble in blood, the mass transfer characteristics are similar to heat and mass transfer from solid spheres to moving liquid.

We also addressed ourselves to problems of bubbles in tissues. In a first study (33), rates of exit of O_2 and N_2 from subcutaneous gas pockets in rats were measured while tissue blood flow was elevated due to injections of cobalt chloride. Exit rate of N_2 doubled whereas O_2 exit rate changed only slightly. Blood flow was estimated to have increased fourfold. These findings are in accordance with theoretical predictions that inert gas uptake is proportional to the square root of perfusion rate but the O_2 uptake depends on local metabolic rate and is independent of perfusion. Comparison of O_2 and N_2 exit rate allows estimation of the diffusion limitation of tissue-to-blood exchange. For N_2 blood appears to come only 50 to 75% of the way to equilibrium as it passes through capillaries of the tissue around the gas pocket.

Another way of testing the role of perfusion is based on the idea that one can render perfusion more efficient by increasing the solubility of bubble gases in the circulatory blood. Our experiments (34) tested whether infusion of fluorocarbons (FC),

compounds in which nitrogen is highly soluble, would increase N_2 removal ($\dot{V}N_2$) from subcutaneous air pockets in rats. FC emulsion was injected so that FC constituted about 12% of blood volume in treated animals. $\dot{V}N_2$ was measured under three conditions: 20 hrs in air, 20 hrs or 5 hrs in 100% O_2. Infused rats showed $\dot{V}N_2$ increases over controls of 175%, 148%, and 124% under the three conditions respectively. Calculations based on N_2 solubility predicted larger changes. The failure to reach predicted $\dot{V}N_2$ was partly explained as a decrease in pocket perfusion. The remaining discrepancy may represent diffusion limitation.

7. Exercise

Our unique facility has permitted us to embark on a comprehensive study of energetics of swimming in man. Past and current work covers several aspects of the problem; a fundemental aspect, the study of the physical forces involved, can serve as an example (35, 36). In that particular series of experiments, body drag, D_b, and mechanical efficiency, e, during actual swimming were measured by a raw method on 10 men swimming the overarm crawl at velocities v, of 0.55 and 0.9 $m.s^{-1}$ in a 60-m-circumference annular pool. D_b was measured during swimming and was double that for passive towing, as was e. The ratio, e/D_b, was observed to the same for a given individual at the two velocities averaging 0.8 $kg^{-1} \times 10^{-2}$, but varied from 0.42 to 1.05 $kg^{-1} \times 10^{-2}$ among individuals. It can be shown theoretically that $v = \dot{V}O_{2_{net}} \cdot (e/D_b)$ for aerobic swimming; hence the ratio e/D_b establishes the velocity a person can achieve for a given $\dot{V}O_{2_{net}}$ and is an index of individual proficiency in swimming. The reciprocal of e/D_b is equivalent to $\dot{V}O_2/v$, e.g., the energy cost of swimming 1 m. This proved to be independent of the two velocities studied and averaged 58.5 ml $O_2 \cdot m^{-1}$ about four times the cost of running for men of this size.

Since one of the problems encountered by divers may be the increased work of breathing due to higher gas density, we addressed ourselves to the problem of effects of increased airway resistance on ventilation and gas exchange during exercise by having two trained subjects breathe through graded resistances, while walking on a treadmill (37). At any exercise level, the minute volume decreased as the resistance was raised. The maximum O_2 uptake and exercise tolerance was decreased by addition of resistances but the relationship between $\dot{V}O_2$ and work load remained unchanged. Thus, there is no indication that limitations placed on the ventilatory apparatus cause a shift to anaerobic metabolism. The ventilatory response to exercise when the airway resistance is increased is neither a "minute volume" response nor a "work of breathing" response, but falls between the two. In terms of its effects on the ventilatory drive, an increase in work load of 1 cal min^{-1} kg^{-1} is equivalent to an increase in $P_{A_{CO_2}}$ of 0.15 mm Hg.

8. Temperature and Acid-base Balance

The problems of working divers immersed in water of low temperature has been treated in terms of thermoregulatory responses. We have opened an entirely new area of investigation following our initial description of the changes in pH that follow changes in temperature in various poikilotherms. Our path has led us to describe the basic relationship between temperature and hydrogen ion concentration, study this in a number of species, and finally end up with a hypothesis that can explain these changes in all animals, including man.

The initial observation, namely that at different temperatures, plasma hydrogen ion concentration varied, but that the variation in the $[H^+]/[OH^-]$ paralleled that of distilled water, led us to realize that this constant "relative alkalinity" appeared to be a fundemental law of life (38, 39). The various factors that govern pH (or are governed by it) were studied (40) in a variety of poikilotherms:

The normal arterial H, PCO_2, P_{O2}, and plasma HCO_3^- values of unanesthetized fish, amphibians, and reptiles, living at a mean temperature of 28°C in the Amazon basin are described and compared with similar values of ectotherms reported by others. Since the (H^+) and P_{CO_2} of ectotherms increase directly with body temperature, a comparison of the acid-base status of different species is only valid at a common temperature. At 28°C the average arterial pH value is 7.61 ± SD 0.10 for 14 species, but their P_{CO_2} varies from 3.5 to 38 torr and their plasma HCO_3^- varies from 4 to 45 mM, respectively.

The fish presents an unusual model, because the low solubility of O_2 in water forces these animals to maintain a low PCO_2, which introduced another constraint into the system (41).

To examine whether the relationships found in fish, amphibians and reptiles was truly fundemental, we studied (42) the pH of the hemolymph of selected invertebrates which decreases as their body temperature increases. The magnitude of this change ($\Delta pH/\Delta^oC$) is very similar to the change of the pH of water with temperature ($\Delta pN/\Delta^oC$) and suggests that these invertebrates, like poikilothermous vertebrates, regulate the pH of their extracellular fluid so that its degree of alkalinity relative to the pH of water remains constant. The degree of alkalinity (pH_{blood}-pN) varies between species, but seems to be fixed for any given species. In Limulus pH-pN was essentially the same for in vivo samples, measured after the whole animal had been acclimated to different temperatures, as it was for in vitro samples in which the hemolymph was cooled or warmed anaerobically, suggesting that the CO_2 content of the extracellular fluid is constant as the temperature changes. The PCO_2 of the hemolymph is invariably lower in animals breathing water than in

those breathing air. In the invertebrates, as in the vertebrates, manipulation of P_{CO_2} and HCO_3^- is probably the major mechanism in the regulation of the relative alkalinity of the extracellular fluid.

Finally, we were able to propose a hypothesis that explained the phenomenon (43): a chemically designed model system consisting of two weak acid-conjugate base buffer pairs, one of which is carbonic acid-bicarbonate and the other the imidazole group of protein histidine residues, will quantitatively account for the change in blood pH and P_{CO_2} with temperature observed in closed in vitro blood samples at constant carbon dioxide content (Rosenthal pH-temperature curve). Application of the same equations to open systems in the steady state, poikilotherm vertebrates, will also quantitatively describe the temperature dependence of blood pH and P_{CO_2} in frogs, toads, and turtles. A necessary condition for this application, constant CO_2 content of blood over wide body temperature excursions in vivo, is shown to hold for bullfrogs. The regulation of ventilation in the in vivo animal can be viewed as one in which blood P_{CO_2} is regulated to maintain a constant fractional dissociation (alpha) of imidazole groups. Data from striated and cardiac muscle suggest that alpha imidazole values in these compartments are independent of changes in body temperatures as well. It is proposed that acid-base regulation in all vertebrates is consistent with primary regulation of alpha imidazole resulting in a stable OH^-/H^+ ratio and the observed change in blood pH with temperature, $dpH/dt = 0.015$ to $0.020\ \mu/^oC$.

9. The Avian Egg Shell: A Biological Model for Testing Problems of Gas Diffusion

We have already alluded to the fact that changes in ambient pressure, by altering the mean free pattern of molecular gas diffusion, will affect gas mixing. That this occurs in man under hyperbaric conditions was demonstrated in our laboratory more than ten years ago; in section 4, we have described some of our more recent work. Unfortunately, the interaction of convection and diffusion in mammalian respiration makes it extremely difficult to assess the exact role of diffusion per se. We have attempted to circumvent this difficulty by studying the movement across the avian egg shell, since this exchange is governed entirely by diffusion across the shell pores.

We were able to describe the physical characteristics of the diffusion barrier (44) on the basis of water vapor movement across the egg shell, and to establish the relationship between surface area, volume, and pore density (45). We then addressed ourselves to O_2 and CO_2 exchange in the fertilized egg (46). On the basis of our measurements, equations were developed to predict the gas composition in the air cell of the egg as well as the rate of exchange of O_2, CO_2 and water vapor. P_{O_2} and P_{CO_2} values were

obtained from the air cells of chick embryos of various ages, and when these results are considered together with metabolic rate and measured egg shell permeability data they are found to be consistent with the hypothesis that gas exchange by the avian embryo is limited by diffusion through its porous shell. The implications of this are discussed in terms of water vapor loss from the egg during incubation, development of the embryo's blood buffer system and the importance of the permeability of the egg shell to embryo survival.

To ascertain the nature of altitude adaptation, we studied gas exchange in chickens acclimatized to an altitude of 3,800 meters (47). The P_{O_2} and P_{CO_2} differences across the egg shell were measured and found to be less than the values previously reported for sea-level eggs by about a factor of two. Further measurements of embryonic oxygen consumption ($\dot{M}O_2$, and shell conductivity to oxygen (G_{O_2}) indicated that compared to eggs at sea level, $\dot{M}O_2$ was reduced by a factor of 0.58 while G_{O_2} was increased only by a factor of 1.07 in the high-altitude eggs. These independent measurements predict the ΔP_{O_2} across the egg shell of the high altitude eggs to be only 0.54 times that of sea-level eggs, the directly measured factor was 0.53. The authors conclude that at high altitude a major adaptation of the chick embryo is a reduced metabolism which decreases the ΔP_{O_2} across the egg shell since its gas conductivity remains essentially unchanged.

10. Regulation of Respiration

The steady state ventilatory responses of Dial-anesthetized cats to constant positive-pressure breathing (CPPB) and expiratory threshold loading (ETL) were studied before and after vagotomy (48). Minute ventilation, tidal volume, frequency of breathing, alveolar P_{O_2} and P_{CO_2}, airway pressure, and the activity of diaphragm and abdominal muscle were continuously recorded. Both maneuvers, CPPB and ETL, depressed steady-state ventilation: the depression was more severe during ETL. When applying small to medium loads, vagotomy changed the breathing pattern but not the degree of ventilatory depression. There is evidence that a vagal feedback mechanism influences the division of labor between inspiratory and expiratory muscles to achieve maximum efficiency of the respiratory apparatus.

To assess two major feedback circuits regulating ventilation, changes in diaphragm and abdominal muscle EMGs have been compared during chemostimulation alone and its combination with proprioceptive stimulation before and after vagotomy (49). Cats, anesthetized with Dial, were exposed to three levels of continuous positive pressure (Pb) while breathing air, 5.25% of CO_2 in air, or 12.4% O_2 in N_2. With air breathing PB depresses the diaphragm and induces abdominal expiratory activity. However, CO_2 and hypoxic mixtures when substituted for air during PB override the vagal inhibition of the diaphragm without influencing the abdominal

expiratory response. When the proprioceptive inhibition of inspiratory neurons is abolished by vagotomy PB on air as well as in other gases augments diaphragm activity. However, vagotomy abolishes all expiratory activity in the abdominal muscles. The results indicate that multiple sensory systems govern diaphragm activity, whereas vagal signals are the major activators of abdominal expiratory activity.

Strong stimulation of baroreceptors not only inhibits medullary vasomotor neurons but may depress ventilation as well. Whether baroreceptors project to both inspiratory and expiratory neurons to decrease ventilation is not known. We elucidated (50) baroreceptor projections to respiratory neurons by measuring the change in the integrated electromyograms of the diaphragm and abdominal muscle in response to changes in baroreceptor firing in 10 Dial-anesthetized cats. Baroreceptor firing was decreased by common carotid occlusion and increased by release of carotid occlusion or by saline distension of the carotid sinus. Since abdominal muscles are silent during quiet respiration, they cannot reveal expiratory inhibition. Therefore, positive-pressure breathing was used to excite abdominal expiratory activity. Decreased baroreceptor firing increased diaphragmatic and abdominal expiratory activity, whereas increased firing reduced diaphragmatic and abdominal activity. Since changes in baroreceptor firing altered diaphragmatic and abdominal activity in similar directions, it was concluded that carotid baroreceptors make inhibitory connections with both inspiratory and expiratory neurons despite the reciprocal organization of the respiratory center.

Continuous recordings of minute ventilation, integrated FMG's of the diaphragm and abdominal muscle and mass spectrometer analysis of airway gases were obtained during PB on air, 5.25% CO_2 and 12.4% O_2 in eight Dial-anesthetized cats (51). Between 0 and 15 cm H_2O the steady-state end-tidal CO_2 rises about 0.6 mm Hg/cm H_2O, diaphragm activity decreases - and AMR increases exponentially with each increment in PB. When 5.25% CO_2 is inspired, diaphragm activity is augmented at every pressure suggesting algebraic summation of proprioceptive and chemoreceptive effects at the respiratory centre. In contrast, the AMR is not significantly altered by hypercapnia. The absence of all abdominal muscle expiratory activity after bilateral vagotomy suggests that the role of active expiration is to regulate thoracic-lung volume, not blood gases.

Ventilatory responses of conscious man to continuous positive pressure breathing were studied (52) by recording the integrated electromyogram of the external abdominal oblique muscle's tidal volume, and frequency of breathing and end-tidal P_{CO_2} during +10, +20, and +30 cm H_2O. Abdominal expiratory activity reflexly evoked by the pressure breathing increased with the level of pressure and showed progressive recruitment throughout exposure to elevated pressure. Tidal volume and frequency of respiration were increased by the elevated pressure, thus making minute ventilation greater the higher the level of pressure.

As a result of this increase in minute ventilation, end tidal P_{C0_2} decreased with each level of pressure breathing. Thus, man reflexly compensates for continuous overinflation of the lungs by active expiration and an increase in ventilation.

11. Environmental Factors in Cardiopulmonary Performance

The effects of environmental changes on specific functions or processes have been described in the appropriate sections (as an example, the ventilatory response to pressure breathing appears in the section devoted to regulation of ventilation). This part of the report concentrates on more general aspects of changes in physical factors in our environment.

As an example, acceleration from head to foot ($+G_z$) handicaps gas exchange by shifting blood from thorax to dependent veins and creating a ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch in the lung. At 1 G leg exercise improves $\dot{V}/\dot{Q}$ matching. Gas exchange was measured in six subjects at +1, +2, and +3 G_z during rest and two levels of exercise, either unloaded pedalling or 600 kpm/min (53). The $\dot{V}0_2$ for pedalling was clearly related to G level, but work efficiency was unaffected. Acceleration lowered resting Pa_{0_2} while raising $\dot{V}_E/\dot{V}0_2$, HR, AaD_{0_2}, V_D, and V_D/V_T. Unloaded pedalling returned $\dot{V}_E/\dot{V}0_2$ and HR toward their 1-G values. In contrast, at 3 G each increase in $\dot{V}0_2$ caused a fall in Pa_{0_2} and a rise in AaD_{0_2}. The V_D showed no further change with exercise, while V_D/V_T decreased at all G levels. It thus appears that only some of the effects of acceleration are counteracted by exercise, probably by the peripheral muscle pump. Any accompanying rise in $\dot{V}0_2$ adds to the stress of acceleration, due to limitations on gas transport.

The effects of head-out immersion in water (temp: 22-36°C) on mixed venous gas tensions ($P\bar{v}_{0_2}$ and $P\bar{v}_{C0_2}$), cardiac output ($\dot{Q}$), heart rate (f), stroke volume (q_{st}) and limb blood flow were studied (54) in resting and exercising subjects ($\dot{V}0_2$ range: 0.3-3.1 $L \cdot min^{-1}$). Expired air 0_2 and $C0_2$ and heart rate were recorded continuously. $\dot{V}0_2$ was measured at rest and throughout each 5 minute exercise period by a closed circuit spirometer. $P\bar{v}_{0_2}$ and $P\bar{v}_{C0_2}$ for the determination of $\dot{Q}$ were measured by the 92% N_2-8% $C0_2$ rebreathing method with corrections for changes in lung volume during immersion. Limb blood flow was measured by venous occlusion plethysmography and mercury-in-rubber circumference gauges. In 3 trained subjects resting in 36°C water, f remained the same as in air. However, in water <34°C, the resting values for f, $P\bar{v}_{0_2}$ and $\dot{Q}$ were reduced 25%, 20% and 12% respectively below air values. These effects coincide with the onset of intense vasoconstriction in the limbs in water <34°C.

At moderate work loads in water <34°C ($\dot{V}O_2$ = 2.3 L · min) f remained 20-25% lower than in air and did not become equal to air values except during heavy work ($\dot{V}O_2$ = 3 L · min). $P_{\bar{v}O_2}$, $P_{\bar{v}CO_2}$, and $\dot{Q}$ for exercising subjects were the same in water as in air. Therefore, stroke volume was 20-25% greater in water <34°C at rest and during moderate exercise. We conclude that resting f and $\dot{Q}$ are reduced in water <34°C in response to cold stress probably mediated through the baroreceptor response to cold vasoconstriction, and that the relative bradycardia persisting during moderate exercise in water <34°C is also due to cold. The slower heart rate plus the pulmonary mechanical effects of head-out immersion both contribute to the marked increase in stroke volume and presumably stroke work in water cooler than 34°C.

The degree of functional inhomogeneity of the human lung was assessed at low altitude (2,000 ft) and during the first 5 days of exposure to an altitude of 11,500 ft by measuring the arterial-alveolar N_2 and CO_2 differences (55). Neither one of these was modified by ascent to altitude and there was no significant change during the experimental period. Had $\dot{V}_A/\dot{Q}$ distribution remained unchanged, the decrease in ambient pressure would have lowered substantially the $(a\text{-}A)D_{N_2}$. It is concluded that the transition from low to high altitude alters the scatter of ventilation or perfusion, or both, in such a way as to decrease the gas exchange efficiency of the lung. This change offsets partly the benefits derived from the hyperventilation response.

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