1942

Respiratory regulation as influenced by altitude, cold and anoxia

Kenneth Earl Penrod
Iowa State College

NOTE TO USERS

RESPIRATORY REGULATION AS INFLUENCED BY ALTITUDE, COLD AND ANOXIA

by

Kenneth Earl Penrod

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Physiology

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State College

1942

TABLE OF CONTENTS

INTRODUCTION

Respiration and its control at very high altitudes are very important questions at this time. Until comparatively recent times altitudes have been thought of only in connection with mountains and 25,000 feet seemed excessive. With the development of the airplane, however, man has been exposing himself to higher and higher altitudes entailing progressively lower temperatures and lower barometric pressures. The stimulus of war has prompted the aircraft industries to seek higher levels for their planes, since being "on top" gives an undoubted advantage in tactical efficiency.

The men who take these planes to extreme heights are subjecting themselves to very abnormal conditions. The temperatures encountered will approach or even exceed the most extreme cold experienced anywhere on the surface of the earth. The temperature found at a given altitude varies with the latitude. The Army Extension Course Special Text No. 193 states:

> The height at which the temperature ceases to fall divides the atmosphere into two distinct layers or shells, the lower being known as the troposphere, the upper as the stratosphere, and the dividing surface itself as the tropopause. The temperature of the stratosphere varies inversely as the height of its under surface above the earth. For this reason it is colder over the Equator than over the Poles, reaching approximately -50° F. over the Poles and -110° over the Equator. Temperature throughout the stratosphere is fairly constant.

This text also indicates the altitude of the troposphere

to be 56,000 feet at the Equator and 30,000 feet at the Poles (96).

An additional hazard of very high altitudes is anoxia. The altitude at which supplementary oxygen begins to be breathed varies considerably, but it is rare that 20,000 feet is ever reached without using this supply. Oxygen is advocated above 10,000 feet. If 100 per cent oxygen is then breathed an adequate supply is assured until an altitude of above 37,600 feet is reached. At this altitude the total barometric pressure is 157 mm. Hg. A fact often omitted in the calculation of partial pressures of gases in the lungs is the pH_2O = 47 mm. Hg, this being the vapor tension of water at 37° C., at all times regardless of the other pressures. The normal partial pressure of carbon dioxide is 40 mm. during normal breathing. Thus, of the 157 mm. total pressure in the lungs at 37,600 feet, 87 mm. (47 + 40) is taken up with water and carbon dioxide, leaving 70 for the partial pressure of oxygen in the alveoli. At this pO_2 the dissociation curve of oxygen shows the blood to be saturated to the extent of 93 per cent. Lower pO_2 values are associated with progressively decreasing arterial oxygen saturations.

Thus at altitudes beyond 37,600 feet the person is confronted with a decreasing pO_2 in spite of the inhalation of 100 per cent oxygen. Does this reduced pO_2 have the same effect on respiration as simple anoxemia that is sometimes encountered at ground level? What is the effect on respira-

tion if the partial pressure of carbon dioxide in alveolar air is increased or decreased? These are the questions about which very little information is at hand.

Obviously hyperventilation is a distinct benefit to a person at altitudes above 37,600 feet. In addition to increasing the arterial oxygen saturation by increasing alveolar pO_2 through a more rapid exchange, the hyperventilation causes a blowing off of carbon dioxide which results in an increased pH of the blood which in turn is associated with a shift to the left in oxygen dissociation curve. Thus, for a given pO_2 value a greater arterial oxygen saturation will be enjoyed. While these two effects will be of benefit to a person in the rarefied atmosphere of high mountains also, still a third benefit is derived above 37,600 feet. This is in consequence of the low total pressure. As was stated previously, the alveolar pO_2 is equal to the barometric pressure minus the sum of the pH_2O and pCO_2. If the pCO_2 is reduced this allows an increase in the pO_2. This, of course, lends greater saturation of the blood.

Since the carbon dioxide may easily be removed from the lungs and blood the degree of oxygen lack must regulate the respiration. This is thought to not be the normal stimulus for respiration so what is the reaction to this new stimulus? An adequate and efficient regulator must be present if the person is to survive, since he is approaching the borderline of tolerable conditions.

A large low pressure chamber in the laboratory of the Army Air Forces' Aero Medical Research Laboratory has made possible research in this field. By pumping the air out of the chamber--which will hold several men--many of the conditions of altitude can be simulated. A second low pressure chamber in this laboratory is equipped with a refrigerating unit so that both cold and low pressures may be experienced simultaneously.

The nature of the work in this laboratory is such that the practical side of every question must be foremost. The pressure of time does not permit the pursuit of many problems which appear to be of academic interest only. Hence some of the results herein reported may appear to be incomplete from the standpoint of statistical significance. However, where time permitted it was always the policy to carry an experiment to the point of satisfaction of the experimenters. Hence by summarizing the numerous observations of respiration under such conditions as those described above it is hoped some new light might be thrown on the question of how respiration is controlled in altitude, cold and anoxia.

REVIEW OF LITERATURE

Prior to the middle of the seventeenth century very little was known about breathing beyond its mechanical nature and the fact that it was necessary to life. As was the case with so many other phenomena, Aristotle had given some consideration to the problem and had taught that the main function of respiration was to cool the blood. This theory was generally held until Boyle (10), Lower (70) and Mayow (73) made their contribution. Boyle, with his air pump, proved air was necessary for life and Lower and Mayow concluded from analogies of respiration, combustion in air and combustion of gunpowder that a "nitro-aerial spirit" combines with "sulphur". These authors, concurring in the teachings of Descartes, thought the nitro-aerial spirit was carried by the blood to the brain where it passed into the ventricles and thence down the supposed nerve tubules to the muscles. They thought the increased breathing of muscular exercise a consequence of an increased consumption of nitro-aerial spirit. At about the same time, Hooke (61) showed that an animal whose lungs had collapsed after the chest was opened could be kept alive by artificial respiration.

It was not until the middle of the eighteenth century that the next significant advance in respiration was made. Joseph Black then discovered that exhaled air contained "fixed

air" (carbon dioxide) not unlike that given off by the action of acids on carbonates. Priestley, soon afterward, showed that what he called "dephlogisticated air", after the prevailing phlogiston theory of Stahl, disappeared both in ordinary combustion and in animal respiration. Lavoisier pursued this idea naming "dephlogisticated air" oxygen, and showing that oxygen combines with carbon and other substances and that the combination of carbon and oxygen produces carbon dioxide. He, together with Laplace, later demonstrated that the carbon dioxide produced by an animal is nearly equivalent to the oxygen consumed and that the amount of heat formed in an animal body is nearly equivalent to that formed when an equal amount of oxygen is used in the combustion of carbon elsewhere.

Lavoisier made no contribution to the knowledge of how respiration is controlled. He believed oxidative processes were localized in the lungs and looked upon the speeding up of respiration with exercise as an unfortunate circumstance since it entailed the using of more food by the laboring class of people than by the wealthier class. It remained for Mayer, a German, to point the way with his doctrine of conservation of energy.

The problem of how the respiratory activity is correlated with other body activities was relatively neglected until comparatively recent times. As pointed out by Haldane, this failure to detect the delicacy of physiologic regulation was a consequence of the crudeness of early experimental apparatus

and techniques.

Legallois, in 1812, discovered and ascribed the portion of the medulla oblongata which subsequently became known as the respiratory center. He demonstrated the automaticity of this center by severing all apparent nerves to the center.

Hering and Brewer, in 1868, made the striking discovery that the inflation and deflation of the lungs themselves, at least in part, influence the rhythmicity of the respiratory center. They showed that when the vagi are intact, filling of the lungs on inspiration appears to stimulate the pulmonary nerve endings of the vagi, causing a termination of inspiration and a beginning of expiration. Deflation produces a corresponding stimulus acting oppositely. The surprising closeness with which these findings conform to modern concepts will be shown later. This theory of "self-regulation" as proposed by Hering and Brewer remained unchallenged until Haldane (43, p.10) pointed out how such a process of regulation is, by itself, completely out of relation with the physiologic needs of the body.

Chemical influence on respiration was discovered near the middle of the nineteenth century when Kussmaul and Tenner (66), by rendering the brain ischemic, showed initial stimulation and subsequent exhaustion and collapse of the respiratory center. Rosenthal (86) a short time later showed that overventilation of the lungs is followed by a period of rest, a condition he designated as "apnea". Doctors Cheyne and Stokes described

the pathological condition of breathing which has since been associated with their names. John Hunter, the famous English physician of the eighteenth century had earlier described this condition, but his work had been overlooked. Influenced by the difference in color of oxygenated and unoxygenated blood together with animal experiments in which a very large excess of carbon dioxide did not stimulate respiration Rosenthal op. cit. came to the conclusion it was solely, or almost solely, the oxygen content of the blood which influenced the respiratory center. As Haldane (43, p.12) subsequently pointed out, Rosenthal was misled by the narcotic effect of very high concentrations of carbon dioxide. Pflüger and Dohman (82) demonstrated conclusively that both mild excess of carbon dioxide and want of oxygen excite the respiratory center.

The concept of another type of apnea--vagus apnea--grew out of the experiments of Head (49) in which he followed the activity of the diaphragm muscle. He interpreted this relaxation except during inspiration as apnea. Apnea thus came to be regarded as vagal in origin and remained so until when Fredericq (18) with his cross circulation experiments showed clearly the existence of true "chemical" apnea.

Regarding the relative importance of oxygen want and CO_2 excess in control of respiration Miescher-Rusch (76) in 1855 showed in man that a small increase in CO_2 stimulates breathing, but a corresponding diminution of oxygen has no effect. He formulated the theory that for ordinary breathing of air it

is the CO_2 which effects the regulation. This theory soon found much experimental support.

Geppert and Zuntz (31) concluded from animal experimentation that exercise leads to a lowered CO_2 and a slightly increased O_2 content of the blood and accordingly that neither of these substances is responsible for the accompanying hyperpnea. They suggested that some acid substance produced in the blood stimulated respiration advancing in support of this idea the work of Walter showing the effects of acids on breathing (102).

For contribution of knowledge and stimulus to a great deal of research by others in the field of respiration and its control we are deeply indebted to the late Prof. J. S. Haldane. His works and concepts are well presented in his Silliman lectures (43) and are briefly summarized here.

Haldane, together with Lorrain Smith, in 1893, began a series of experiments designed to clarify the knowledge of the control of respiration. They found that when the CO_2 in the air in a sealed chamber rose to about three per cent and the oxygen simultaneously fell to about 17 per cent, the breathing of the men was noticeably increased. Hyperventilation was progressively increased until with about six per cent CO_2 and 13 per cent O_2 respiration became great enough to cause exhaustion. If the CO_2 were removed they found no increase in respiratory volume until the percentage of O_2 reached about 14. Also, if O_2 were supplied so as to be kept constant, but CO_2 were al-

lowed to accumulate the results were roughly the same as in the first experiment. Other experiments showed that the limit of endurance was reached when the CO_2 concentration reached about 10 per cent, regardless of the concentration of oxygen. If the CO_2 was absorbed, percentages of O_2 below 12 caused much hyperventilation until they were extremely low, i.e. about two per cent, where consciousness was quickly lost before hyperventilation could ensue. They arrived at the same conclusion as Miescher-Rusch, namely, that it is the concentration of CO_2 which controls variations in ordinary breathing.

In 1905 Haldane and Priestly (43, p.18) began an investigation of alveolar air and demonstrated a remarkable consistency in this air for each individual under conditions of rest. They showed further, that when the composition of inspired air is varied, breathing is regulated so as to give a constant percentage of CO_2 and not of oxygen. They calculated from their results that for a rise of about 0.23 per cent CO_2 in the alveoli, i.e. increasing the mean alveolar CO_2 percentage from, say, 5.62 to 5.85, there is a consequent 100 per cent rise in resting alveolar ventilation. Haldane pointed out (43, p.24) that the effects of varied CO_2 tension in the alveoli, and consequently the blood, are not immediate but these tensions must be maintained constant for some time.

Regarding the question of apnea it was shown by Haldane that when the alveolar CO_2 percentage was reduced by more than 0.2 per cent, apnea was produced. To Haldane the vagus theory

of apnea was untenable (43, p.27).

Haldane (43, p.20) investigated the relative importance of rate and depth of breathing and found a reciprocal reaction. In all cases adjustment was such as to maintain alveolar CO_2 tension nearly constant.

The fact that the increase in ventilation was always nearly exactly proportional to the increase in alveolar CO_2 tension seemed to Haldane well established until he began his experiment on exercise with Douglas (43, p.30). Then it was found that in high rates of CO_2 production during muscular exercise the ventilation increased more or less independently of the CO_2 concentration. It was apparent that the presence of an additional factor was causing this reaction. This factor, it was decided later (43, p.94) was pH of the blood. The same conclusion had been reached earlier by Geppert and Zuntz, as referred to earlier.

Led to the concept by Paul Bert (5), Haldane verified that it is the partial pressure of CO_2 in alveolar air and not the mere percentage which regulates breathing (43, p.32).

In 1908 Boycott and Haldane (8), after examination of their own observations together with those of Ward, Galliotti and Walter, concluded that the real stimulus to the respiratory center is the combined effects of carbonic and other acids on the reaction of the blood. Later work by Douglas and Haldane (23), Winterstein (104), and Hasselbalch (48) strengthened this conclusion. However, the work of Lacquer

and Verzar (67) indicated that, for a given H-ion concentration, carbonic acid was a more effective respiratory stimulant than mineral acids when injected into animals. This evidence was in accord with the original view of Haldane and Priestley, namely, that carbon dioxide exerts a specific effect on respiration. The work of Collip (13), Mellanby (75), Ege and Henriques (27) and Heymans, Bouckaert and Dautrebande (57) also pointed in this direction.

The apparent dilemma was explained by Jacobs (62) when he showed that undissociated carbonic acid penetrates the living cell much more readily than other acids or the hydrogen ion itself. From these data Haldane concludes that:

> It is in virtue of changes in the hydrogen-ion pressure of arterial blood that CO_2 affects the respiratory center, but that considerable changes in hydrogen-ion pressure produced in other ways may fail to cause comparable effects owing to failure of these changes to be communicated from the blood to the reacting tissue.

Haldane's contributions to the knowledge of the function of oxygen in control of respiration also were great. Prior to the work of Haldane, Paul Bert (5, p.27) had demonstrated the importance of a sufficient supply of oxygen at all times. Haldane and Poulton (43, p.140) found that respiratory reaction to anoxia was a function of the suddenness of exposure to low oxygen tensions. This difference in reaction they explained on a basis of the rapidity with which the CO_2 was washed out of the lungs by hyperventilation. It was Haldane's contention that the effect of want of oxygen on the breathing was largely

mediated through its influence on the CO_2 pressure (43, p.184). Haldane realized early that the effects of oxygen want are usually masked by the counterbalancing effect of the hyperpnea produced with its resultant washing out of CO_2, thus removing one natural stimulus. However, he recognized that if the CO_2 pressure in the alveoli was kept high the two effects were synergistic and the added effect of anoxemia manifested itself chiefly in the form of increased frequency of breathing (43, p.180). Bohr, Hasselbalch and Krogh had previously demonstrated another interlocking effect of O_2 and CO_2 on respiration, i.e. the effect of CO_2 and the resulting pH on the rate of dissociation of oxygen. As Haldane pointed out (43, p.188), however, since the oxygen is held more tightly by the hemoglobin in the presence of excess CO_2 the extra oxygen attained by virtue of this "Bohr effect" is never of service in increasing the real oxygen supply to the tissues.

During anoxemia, when the respiration is stimulated by a decrease in O_2 tension of about one-half in alveolar air, there is found a higher pH of the blood due to the washing out of CO_2. The effect of this on respiration is in opposition to that of the anoxemia <u>per se</u>. It was early assumed that in response to the stimulus of anoxemia a condition of acidosis existed in the blood (43, p.105). Haldane's later investigations on the effect of pH variation on respiration led him to the conclusion that the acidosis theory in low atmospheric pressures was wrong. The idea of an acidosis effect on high altitudes had

grown up from the observation of a lower titratable alkalinity of the blood after prolonged exposures to low pressures. Haldane showed that no abnormal acids accumulated in the blood at high altitudes, hence this cannot contribute to an acidosis. From the Pike's Peak Expedition results he concluded that anoxemia alters the kidneys in such a way that they regulate the blood to a lower level of alkalinity. Later investigations by Haldane, Kellas and Kennaway (43, p.107) on the urine excretion showed that much base was excreted during prolonged exposure to high altitude. The release of this base continues until such time as the original pH of the blood is returned. So if the fixed base is removed it is obvious the titratable alkalinity will be lowered. Hence Haldane showed the supposed acidosis was not an acidosis, but an incomplete compensation of an alkalosis. Due to the slowness of the adjustment, Haldane states (43, p.108):

> There is no doubt that the regulation of the respiration by slight variations of the H-ion concentration of the blood is liable to be modified by conditions which vary the O_2 pressure of the blood.

Haldane and Mavrogordato (45) focused their attention on the nervous control of respiration where again the knowledge was inadequate. Since the work of Hering and Brewer (54) very little had been done on this phase of respiratory control. From his experiments Haldane concluded that although inspiration does quickly follow on the heels of expiration as though the completion of expiration were a stimulus to inspiration,

as Hering and Brewer thought, it need not follow immediately. The same authors showed that the continuance of an inspiratory or expiratory discharge of the respiratory center depends on the extent to which actual inspiration or expiration accompanies the discharge. Thus the respiratory center does not naturally act independently of the lung movements, but tends to go hand in hand with them, as if closely connected (43, p.126).

More recent work on the role of the vagus nerve in respiration has revealed some interesting facts. Adrian (1) has presented evidence by measuring the impulses passing along the vagus which shows that afferent impulses passing up the vagus in normal breathing are purely inhibitory of the inspiratory act. The afferent vagal endings, according to this author, are unaffected by CO_2 or oxygen want. Head (49) showed that if the vagi are frozen after the inspiratory or the expiratory phase has been initiated this phase still continues. The influence transmitted through the vagi appears to initiate expiration and its absence permits inspiration to continue; the center persists in one phase until the vagus gives the signal to terminate that phase (43, p.129).

Chemical regulation of respiration fits into this picture as being the regulator of when the vagus asserts its effect. Thus CO_2 increases depth of breathing by causing a greater degree of inflation of the lungs to be necessary before the stimulus becomes effective (43, p.129).

The importance of oxygen-want as a regulator of breathing was regarded somewhat lightly by Haldane. He states:

> Though an important and early consequence of want of oxygen is increase in the respiration it is found that, even when simple anoxemia is so extreme that consciousness is on the point of being lost, the breathing in man, except at first, is hardly more than doubled, as shown by the fact that the alveolar CO_2 pressure is only reduced to about half.

Haldane had at his disposal a steel chamber in which the air pressure could be varied as he wished. In 1908 Boycott and Haldane showed that when the atmospheric pressure is reduced by one-third the CO_2 pressure is very little disturbed. However, this reduction in pressure effects a reduction in the pO_2 of the lungs from about 13 per cent to about 6.5 per cent of a normal atmosphere which, they showed, is accompanied by a fall in arterial oxygen saturation to about 80 per cent. Their conclusion was that a reduction of 15 per cent in arterial oxygen saturation or a drop of one-third in atmospheric pressure had no apparent physiologic effect on the body. They later concluded the length of exposure to these reductions is extremely important, however. Haldane well understood the effects of prolonged exposure to low oxygen tensions, or "mountain sickness" for he, together with Douglas, Schneider and Y. Henderson spent five weeks of the summer of 1911 on Pike's Peak (altitude 14,100 feet) studying physiologic adjustments to high altitude. It was during this expedition that Haldane observed for the first time the fundamental relation of oxygen tension to the base-binding capacity of the

blood, or as he called it, the blood alkali. Acclimatization to the low oxygen tensions of higher altitudes entailed reduction in the blood alkali.

While at Pike's Peak Haldane observed the periodic breathing often described by mountaineers. This condition could be abolished by the administration of oxygen, thus demonstrating control of respiration by oxygen lack.

The foregoing is by no means an exhaustive summary of Haldane's contributions to our knowledge of respiration but is meant merely as a brief discussion of his findings pertaining to the control of breathing. During the same period, both before and after the Pike's Peak Expedition, Yandell Henderson was making independent observations which also lend a clearer concept of this function.

The paper of Geppert and Zuntz (31) was referred to above in which they concluded that the oxygen used or the CO_2 produced was not enough to account for the hyperpnea of exercise. Based on Walter's work, they proposed an acid substance being liberated by the muscle. Y. Henderson rejected this concept, but agreed that there was some mysterious respiratory stimulant of a non-acidic nature: this hypothetical substance he termed "hyperpnein" (52, p.56).

During the first World War Henderson and Pierce (53) introduced a rebreathing device designed to record reaction to low oxygen tensions as a test for flight candidates. With this instrument they found wide variations in ability to tol-

erate low oxygen pressures. They observed that some men began hyperventilating with a slight reduction in oxygen percentage (as little as one or two per cent) whereas others showed no hyperpneic reaction even to collapse. They found a positive correlation between hyperpneic response and tolerance of low oxygen percentages.

A second contribution by Y. Henderson made with his rebreather was proof that oxygen consumption by the body is independent of the supply up to the point of collapse (51, p.64).

Henderson contributed a great deal to the knowledge of chemical regulation of respiration. He performed many experiments on the transport of gases by the blood and on the function of the blood alkali in the carrying of CO_2 (42). He made many observations on the changes in acid-base equilibrium of the blood coincident with altitude, particularly during his stay on Pike's Peak with Haldane, Douglas and Schneider in the summer of 1911. As to the role of pH as the mediator of the CO_2 stimulus to the center, Henderson favored such a theory.

In the early days of Henderson's work the theory of an "acidosis" accompanying exercise and hyperventilation was prevalent. He, at approximately the same time as Haldane and others, helped to disprove this theory and show that on the contrary a state of alkalosis occurs. He was able to cause such a shift in pH of the blood by forced hyperventilation in animals that irreparable damage was done to the respiratory

center (52). This is true for voluntary hyperventilation but not for exercise. Regarding the threshold of the CO_2 stimulus to the respiratory center Henderson found this to be markedly altered by certain drugs such as ether (72) and strong afferent stimuli such as sharp pain (51, p.56).

Working with alveolar air Henderson, Chillingworth and Whitney (43, p.37) found that the effective dead space of the lungs is enormously increased during hyperpnea simply by mechanical factors and regardless of the source of stimulus to the respiratory center. This fact has an influence on the calculation of gaseous exchange in the lungs during hyperpnea.

Henderson was a staunch advocate of CO_2 as a respiratory stimulant and constantly advocated its use in resuscitation. He agreed with Haldane in the concept that in normal activity and rest the CO_2 controls respiration. They thought that the excitability of the respiratory center is largely determined by the tension of oxygen; or, more precisely, by the relation between the tension of O_2 and the amount of alkali in use in the blood (51).

The outstanding contributor to our knowledge of acid-base balance in the blood and its effects on respiration was the late L. J. Henderson. The unsettled question of whether CO_2 affects the respiratory center directly or through pH has been mentioned before. In 1909 L. J. Henderson (50) pointed out:

> Since the concentration of free carbonic acid, H-ions and OH-ions are not independent variables, any one of them might be the stimulus of respiration, but

the action of blood on the respiratory center might also take place through a complicated heterogeneous equilibrium.

After L. J. Henderson contributed the formula $\frac{H_2CO_3}{BHCO_3} K^1 = H +$ for an expression of the manner in which much of the CO_2 is carried, a clearer conception of the relation of CO_2 and pH of the blood was possible. It is easily seen that if some acid other than H_2CO_3 enters the blood, such as lactic acid, it will combine with the bicarbonate and thus reduce the available bicarbonate for CO_2. Yandell Henderson in his book (51) gives a good discussion of the theories of "acidosis", "acarbia", etc. which grew out of application of the above formula to conditions in the blood. The observations of L. J. Henderson on the interrelationship of all the changes appearing in the blood during exercise led him to conclude that there is no specific respiratory stimulus and that the stimulus to respiration is the blood as a whole (50, p.371). His work has done much to integrate the various theories of respiration control. He has shown that CO_2, O_2 and pH are not independent variables, but rather a change in one automatically implies a change in the others. This is shown clearly by the nomogram (Fig. 1) constructed by L. J. Henderson (50). This nomogram is constructed for one person's blood, but the implication is the same for all bloods. As shown on this nomogram the location of any two of the five variables automatically fixes the other three. From this figure a vast number of things can be determined and although it is not exact for all bloods, it does

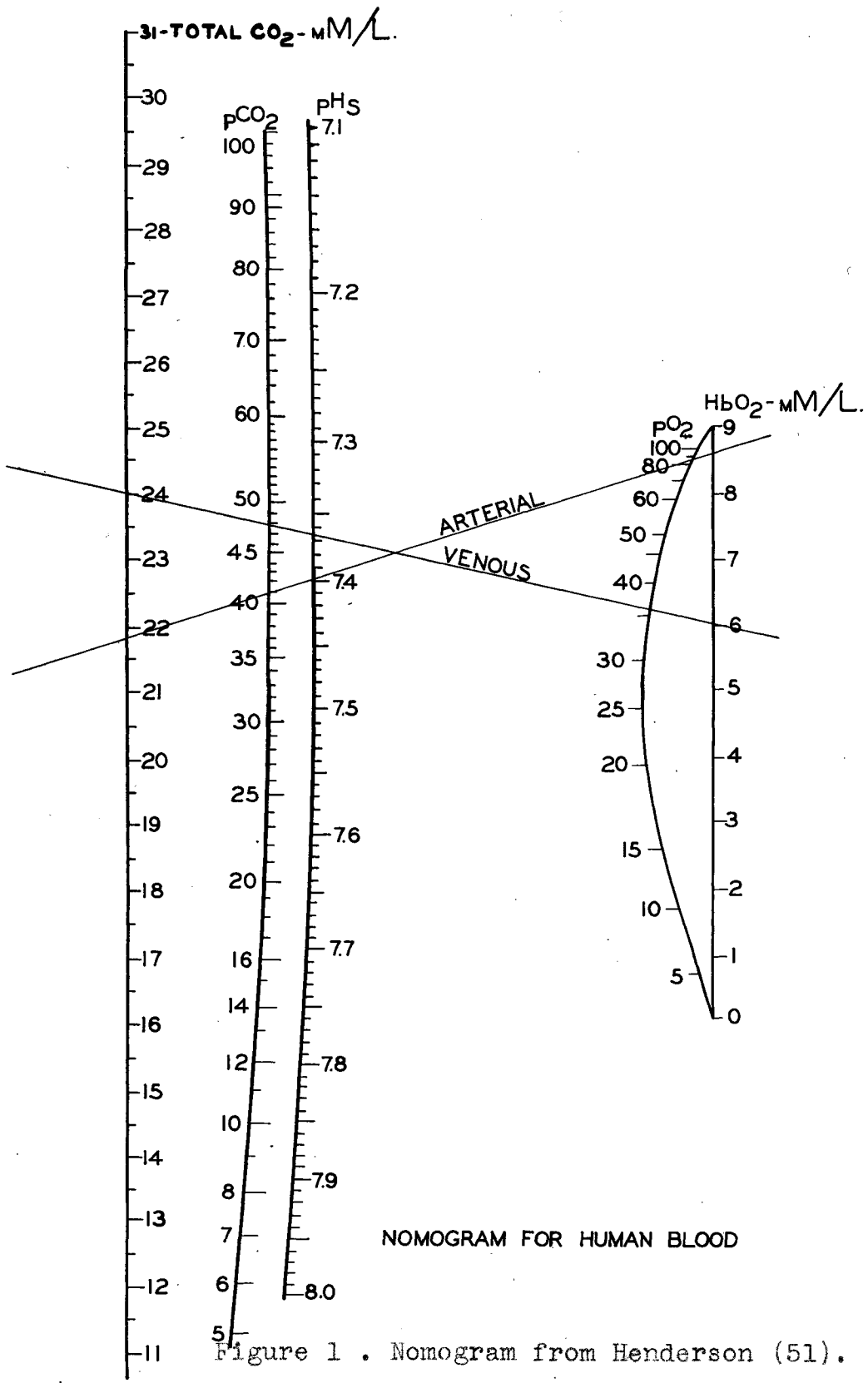

Figure 1 . Nomogram from Henderson (51).

answer very nicely for all bloods of the same, or nearly the same, combining power.

This theory of L. J. Henderson's of no specific stimulus but rather a generalized blood stimulus to respiration would seem to fit in well with the ideas of Gesell, who holds that the real stimulus to respiration is the pH of the cells of the respiratory center.

An entirely revolutionary theory as to the control of respiration has appeared comparatively recently, throwing a new light on this phase of physiology. Heymans and his collaborators in Belgium and Schmidt and Comroe in this country have contributed much to our knowledge here.

In 1927 Hering (54) showed that afferent impulses from the vicinity of the carotid sinus have an important reflex effect on breathing. J. F. and C. Heymans (60) demonstrated similar afferent stimuli from the aortic region and C. Heymans, Bouckaert and Dautrebande (58) verified Hering's findings. These latter authors found by profusion of the carotid artery that the breathing could be affected, increased pressure causing apnea. They next found that the chemoreceptors of these areas react to all three of the long-known respiratory stimulants, namely, fall in pH, rise in CO_2 and anoxemia.

By both exposing an intact anesthetized animal to low oxygen tensions before and after severing the sinus and aortic depressor nerve and using perfused ligated vascular beds with the innervation intact, Heymans et al. demonstrated the effects

of anoxemia are propogated through this medium (60). However, these authors could find no consistent response in their animals to increased CO_2. They concluded the carotid chemoreceptors have a lower threshold to CO_2 than the center itself (59). As to the effect of pH on these carotid chemoreceptors Heymans et al. found a reaction, but pointed out the changes required a wider range of pH than 7.1 to 7.6 (90, p.135).

The work begun by Heymans and his school has been carried on and extended by Schmidt and Comroe in this country. These authors have done a great deal to clarify the role of the peripheral reflexes in breathing as well as draw more definite boundries for the chemoreceptor nerve endings concerned in these reflexes.

The original papers of Heymans et al. described the reflex stimuli as coming from the "vicinity of the carotid bifurcation and from the aorta". However, they attempted to localize the area more closely (90, p.116) but the best evidence of the exact location of these nerve endings came from the work of Schmidt (88). He showed that the chemoreceptors are limited to the area of the carotid body and the pressoreeptors concerned with blood pressure and circulatory response are confined for the most part to the sinus area. However, the latter are not always so greatly restricted and De Castro (90, p.117) contends their presence in the walls of the arteries in and near the carotid body as well as in the sinus. Comroe is chiefly responsible for locating precisely the aortic chemoreceptors in

the aortic body (14).

That the respiratory center is reflexly stimulated by reduction in the oxygen pressure in the carotid blood seems well established (90, p.120). The question as to whether or not this mechanism is the sole mode of action of low oxygen tensions is not so well settled (33). The carbon dioxide effect on the carotid and aortic reflex mechanism is not so pronounced as that of anoxia. Schmidt and Comroe contend, however, that the reflex effects of CO_2 are distinctly less powerful, well sustained or consistent than those of anoxia (15) (91). These same authors conclude from their experiments that changes in pH are capable of stimulating the chemoreceptors almost as strongly as anoxia, and much more consistently and strongly than excessive CO_2. It is the contention of Schmidt and Comroe that relative insensitivity of the reflex mechanism when compared to that of the center itself prohibits its being of major importance in the normal control of breathing, but rather functions as an accessory mechanism to aid in emergencies (90, p.136).

Carbon dioxide, as was pointed out in connection with the work of Haldane, has long been known as a regulator of respiration. However, its relative importance and mechanism of action have had wide interpretation. Its dual role of stimulation and depression have led to conflicting conclusions. It is now known that alveolar concentrations of CO_2 up to about 30 to 35 per cent stimulate respiration and values above this level

tend to depress the center (92).

The argument has long persisted as to whether carbon dioxide exerts its influence directly on the respiratory center or through the pH change it evokes in the blood. Haldane favored the latter view and presented some very convincing arguments. Haney states (47), after the work of Jacobs, that the reason CO_2 is a more effective stimulant than other acids is because it crosses the cell membrane at a more rapid pace. However, Nielsen (80) vigorously opposes this view and has presented much evidence showing CO_2 affects the respiratory center per se. More on the role of pH as a respiratory stimulant will be given later.

Since the work of Heymans the site of action of CO_2 has received much attention. As was mentioned in connection with the work of Heymans, et al. and of Schmidt and Comroe the evidence seems to point mostly in the direction of the respiratory center itself caring for this action. According to Gollwitzer-Meier and Lerche (40) the respiratory center has a much lower threshold for CO_2 than does the chemoreceptor mechanism. They state that the stimulus at the center is, however, developed rather slowly. Schmidt and Comroe concur in this and state that the only place that the chemoreceptors appear superior to the center itself as regards CO_2 is in their much greater resistance to adverse conditions such as excessively high concentrations of CO_2 (89). These investigators do not think the chemoreceptors play an important part in the adjust-

ment of normal, or eupneic, breathing. Objection is voiced by Von Euler and Liljestrand (101) who, as the basis of their experiments with dogs in which they found an increased alveolar CO_2 content and a decrease in ventilation after denervation of the carotids, conclude that arterial pCO_2 under physiological conditions stimulates respiration through the reflex mechanism as well as directly on the center. The finding of Shock (93) that the alveolar CO_2 tension is correlated with age should lend aid to this investigation.

It is of interest to note that although the pCO_2 of the blood is a cause of respiration it may also be a result. Thus when the control of respiration is taken over by some other regulator, such as O_2-lack, the resultant hyperventilation will result in an excessive "blowing off" of CO_2, thus removing this source of stimulus. Y. Henderson emphasized this point in connection with the breathing of patients under anesthesia (51, p.19). Knowledge of this fact has been the basis for his advocation of an O_2-CO_2 mixture for use in resuscitation.

The effect of carbon dioxide on respiration cannot be isolated from the other true effectors of this phenomenon, i.e. anoxia and pH. A great deal of evidence has been produced to show that the sensitivity of the respiratory center to CO_2 is greatly altered by the amount of oxygen present (29). Dumke, Schmidt and Chiodi (26) showed that when 3.5 per cent CO_2 is inspired by a normal dog if ample oxygen is given the response is less than if anoxia is also present. This effect, they

showed, is reversed after chemoreceptor denervation. This may be interpreted as meaning anoxia exerts a synergistic action to hypercapnea and this action is effected through the chemoreceptors. Evidence that possibly other things than anoxia may synergize the effect of CO_2 on the center is given by Kramer and Ganer (65) who found that CO_2 excitability of the respiratory center diminishes with increasing arterial blood pressure in rabbits and cats.

Recently some light has been thrown on the way in which anoxemia affects respiration in humans and the role of the carotid chemoreceptors in this function by the work of Asmussen and Chiodi (3). They produced anoxemia in two distinctly different ways, one by breathing carbon monoxide (CO-hypoxemia), the other by breathing an air-nitrogen mixture low in oxygen, (anoxic-hypoxemia). Their observations on the affect of these two anoxemias on respiration are shown in Table 1. It is obvious that in rest and light work no appreciable affect on respiration was noted in the subjects poisoned with CO to the extent

TABLE 1. A COMPARISON OF TWO FORMS OF HYPOXEMIA

(Adapted from Asmussen and Chiodi (3).)

	Relative Respiratory Volumes (% Normal)		
	Rest	Light Work	Heavy Work
Normal	100	450	750
CO Hypoxemia	100	440	950
Anoxic Hypoxemia	160	650	1360

of 20 to 30 per cent. In heavy exercise the results were less consistent, with some stimulatory affects. In contrast to this, marked hyperventilation was noted even in rest and light exercise in the same subjects when breathing low (about 10 per cent) oxygen mixtures. In both cases the per cent saturation of arterial blood with oxygen was about the same, i.e. 70 to 80 per cent. The alveolar pCO_2 was in all cases lower after breathing the low oxygen mixture than after breathing CO. This is, of course, in consequence of the hyperventilation. The authors point out further that while breathing low oxygen mixtures the circulation is increased while after breathing CO this reaction is not evident. Hence ischemia of the respiratory center as a causitive factor in hyperventilation may be ruled out.

The dissociation curve of the available hemoglobin is displaced to the left in carbon monoxide poisoning (94). In this state the oxygen saturation of the available hemoglobin and the arterial pO_2 will be normal. However, while breathing low oxygen the oxygen dissociation curve is unchanged. Hence the oxygen saturation of the available hemoglobin and the pO_2 of arterial blood will be reduced. The difference in arterial pO_2 in the two cases is evident when the dissociation curves are compared (24). The pO_2 in the case of the experiment with low oxygen mixture is approximately 18 mm. Hg lower. For an explanation of the respiration stimulatory effect in the second case and not in the first the authors allude to the carotid

body chemoreceptor theory. They presume that in the former case there is no oxygen lack in the glomus of the carotid body while in the second case there is. This explanation rests on the assumption of a low oxygen consumption by this body in relation to its arterial supply, which we know is abundant. So the reduction in combined oxygen, and hence in pO_2, is small. Thus when the pO_2 is normal as it is in CO poisoning the carotid body does not respond. However, if the pO_2 of the arterial blood is lowered, as at high altitudes or when a low oxygen mixture is breathed, the pO_2 within the glomus will be still lower and will thus cause a strong stimulus to be sent to the respiratory center.

Chiodi et al. (12) have shown that the direct action of CO on the respiratory center is purely depressive in nature. CO_2 produced less hyperventilation in their subjects after poisoning with CO.

Haldane early (43) pointed out that oxygen lack is a stimulus to respiration. Since then this concept has been borne out in a number of ways. The exact manner in which this function is brought about is not so well agreed upon, however, "the role of alveolar and blood oxygen saturation in the direct regulation of respiration has been underestimated", according to Zaeper (106). "The attempt on the part of the organism to maintain a sufficient alveolar oxygen tension to maintain adequate blood saturations under normal and pathological conditions is the most important factor in the regulation of

respiration. The exact physiological mechanism involved . . . requires further study" he continues.

The response to anoxia is a complicated one. Simple anoxia appears to stimulate the center to evoke increased breathing which results in a washing out of CO_2, one of the natural stimuli. This reaction is opposed to the stimulus of oxygen-want and causes lessened response to anoxia after a short time. If the conditions are such that CO_2 is not lowered, such as in an atmosphere of high CO_2, the combined affects of increased CO_2 and anoxia bring about enormously greater affects both on the rate and depth of breathing. This is in contrast to the usual affect of each stimulus individually which is, for excess CO_2, principally an increase in depth of breathing, while for anoxemia, a marked increase in frequency and only a moderate increase in depth (43, p.193).

The effects of the combination of oxygen lack and CO_2 were shown quite conclusively recently in a series of experiments conducted by Keys, Stapp and Violante (64) who found a 132 per cent ventilation in subjects breathing an air-nitrogen mixture with a pO_2 of 64 to 79 mm. Hg while the same subjects, breathing a mixture with a pO_2 of 56 to 81 mm. Hg and a pCO_2 of 16 to 24 mm. Hg, gave a ventilation of 178 per cent of normal. The experiments of Dill and Zamcheck (21) threw a great deal of light on the relation of CO_2 and O_2 in control of respiration. They plotted the ventilation per minute against the pCO_2 in inspired air (see Fig. 2). The ventilation value is the mean

last five minutes of the experiment.

The additive nature of the combined response to low oxygen and increased CO_2 is very apparent. For any given pCO_2 the response is much greater with a lower pO_2 than with a higher pO_2. This relation holds until severe anoxia is reached, then the results become less predictable.

The relation of pH to the various combinations of O_2 and CO_2 the authors have pictured diagrammatically (see Fig. 3). It is apparent that with no CO_2 in the inspired air the pH is higher with increasing anoxia. However, when the CO_2 is increased to about 40 mm. Hg, the pH in all cases tends to return to the normal, 7.37. Another item of considerable importance shown on this diagram is the fact that when an adequate oxygen saturation is assured by a high pO_2 (155 mm. Hg) the CO_2 may vary through a considerable range with no change in pH. The authors conclude, "It is difficult to reconcile the theory that a simple relation exists between arterial pH and pulmonary ventilation with the foregoing observations".

The beneficial effects of adding CO_2 to the inspired air in anoxia are apparent from this work. They have pictured graphically (Fig. 4) the effect of increasing the CO_2 upon each of the pO_2 values. It is seen that if the pCO_2 of the inspired air is kept at zero and the pO_2 reduced from 75 to 54, the arterial oxygen saturation is reduced from 66 to 41. However, if 32 mm. Hg. CO_2 is added to the 54 mm. Hg of O_2 the saturation again rises to 66. This rise is entirely in consequence of the

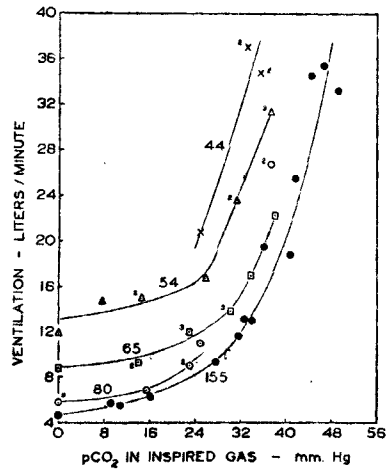

Fig. 1

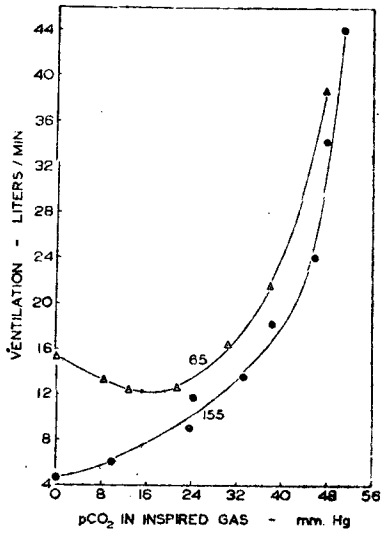

Fig. 2

Fig. 1. Total ventilation of subject P. in relation to pCO_2 and pO_2 in the inspired gas. The pO_2 values are 44, 54, 65, 80 and 155 mm., as shown along the curves Some of the points correspond to the averaged results of two or more experiments. the number being indicated in the figure.

Fig. 2. Total ventilation of subject Z. in relation to pCO_2 and pO_2 in the inspired gas. The pO_2 values are 65 and 155 mm.

Figure 2. Graph from Dill and Zamcheck (21).

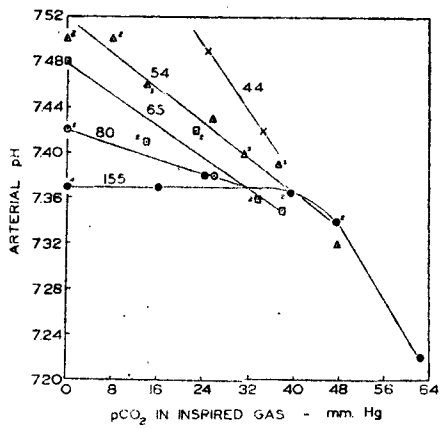

Fig. 3

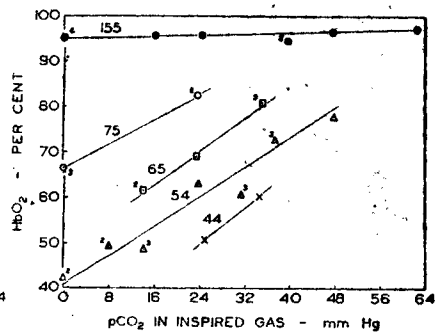

Fig. 4

Fig. 3. Arterial pH in relation to pCO_2 and pO_2 in the inspired gas for both subjects. The number of experiments averaged for each point is indicated.

Fig. 4. Percentage saturation of arterial blood in relation to pCO_2 and pO_2 in the inspired gas for both subjects. The number of experiments averaged for each point is indicated.

Figures 3 and 4. Graphs from Dill and Zamcheck (21).

hyperventilation induced since the resultant lowering if pH tends to shift the oxygen dissociation curve to the right. From these data the authors postulate that if the oxygen saturation is to remain at, say 80 per cent, a decrement in pO_2 of 10 mm. calls for an increment in pCO_2 of 14 mm. Thus in the range they have studied the arterial oxygen saturation will be raised more by a given increase in pO_2 than by an equal increase in pCO_2.

Since Heymans' early work on carotid and aortic reflexes it has been known these reflexes are profoundly concerned in oxygen want. Bouckaert, Dautrebande and Heymans concluded in an early paper (6) that the respiratory effects of anoxemia were predominantly if not exclusively reflex in origin. This original observation has been verified many times both by themselves (7) and others, the literature on which is cited by Schmidt and Comroe (90). Dumke, Schmidt and Chiodi (26) in a recent publication determined the threshold of anoxemia hyperventilation in lightly anesthetized dogs to be at an arterial oxygen saturation of about 85 per cent and an arterial pO_2 of 50 to 55 mm. Hg. They determined that there is no stimulation of the respiratory center by anoxemia since respiration was depressed by anoxemia after complete chemoreceptor denervation. After chemoreceptor denervation these animals did not show the customary hyperpnea induced by the synergistic action of anoxemia and the inhalation of 3.5 per cent CO_2. The reaction was, in fact, in the opposite direction--inhibitory to hyper-

ventilation. This indicates that anoxemia only depresses the response of the respiratory center itself to CO_2. This latter view is contrary to the widely accepted earlier view that anoxemia manifested itself by increasing the sensitivity of the respiratory center to changes in CO_2 (51, p.51). It appears that the reaction of anoxemia through the carotid body is so well integrated with the respiratory center the distinct effects are well masked.

Von Euler et al. (100) hold an interesting view as to the nature of the stimulus arising from anoxia. They say the initial stimulation of respiration brought about by oxygen lack is essentially an acid effect on the chemoreceptors of the carotid body. Oxygen want, they say, is in no sense a true stimulant and it induces physiologic response only as a result of injury. This observation may be in line with the recent work of Willman and Behnke (103) who state that some individuals either are, or can become, sensitive to oxygen. However, no attempt is made on the part of Von Euler to explain why an acid effect of oxygen want is harmful to the chemoreceptors while large quantities of acid may be injected directly into the blood stream with no apparent harmful affect.

Gesell and his collaborators do not fully accept the now widely held views of CO_2 control of breathing directly through the center and low oxygen control through chemoreceptor reflexes. It is their thesis that the metabolism of the nerve cells comprising the respiratory center itself is of utmost

importance. Oxygen lack, they contend, leads to decreased oxidations and a consequent increased intracellular acidity while carbon dioxide excess leads to increased intracellular acidity and a consequent decrease in oxidations (33, p.189). In support of this theory Campbell (11) states that the cause of death from anoxia of white rats is intoxication from breakdown products of histamine and histidine which are normally oxidized. This conception of increased acidity of the cells of the respiratory center, at least in oxygen want, is very difficult to reconcile following the work of Asmussen and Chiodi (3) mentioned previously. It was this contention that the oxygen consumption of the glomus was very low in relation to the abundant arterial supply since the anoxemia of CO poisoning showed no response while a lowering of the pO_2 of arterial blood effected a great response in hyperventilation. It would thus seem that oxidative processes could not be responsible for this action.

With the exception of the reference made to Legallois' discovery of the respiratory center and the work of Hering and Brewer our discussion has so far pertained wholly to the chemical control of respiration. It appears, in the light of some recent observations in this field, the nervous side of this question cannot be neglected. The division of the once single respiratory center into an inspiratory center and an expiratory center has now been proposed by Pitts, Magoun and Ranson (84), and by Magoun (71) following his work on cats and

and monkeys. Pitts (83) points out that such a subdivision had a morphological basis. He has also shown that the nerve cells comprising the two half-centers are anatomically as well as functionally different. This is in confirmation of an earlier work by Lunsden (cited by Pitts). Lunsden also found that if the respiratory portion of the medulla is isolated both from impulses from higher neuroaxis stations and vagus stimuli its discharges are not rhythmical but tend to induce a sustained inspiration, which he termed "apneusis". Pitts and Stella (85) confirm this view. The rhythm of the apneustic respiratory center of the medulla is controlled by efferent stimuli from another center in the upper part of the pons, which Lunsden named the pneumotaxic center, or afferent vagus stimuli.

The work of Hering and Brewer on the role of the vagus nerve in respiration has been reinvestigated and expanded recently. Gesell and Hamilton (36) found that stimulation of the vagus during expiration prolonged expiration and stimulation during inspiration prolonged inspiration which was then followed by a long expiratory phase. Because the expiration is more powerful, they regard the vagus as predominantly expiratory. Hering's nerve was found to be predominantly inspiratory. Cutaneosensory nerves (such as saphenous) were midway between. All appear to enhance the phase in process at the time of stimulation. Apparently the susceptibility of each half center of the respiratory center

to stimulation depends upon the phase of activity then prevailing.

By effecting a freezing technique it is possible to quickly remove the influence of the vagus nerve. Using this technique Ter Braak (95) showed that if lung volume is small, vagal block has no affect on respiration. With increasing lung volume to block off the vagi produces more and more pronounced shortening of the expiration and a less marked prolongation of inspiration, thus resulting in an increased respiratory frequency. However, when the lungs are collapsed these authors found the blocking of the vagi has the opposite effect. In normal respiration the only vagal endorgans involved in respiratory reflexes are stretch receptors, the sensitivity of which increases with lung volume, they conclude. This vagal stretch reflex is an excitatory phenomenon in which each stretch proprioceptive ending drives both the inspiratory and expiratory half-centers by virtue of their dual connections at the center. Coordinated alternate reflex activity of the two half centers is dependent upon reciprocating intercommunications. Vagal inhibition of the inspiratory half center is regarded as a secondary response to vagal excitation of the expiratory half center and <u>vice versa</u>, thinks Gesell and Moyer (39).

Although Boyd states (9) that in quiet breathing and during hyperpnea produced by rebreathing the net influence of the vagi on the inspiratory mechanism is inhibitory, Gesell

has a slightly different interpretation. He found, by correlating action potentials of the vagi with respiratory movements that during inspiration there is an ever increasing action of the vagi which is in direct proportion to the pulmonary inflation. This slowly augments the inspiratory act. Then at the beginning of expiration the vagal action is shifted to the expiratory center, but rapidly subsides (32). This interpretation of the shifting of the vagal action from the inspiratory muscles to the expiratory muscles is in line with the conclusion Wyss drew from his work, namely, that there exists no specific expiratory afferent vagal fibers (105). If Gesell's interpretation is to be accepted we must abandon the original Hering-Brewer view that vagal impulses are inhibitory and now conceive of the vagal fibers an excitatory action which is first to the inspiratory act in increasing amount proportional to the inflation of the lungs and then at the conclusion of inspiration rapidly shifted to the expiratory act with rapid subsidence.

A pertinent and interesting observation was made by Graham (41) who, using fowls, found an expiratory air stream through the separated (in situ) trachea caused interruption of the inspiration. An inspiratory air stream had no effect on respiration. The former effect was abolished by section of the vagi.

Gesell, Lapides and Levin (37) have also investigated the nervous action of the respiratory center. They conclude

two forces drive the respiratory act--the inherent physico-chemical forces arising directly within the automatically discharging respiratory neurous, and the physico-chemical forces set up in these same cells by impingement of nerve impulses coming from outlying receptors. These two (direct and indirect) have much in common. Both are thought to bring about a rhythmic activity and both create a similar pattern of discharge. Going still further Gesell and collaborators propose three patterns of stimulus being sent out of the respiratory center--a rapidly augmenting, a slowly augmenting and a steady state. They believe the rapidly augmenting pattern is a reflex modification of the steady state pattern (35). They have shown the inspiratory potentials to have only one pattern of discharge, that being slowly augmenting. This corresponds with a usually recognized slow filling of the lungs. The expiratory pattern is, however, of two types--a rapidly augmenting in which the strength of contraction falls off slowly and a steady state type. By virtue of reciprocating collaterals the two half-centers alternately affect each other--increasing activity in one tends automatically to inhibit the activity of the other (38).

Gesell's explanation of eupneic breathing on the basis of his findings is this: oxygen lack and carbon dioxide excess both hamper oxidation in the living cell. Thus these forces act directly upon the cells of the respiratory center

and reflexly through the outlying chemoreceptors. Though providing steady drives they provoke periodic respiratory activity. As the cells of the inspiratory half-center begin to act they, through intercommunicating collaterals, inhibit the cells of the expiratory half-center. The frequency of impulses from the inspiratory half-center to the inspiratory muscles increases, primarily through vagus afferents coming from the expansion receptors in the lungs until, at a certain point these vagal impulses are transferred from the inspiratory half-center to the expiratory half-center, followed by rapid subsidence of the vagal impulse. The afferent expiratory impulses then follow one of two patterns--rapidly augmenting with slow fall off or a steady state throughout the expiratory act--depending upon the afferent impulses (32). Increased depth of respiration is explained as a combination of recruitment of new muscle units and an intensified activity of those units already engaged. The same principle holds for hyperpnea from O_2 lack or CO_2 excess (34). Parts of this explanation appear to have merit, but as mentioned before, the assumption of an acidity within the center appears untenable.

The hyperpnea of muscular exercise is now thought to be principally reflex in origin rather than of a chemical stimulus. Thus it resembles the stimulus of anoxemia. Nielsen (80) has suggested the hyperpnea of exercise could be attributed to impulses destined for the muscles irra-

diating into the respiratory center, or to excitatory reflexes from the muscles. Harrison and collaborators (89) have confirmed the latter view.

All nervous tissue is sensitive to oxygen lack. Lernox, Gibbs, and Gibbs (68) showed that unconsciousness occurs when jugular blood contains less than 25 per cent saturation. It appears prolonged exposure to such low pressures of oxygen will lead to definite brain injury, this tissue being much more sensitive than muscle tissue, (17). Gellhorn, Cortell and Carlson (30), observed in cats that partial anoxia appeared to increase the excitability of the hypothalamic sympathetic centers. This effect depends upon the presence of afferent impulses from the chemoreceptors of the sino-aortic area. Somatic responses obtained from the same level, however, appear to decrease.

The degree of anesthetization appears to profoundly affect the respiratory response to stimulus. Ignorance of this fact has led to many misinterpretations in animal work. Especially is this true in the case of the response of dogs to low oxygen. If significant stimulation by anoxemia is to be obtained the dog must be lightly anesthetized (78). Moyer and Beecher (79) state that the hyperpneic effect of low oxygen is not abolished by deprivation of peripheral chemoreceptor reflexes, but Dripps et al. (25) do not find significant difference in unanesthetized and anesthetized dogs as regards the mechanism of response to CO_2 and low O_2.

Studies of respiration at high altitudes has added a great deal to our knowledge of control of respiration. Jourdanet, as cited by Van Liere (97) was the first to study systematically the effects of high altitudes on respiration. Paul Bert (5) made early observations on the effect of altitude on respiration. He concluded it was the reduced pO_2 which caused the effects of high altitudes and the correctness of this observation has been borne out. Haldane also studied respiration in high altitudes. His contributions are outlined in his book (43). His researches were carried out both in a low pressure chamber and on mountains. Yandell Henderson and Barcroft also made very valuable observations on this phase of the physiology of respiration. More recently the work of Dill and associates is noteworthy and is summarized in Dill's book (19).

The chemical changes which take place in the blood with prolonged exposure to high altitudes are outlined by Barcroft (4). Principally the changes involved are concerned with the carbon dioxide of the blood. With ascent the stimulus of anoxia causes hyperventilation which results in a more rapid elimination of CO_2. It is the free CO_2 which is lost and this loss entails an alkalosis. Thus we see the stimulus of anoxia is opposed by the inhibition of alkalosis. It varies among men as to which gains the upper hand (21). Free CO_2 is lost rapidly by hyperventilation, but the combined CO_2 is lost much more slowly. After a prolonged period of ac-

climatization, however, the acid-base balance characteristic of lower levels is restored.

The changes concerned with oxygen transport are not so well agreed upon. Barcroft (4, p.42) postulated from his observation on the Peak of Teneriffe (10,000 feet) that the affinity of hemoglobin for oxygen was increased. Haldane (43, p.110) took the opposite view after his experience on Pike's Peak. Hall (46) on the basis of research carried out in the Andes agrees with Haldane.

Dill (21, p.171) found that the acclimatized person is able to supply more oxygen to his tissues than the unacclimatized person, and without excessive overventilation. He suggests this probably depends upon superior internal respiration or upon greater cardiac output, or both. Monge (77) suggests that in some manner altitude changes the capacity of the tissues to fix oxygen. He found a higher oxygen content of venous blood in the fully adapted man than in the unacclimatized person.

In the fully acclimatized person respiratory volume varies but little up to an altitude of 17,500 feet. However, in dealing with respiration at high altitudes another type of person must be reckoned with--the unacclimatized person who is rather suddenly exposed to the rare atmosphere. In his case none of the adaptive measures mentioned in connection with the acclimatized person are seen. Whereas profound readjustments of the internal phase of respiration

are noted in the acclimatized person, with the unacclimatized person all adjustments must be made in the external respiration.

The altitude at which hyperventilation begins is disputed. Schneider (97, p.105) found, using a low pressure chamber, the rate of respiration was not affected particularly until a simulated altitude of 15,000 feet was reached. Armstrong (2, p.255) reported changes as low as 4,000 feet. Haldane and Poulton (97, p.106) reported wide variation in response of subjects to lowered O_2 tension but reported some responding to reduction of five per cent oxygen in the inspired air. This figure, interpreted in terms of altitude, agrees with Armstrong's figure. In severe exercise and anoxia the increase of respiration rate may be as much as fourfold.

The depth of respiration is seemingly affected more by altitude than the rate. Variation among men is greater, however. Dill has emphasized the point that the responsiveness of the respiratory center to anoxia determines in a large measure a man's altitude tolerance (18).

As was pointed out previously, low-oxygen stimulation of respiration tends to wash out the CO_2 from the lungs. This is apparent in one who is suddenly exposed to the low oxygen tensions of altitude. The recovery is quickly made, however, on descent if the exposure has not been too long. It is said an aviator breathes subnormally for a time after

descent until his normal CO_2 tension is retained (97, p.112).

As regards the effect of temperature on respiration, this phase is much more pronounced in those animals who have but few sweat glands than it is in man. High temperature favors the dissociation of oxyhemoglobin (21, p.14).

Gesell offers a hypothetical explanation of the hyperpnea observed in hyperthermia on the grounds of an increased metabolic rate in the nerve cells of the respiratory center. This, he says, produces a greater metabolic gradient between the axon hillock and the neuron, thus increasing the rate of firing (32). He makes no attempt to explain how the degree of this response is controlled which could account for the panting response in some animals and not in others. Temperature not only affects the oxygen combining capacity of the hemoglobin but also its acid-binding capacity (20). Dill and Forbes (20) found in patients under cold anesthesia that despite hyperventilation the pO_2 of arterial blood declines with decreasing body temperature. Slowed diffusion rate, slowed blood chemical changes or some pulmonary edema are offered as possible causes. They found the pH to be on the acid side. They conclude that while the acid-base balance of the blood is the probable cause of the observed hyperventilation the reduced pO_2 may have been sufficient to cause this response through the mediation of the carotid body.

MATERIALS

High altitudes can be simulated by partially removing the air from a sealed chamber. Paul Bert recognized the latter part of the last century that the handicaps imposed by breathing the thin air of high altitudes could be ascribed wholly to the reduction in the partial pressure of oxygen.

The low pressure chamber used in this study is a large cylindrical tank which will hold several men. It is equipped with locks for passing in and out small articles, a large lock for passing personnel in and out and several observation ports. The evacuation is effected by a pump which is operated from outside the chamber. A two-way communication system is installed so that one or more persons on the inside can communicate with the operator outside. Both the inside and the outside are equipped with anaeroid altimeters. In addition, there is installed outside a large mercury manometer. As a safety precaution, a valve which can be operated from the inside will quickly admit air to the chamber. At least two persons are present in the chamber on each experiment and two observers on the outside are always present. In this chamber no attempt is made to regulate the temperature, which ranges from 25° to 29° C. The chamber is high enough to permit full upright position and large enough for considerable moving about.

The oxygen supply for subjects in the chamber is piped in

from the outside and many outlets serve the individual subjects inside. Flow regulators so constructed as to give adequate oxygen supply govern the amount of oxygen to the subjects. Various types of Army Air Corps oxygen masks are available.

In addition to the low pressure chamber just mentioned, the laboratory is equipped with a low pressure-low temperature chamber in which the temperature is lowered to approximate that of substratosphere levels. The usual operating temperature range in this chamber is from -30° to -50° C. and it, too, can be evacuated to any altitude desired. The details of construction of this chamber are similar to the one described above.

In this laboratory we have at our disposal several pieces of equipment which have been recently developed and are not yet available to all laboratories. A brief description of some of these instruments will be given here and, where possible, references will be given which will furnish more details.

The readily observed principle of oxygenated blood having a lighter shade of red color than unoxygenated blood is the basis for an instrument first developed in this country by Dr. Glenn A. Millikan (107) and known as an "oximeter". The early history of this type of instrument dates back through Doctor Adrian's laboratory in Cambridge, to Dr. Hermann Rein's laboratory in Göttingen. The oximeter is designed for measuring the proportion of oxygenated to unoxygenated hemoglobin in the blood. The oximeter is really an electric colorimeter, but is

calibrated to read the proportion of hemoglobin actually engaged in the transport of oxygen.

The colorimeter consists of a photocell together with a small electric lamp which fits over the outer ear and sends a constant intensity light beam from the lamp through the scapha of the ear against the photocell. The color of the light striking the photocell is thus dependent upon the color of the blood it has passed through. One section of the photocell is covered with a red filter, making it sensitive to changes in color of the light beam falling on it. This photocell section is then connected to a galvanometer which records the proportion of oxygenated hemoglobin directly. See Fig. 5 for an example of the ear unit and galvanometer.

The thickness through which the light beam must flow will influence the reading. Ears differ considerably in thickness and a given ear will vary according to the degree of dilitation of its blood capillaries. These variances are taken into account in the setting of the instrument. The second section of the photocell is covered with a green filter which is insensitive to the color of the blood. This filter locates which of the several scales on the galvanometer shall be read. Sufficient time must be allowed for the ear vessels to reach maximum dilitation for the degree of heat applied.

The instrument must now be set on some saturation figure. A person sitting quietly breathing normal room air has about 95 per cent of his available hemoglobin saturated with oxygen.

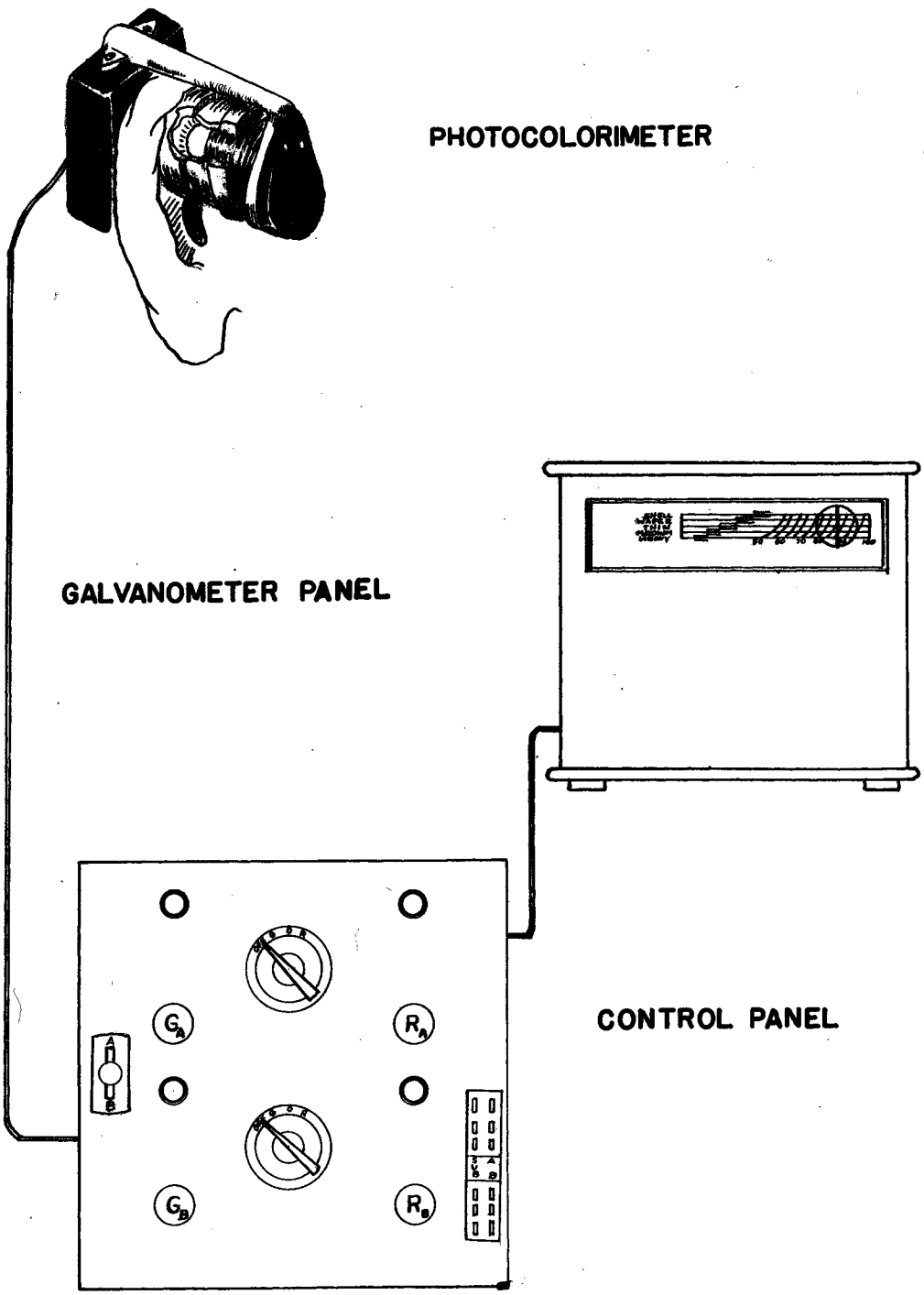

Figure 5. The Millikan Oximeter.

If, however, he breathes pure oxygen for a short time, his saturation will become 100 per cent. The setting is then made according to the conditions. The instrument is now ready to give a constant picture of the oxygen saturation of the blood.

The accuracy of this oximeter is checked occasionally by taking a sample of arterial blood from the brachial artery of the subject while noting the reading of the oximeter. This blood, drawn and kept under oil, is then analyzed on the Van Slyke manometer according to the method of Peters and Van Slyke (83). The accuracy of the Van Slyke manometric method is ± 1 per cent. When checked against this method the oximeter usually falls within the range of ± 5 per cent at the lower saturation levels, i.e., 50 to 60 per cent. The accuracy increases with the rise in saturation. Fuller details on this instrument are available through its manufacturer, the Coleman Electric Company, Inc., Maywood, Illinois.

Mr. Bernard Smaller, a physicist in the laboratory, has constructed a flow meter which can be placed in series with the inspiratory tube and the ventilation rate recorded. This instrument is based on the principle of a heated wire being more resistant than a cool one. Since the rate of cooling is directly proportional to the number of molecules of air hitting the wire, the rate of air flowing past the wire can be measured. The resistance of the wire is measured in a Wheatstone bridge and the recording is on a sensitive microameter which is highly damped.

In some cases respiratory volume was measured by having the subject exhale directly through a gas meter while in still others, the exhaled air was collected for a given length of time in a Douglas bag and later measured in a large spirometer. Samples of this air were then taken for analysis on the Haldane gas analysis equipment. In one series of experiments the exhalation was directly into a large (500 liters capacity) Tissot spirometer, the rise of which was recorded each minute.

Respiratory tracings were obtained by using a specially built Both-Benedict metabolism apparatus modified with pulleys to increase the amplitude of the breathing curve. The speed of the instrument was increased by inserting an electric kymograph motor to drive the recording paper at any desired speed. A drawing of this instrument is found in Fig. 6.

A cardiotachometer has been employed for the purpose of recording heart rate. This instrument consists of three electrodes which are held by straps to the front of the chest wall. Wires leading from the electrodes go to an amplifier which records the beat of the heart with a pen writing on a tape marked off in seconds. The grid of the tube of the amplifier is adjusted to a point just below the discharge potential of the tube. The impulse coming from the heart beat through the electrodes is sufficient to cause a discharge of the tube which in turn is recorded on the tape.

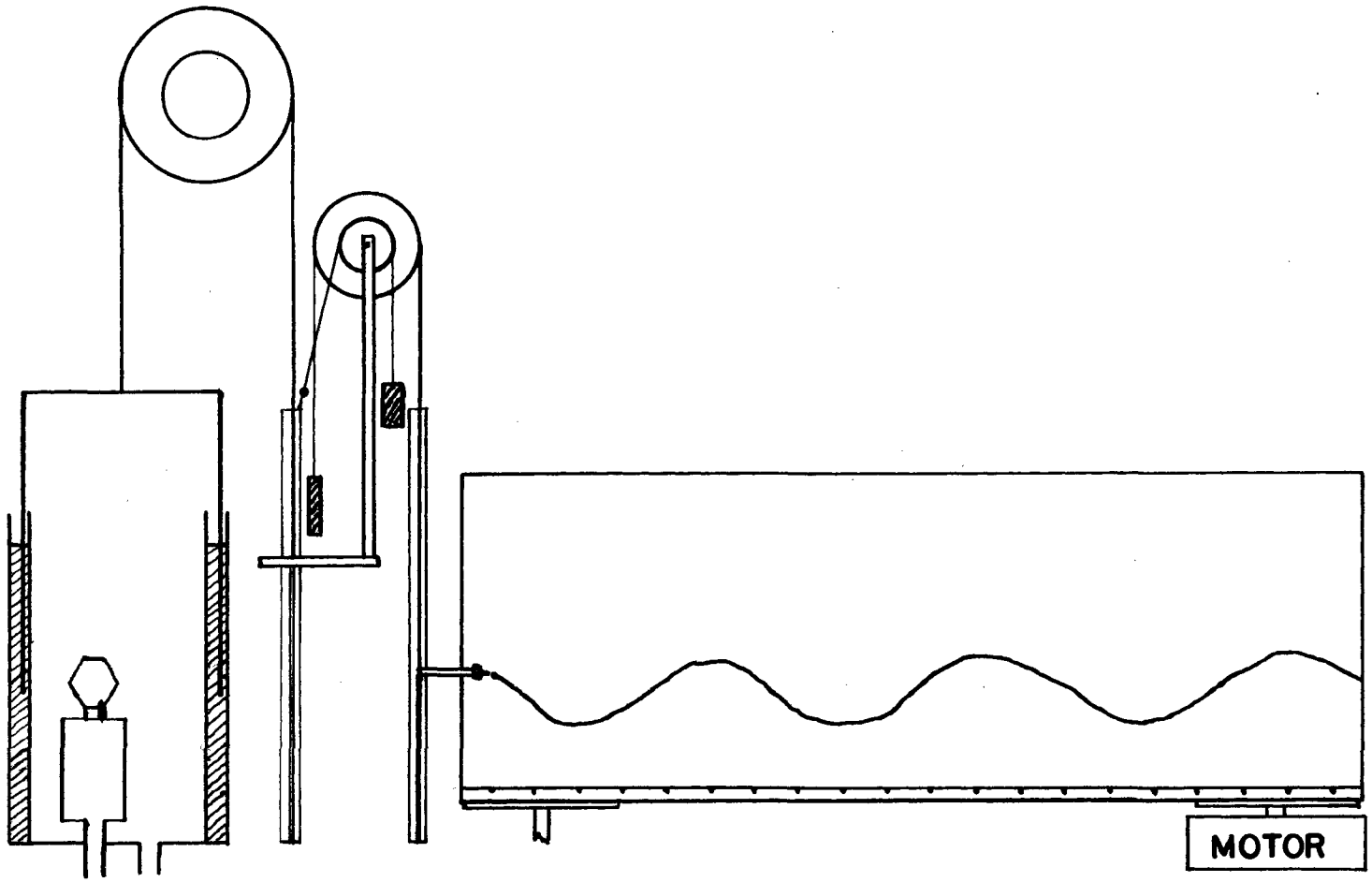

Figure 6. SPIROMETER - KYMOGRAPH SETUP

PROCEDURE

When speaking of ventilation it is customary to speak of the total amount of air breathed in a minute and call this the minute ventilation rate. In furnishing oxygen to a person this figure is of importance, but still another rate is of more importance. This is concerned with the maximum rate at which this air is taken in and given out during periods of inspiration and of expiration.

For this determination it is necessary to take into account the fact that, while six liters may represent the total minute ventilation, this six liters was taken in in slightly less than half of the minute, the remainder of the time being taken up with the exhalations and the intervening pauses. It follows that oxygen equipment must not only furnish an adequate amount for the total minute's ventilation, but also furnish it rapidly enough to prevent discomfort in the breather. With this problem in mind a respiratory apparatus as previously described was constructed and the pattern of respiration of several subjects was recorded at ground level (three levels of activity), altitude (20,000 and 35,000 feet) and while shivering in the cold. From these data it was possible to calculate the maximum rates of inspiration and of expiration.

If a 180-pound man should bail out of an airplane at 30,000 feet he would have to abandon his regular oxygen supply.

The estimated time required to float to the ground if the parachute is opened at 30,000 feet is 19 minutes and 42 seconds (98). During the early part of this descent a considerable degree of anoxia is experienced due to the small amount of oxygen available. The problem of how this will affect the man and what will be his respiratory response has been investigated, using the low pressure chamber and laboratory subjects.

Two types of descent were performed, (a) the subject moved about in the chamber for approximately 30 seconds while still breathing oxygen, then at a given signal he sat down, the oxygen was disconnected and the chamber started down at the proposed rate; (b) the subject moved about as before, but two seconds before starting down he began taking deep breaths of oxygen, then at a given signal held his breath as long as possible. Meanwhile the oxygen supply was cut off and the chamber was descending.

The arterial oxygen saturation, ventilation rate and pulse rate were recorded constantly all the way down. The ventilation response of the subjects was considered important since this has so much to do with the ability to withstand low oxygen tensions.

The altitude at which hyperventilation begins when not breathing oxygen has not been agreed upon (2, p.255). Using the low pressure chamber and a flow meter to measure volume, the per minute volume of five subjects was recorded at each

5,000 feet up to 20,000 feet. Then, breathing 100 per cent oxygen, the volumes were again measured at the same altitudes.

In extreme altitudes even while breathing 100 per cent oxygen conditions of anoxia develop as a consequence of the reduced total pressure. This drop in pressure begins to affect the arterial oxygen saturation at about 36,000 to 37,000 feet. We have recorded the respiratory volumes of a number of subjects while sitting quietly above this altitude, using a spirometer. For an ascent to the most extreme altitudes, such as above 40,000 feet, it is necessary to remove some of the dissolved nitrogen from the body as a prophylaxis against "aeroembolism", or "bends" (2, p.342). This is done by breathing oxygen while exercising on a bicycle ergometer at ground level for at least one-half hour prior to ascent. The exercise usually continues during at least part of the ascent so some little time is required for the respiratory volume to return to resting level. To assure at least one competent observation with the effect of exercise eliminated, an experiment was conducted in which the subject's resting respiratory volume was recorded, then he denitrogenated for 35 minutes, then rested 25 minutes until the respiratory volume returned to the previous level, then ascent was begun to 44,800 feet while the subject remained sitting quietly throughout the experiment making no conscious effort to influence his breathing. At least 15 minutes were spent at each of 25,000, 30,000, 40,000 and 44,800 feet.

The rationale behind the choosing of 44,800 feet as a final height rests upon the pressure associated with this particular altitude. The total barometric pressure of 44,800 feet is 112 mm. Hg. The pH_2O in the lungs is 47 mm. and at this altitude enough hyperventilation will be taking place to reduce alveolar pCO_2 to approximately 30 mm. Thus 77 of the 112 mm. will be taken up in the lungs by H_2O and CO_2. Hence the pO_2 will be 35. Examination of the oxygen dissociation curve corresponding to an alkaline pH reveals a pO_2 of 35 to be associated with about a 70 per cent arterial oxygen saturation, or about the lowest tolerable degree of anoxia.

Although various compensations are adequate to maintain an individual at rest breathing pO_2 values lower than normal, the question arises if he would be maintained in a considerable degree of work. To obtain information on this subject a work bout capable of raising the resting oxygen consumption some ten times has been devised. This exercise consists of lifting a bucket weighing one-third the clothed body weight onto a table 30 inches high and returning it to the floor once every three and one-third seconds, or 18 times a minute. The subject sits down on a chair between lifts, arising to perform the lift. The maximum duration of this severe work is five minutes. During the course of the work the subject's ventilation rate, pulse rate and arterial oxygen saturation were recorded, together with, in some cases, an arterial puncture at the finish of the work, the blood then being analyzed for per cent satu-

ration, available base, pCO_2 and pH.

RESULTS

The results of the analysis of respiratory patterns of various subjects made under each of six sets of conditions are tabulated in Tables 2 to 7 inclusive. The specific information for each table is found with that table.

By maximum second rate of inspiration and expiration is meant the greatest flow, in liters per minute, which is maintained for between 0.7 and 1.5 seconds, and which is exemplified by the steepest portion of the curve. This means that during the inspiratory or expiratory phase the air will be moving at such rate a portion of the time.

By dividing the average maximum inspiratory rate found by the minute rate of ventilation, expressed in liters per minute, we may obtain a factor indicating the number of times the per minute ventilation rate is multiplied during this maximum flow.

It is seen that in the basal reclining state and in the sitting condition the average maximum inspiratory rate is approximately four and one-half times the number rate of ventilation. The duration of this peak is very short, however. The tendency is toward a rapid build-up to the indicated peak, with a slow tapering off. In the case of exercise, however, in which case the per minute volume of respiration is increased three to four times, the maximum second rate of inspiration reached is only about three and one-half times the per minute

TABLE 2. OBSERVATIONS ON SUBJECTS IN THE BASAL STATE

(Except where noted volumes are saturated, at 37° and ambient pressure.)

Name	Oxygen used NTP	Minute rate of Ventilation	Maximum second rate of inspiration		AMI*	Maximum second rate of expiration		AME**
			Average	Range	V	Average	Range	V
	l./min.	l./min.	l./min.	l./min.		l./min.	l./min.	
D	0.25	6.9	28	49-20	4.1	25	30-12	3.5
F	0.21	5.8	26	36-20	4.5	20	27-15	3.4
G	0.32	7.4	33	42-22	4.4	18	28-10	2.5
Ha	0.23	5.3	23	32-17	4.5	20	30-15	3.7
Hi	0.21	8.3	32	49-17	3.9	40	49-26	4.8
He	0.26	6.4	27	53-17	4.2	25	49-16	4.0
Hp	0.21	9.2	31	41-21	3.4	30	42-16	3.3
J	0.21	5.0	26	35-22	5.3	20	27-14	3.9
L	0.21	6.3	31	41-25	4.9	31	57-17	4.9
N	0.23	6.3	31	52-23	4.9	22	33-17	3.6
Pe	0.23	6.2	27	32-20	4.3	17	21-12	2.8
Pi	0.22	5.1	26	35-20	5.1	35	45-26	6.7
R	0.21	4.9	20	27-12	4.1	16	25-10	3.3
Average	0.231	6.39	27.8		4.43	24.5		3.88

* Average maximum second rate of inspiration divided by minute rate of ventilation.
** Average maximum second rate of expiration divided by minute rate of ventilation.

TABLE 3. OBSERVATIONS ON SUBJECTS SITTING AT GROUND LEVEL

(Except where noted volumes are saturated, at 37° and ambient pressure.)

Name	Oxygen used NTP	Minute rate of Ventilation	Maximum second rate of inspiration		AMI*	Maximum second rate of expiration		AME**
			Average	Range	V	Average	Range	V
	l./min.	l./min.	l./min.	l./min.		l./min.	l./min.	
D	0.40	9.5	43	51-32	4.5	32	40-25	3.4
F	0.56	9.6	43	61-26	4.5	31	41-22	3.2
G	0.42	10.0	43	57-25	4.3	33	50-26	3.4
Ha	0.38	8.7	35	42-25	4.0	26	33-16	3.1
Hi	0.39	16.9	64	84-51	3.8	63	88-46	3.7
Ho	0.28	7.5	36	67-31	4.7	27	37-19	3.7
Hr	0.34	8.3	35	42-30	4.2	21	26-16	2.6
J	0.33	9.4	49	60-40	5.1	53	77-40	5.7
L	0.24	7.3	37	57-33	5.1	28	38-21	3.9
N	0.41	15.0	59	99-34	3.9	37	47-25	2.5
Pe	0.36	9.2	36	43-32	4.0	27	33-20	2.9
Pi	0.36	7.2	37	51-27	5.1	38	48-30	5.3
R	0.31	8.0	38	47-25	4.7	27	33-21	3.3
Average	0.368	9.74	42.7		4.45	34.1		3.59

* Average maximum second rate of inspiration divided by mimute rate of ventilation.
** Average maximum second rate of expiration divided by minute rate of ventilation.

TABLE 4. OBSERVATIONS ON SUBJECTS EXERCISING AT GROUND LEVEL

(Except where noted volumes are saturated, at 37° and ambient pressure.)

Name	Oxygen used NTP	Minute rate of Ventilation	Maximum second rate of inspiration		AMI* / V	Maximum second rate of expiration		AMR** / V
			Average	Range		Average	Range	
	l./min.	l./min.	l./min.	l./min.		l./min.	l./min.	
D	0.91	28.2	87	99-74	3.0	73	101-56	2.6
F	1.15	31.4	106	168-73	3.4	62	92-49	2.2
G	1.15	28.2	92	102-77	3.3	75	93-57	2.7
Ha	1.10	31.8	80	113-60	2.5	77	86-54	2.4
Hi	1.04	36.8	146	199-93	4.0	125	154-105	3.4
He	1.36	27.4	87	138-66	3.2	73	93-62	2.6
Hr	0.93	24.3	87	119-75	3.6	55	67-41	2.2
J	2.08	26.5	163	197-117	6.4	118	152-80	4.4
L	1.19	23.6	85	111-68	3.6	60	74-54	2.6
N	0.75	26.6	86	109.65	3.2	67	102-51	2.5
Pe	1.38	26.9	93	110-69	3.5	69	88-50	2.6
Pi	1.70	27.0	84	111-61	3.1	73	83-53	2.7
R	1.13	29.1	93	110-80	3.2	85	110-68	2.9
Average	1.221	28.29	99.2		3.54	77.8		2.75

* Average maximum second rate of inspiration divided by minute rate of ventilation.
** Average maximum second rate of expiration divided by minute rate of ventilation.

TABLE 5. OBSERVATIONS ON SUBJECTS EXERCISING AT 20,000 FEET

(Except where noted volumes are saturated, at 37° and ambient pressure.)

Name	Oxygen used NTP	Minute rate of Ventilation	Maximum second rate of inspiration		AMI* / V	Maximum second rate of expiration		AME** / V
			Average	Range		Average	Range	
	l./min.	l./min.	l./min.	l./min.		l./min.	l./min.	
D	1.26	25.4	88	97-68	3.5	73	83-56	2.9
F	1.39	24.4	86	97-72	3.5	71	83-61	2.9
Ha	0.59	20.7	76	100-56	3.7	61	85-32	2.9
Hi	1.15	38.8	102	131-85	2.6	127	163-100	3.3
Ho	1.40	22.9	93	110-78	4.0	73	93-51	3.2
Hp	1.32	33.4	129	156-105	3.9	124	144-105	3.7
J		24.4	81	93-71	3.3	54	68-39	2.2
L	0.84	22.4	73	85-61	3.3	68	122-56	3.0
Mc	0.94	34.4	146	207-110	4.2	114	170-83	3.4
N	0.85	25.1	100	129-81	4.0	73	105-51	2.9
Pe	0.96	34.2	93	107-76	2.7	83	105-63	2.4
Pi	1.24	25.1	95	124-66	3.8	88	110-68	3.5
S	0.97	27.6	78	127-54	2.8	63	100-49	2.3
W	1.23	23.6	97	139-83	4.1	76	93-61	3.2
Average	1.068	27.32	95.5		3.53	82.0		2.99

* Average maximum second rate of inspiration divided by minute rate of ventilation.
** Average maximum second rate of expiration divided by minute rate of ventilation.

TABLE 6. OBSERVATIONS ON SUBJECTS EXERCISING AT 35,000 FEET

(Except where noted volumes are saturated, at 37° and ambient pressure.)

Name	Oxygen used NTP	Minute rate of Ventilation	Maximum second rate of inspiration		AMI* / V	Maximum second rate of expiration		AME** / V
			Average	Range		Average	Range	
	l./min.	l./min.	l./min.	l./min.		l./min.	l./min.	
D	1.19	25.5	90	110-75	3.5	90	105-75	3.4
Ha	1.16	24.0	85	105-70	3.5	75	100-45	3.1
Hi	1.43	38.0	125	145-100	3.3	130	165-85	3.4
Ho	1.26	27.5	90	115-80	3.3	65	80-45	2.4
Hp	0.98	31.6	130	195-95	4.1	120	155-85	3.8
L	1.05	20.0	75	105-60	3.8	65	130-40	3.3
Mc	1.30	34.5	150	205-135	4.4	115	140-85	3.4
N	1.25	35.0	135	180-100	3.8	95	135-75	2.8
Pe	1.15	23.0	105	130-80	4.5	80	100-65	3.6
Pi	1.10	31.0	145	220-95	4.6	125	230-55	4.1
S	1.32	29.6	97	115-59	3.2	80	104-51	2.7
W	1.16	30.2	110	160-95	3.7	75	95-50	2.5
Average	1.196	29.16	111.4		3.81	92.9		3.21

* Average maximum second rate of inspiration divided by minute rate of ventilation.
** Average maximum second rate of expiration divided by minute rate of ventilation.

TABLE 7. OBSERVATIONS ON SUBJECTS SHIVERING AT -40° C. AT GROUND LEVEL

(Except where noted volumes are saturated, at 37° and ambient pressure.)

Name	Oxygen used NTP	Minute rate of Ventilation	Maximum second rate of inspiration		AMI*	Maximum second rate of expiration		AME**
			Average	Range	V	Average	Range	V
	l./min.	l./min.	l./min.	l./min.		l./min.	l./min.	
B	0.50	17.2	59	72-47	3.5	37	74-23	2.2
D	0.75	29.0	116	153-85	4.0	87	132-72	3.0
F	0.61	22.8	96	139-60	4.2	51	83-42	2.2
G	0.70	25.2	85	147-38	3.4	80	124-47	3.2
Hi	0.75	42.3	117	155-81	2.8	127	199-88	3.0
Hr	0.83	19.8	88	150-53	4.4	47	79-23	2.4
J	1.23	20.4	85	115-38	4.2	53	102-15	2.6
M	0.52	25.3	74	112-41	2.9	62	82-38	2.4
N	0.62	36.7	126	182-62	3.4	137	252-46	3.7
Pe	0.99	25.2	117	165-87	4.4	95	137-64	3.6
Pi	0.57	18.3	59	78-37	3.2	50	92-37	2.7
R	1.06	38.0	143	199-98	3.8	152	228-90	4.0
S	0.71	48.6	148	204-67	3.0	127	192-90	2.6
T	0.65	37.3	181	321-113	4.9	109	164-66	2.9
W	1.05	53.3	166	256-79	3.1	137	212-79	2.6
Average	0.769	30.63	110.7		3.68	90.1		2.87

* Average maximum second rate of inspiration divided by minute rate of ventilation.
** Average maximum second rate of expiration divided by minute rate of ventilation.

rate. The duration of this peak is longer than in the first case. Exercise at 20,000 and 35,000 feet does not appear to materially alter this latter relationship nor does shivering in the cold in which case the per minute volume of respiration and the maximum rates attained compare very closely with those of exercising, both causing an increase in ventilation of about three to four times over rest.

In general the expiratory phase of respiration is of longer duration and the peak rate is less than for inspiration. For basal and rest conditions this maximum rate is from three and one-half to four times the per minute volume, while in exercise at ground level, 20,000 and 35,000 feet and shivering in the cold the maximum rate approximates three times the per minute volume.

The degree of anoxia attained in a parachute descent from 30,000 feet without oxygen is considerable. Fig. 7 shows the average degree of anoxia experienced by the subjects, together with the average per minute volume of respiration. Fig. 8 shows the results of one typical subject, giving the arterial oxygen saturation, pulse, ventilation rate and the results of an analysis of arterial blood drawn three to four minutes after the start of the descent. It is seen the pH of this blood was increased to 7.49 and the arterial pCO_2 was reduced to 29.2 mm. Hg. These changes are usually a result of hyperventilation, but are never thought to be the cause since a lowered pH and an increased pCO_2 are known to stimulate respiration. Another

Figure 7.

Mean results of 15 simulated parachute descents in the low pressure chamber.

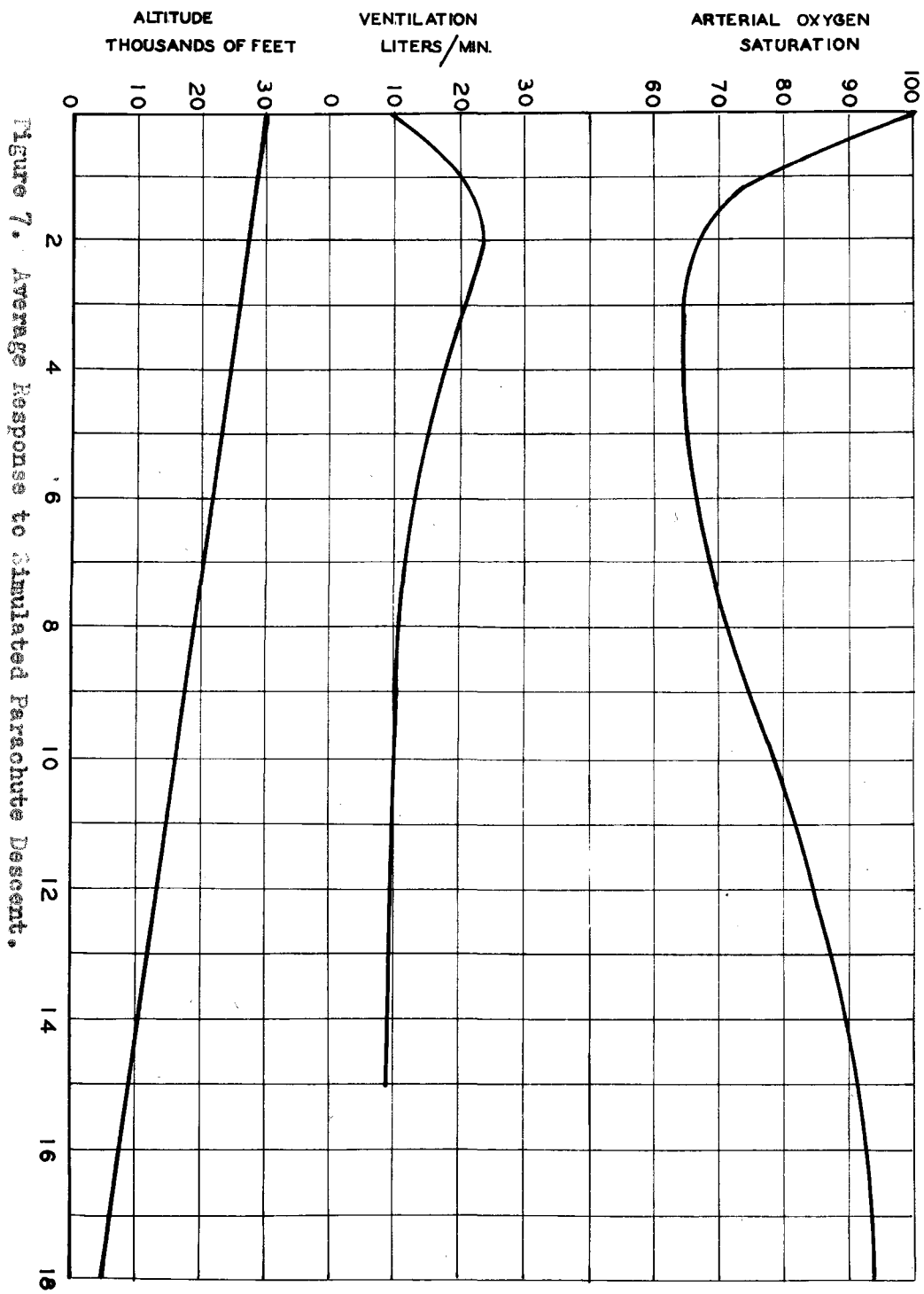

Figure 7. Average Response to Simulated Parachute Descent.

Figure 8.

The subject breathed oxygen at 30,000 feet prior to descent. At signal the oxygen was removed and the air was admitted to the chamber at such a rate as to simulate an open parachute descent. The subject sat quietly throughout the experiment.

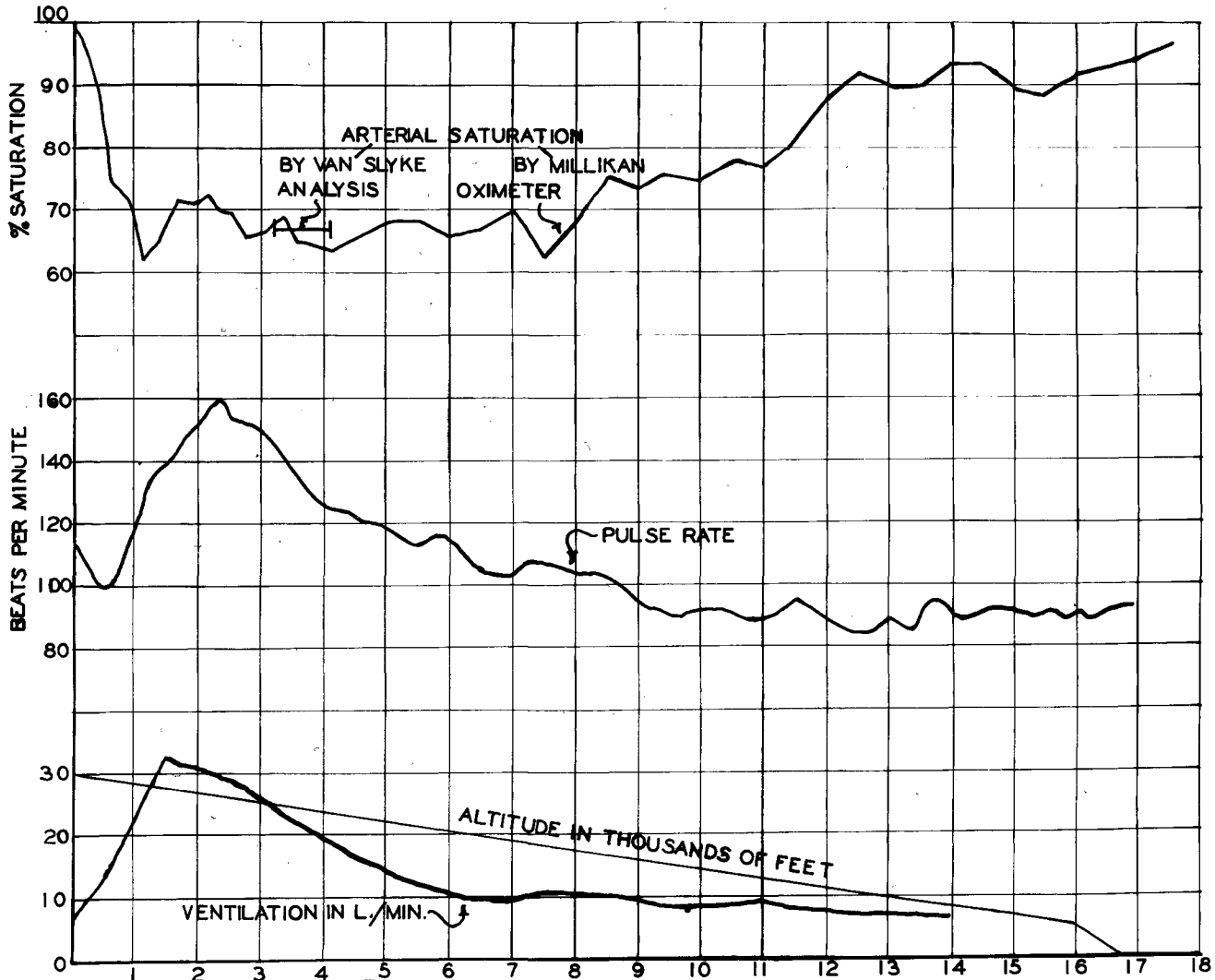

Figure 8. Typical Response to Simulated Parachute Descent.

item of interest from this figure is the immediate response of respiration to the decreasing arterial oxygen saturation. Also the lowest saturation, 62 per cent, is correlated with the greatest hyperventilation. The arterial pO_2, calculated from the saturation level on the oxygen dissociation curve for that pH, is 32, or less than one-third the normal value.

In the second series of experiments the subjects were instructed to hold their breath as long as possible. After filling the lungs with 100 per cent oxygen at 30,000 feet, the oxygen supply was cut off and the descent was started. The length of time for holding the breath varied from 30 seconds to two minutes and 40 seconds. Since the barometric pressure was increasing constantly during the voluntary apnea, the partial pressure of oxygen at the time breathing was resumed varied directly with the length of time the breath was held. Consequently the degree of anoxia attained was inversely proportional to the duration of breath-holding.

The accumulation of CO_2 doubtless accounted for the hyperventilation immediately following the forced apnea. However the CO_2 effects are shortlived as evidenced by the quick return to normal ventilation after holding the breath at ground level for an equivalent duration. Also this fact was varified by analyses of arterial blood drawn shortly after the resumption of breathing. The pH of the blood rises very rapidly in this case and in our experiments was quickly shifted to a distinct alkalinity. Fig. 9 shows a typical response of a subject on

Figure 9.

After hyperventilating 30 seconds subject held his breath as long as possible, then no attempt was made to influence respiration.

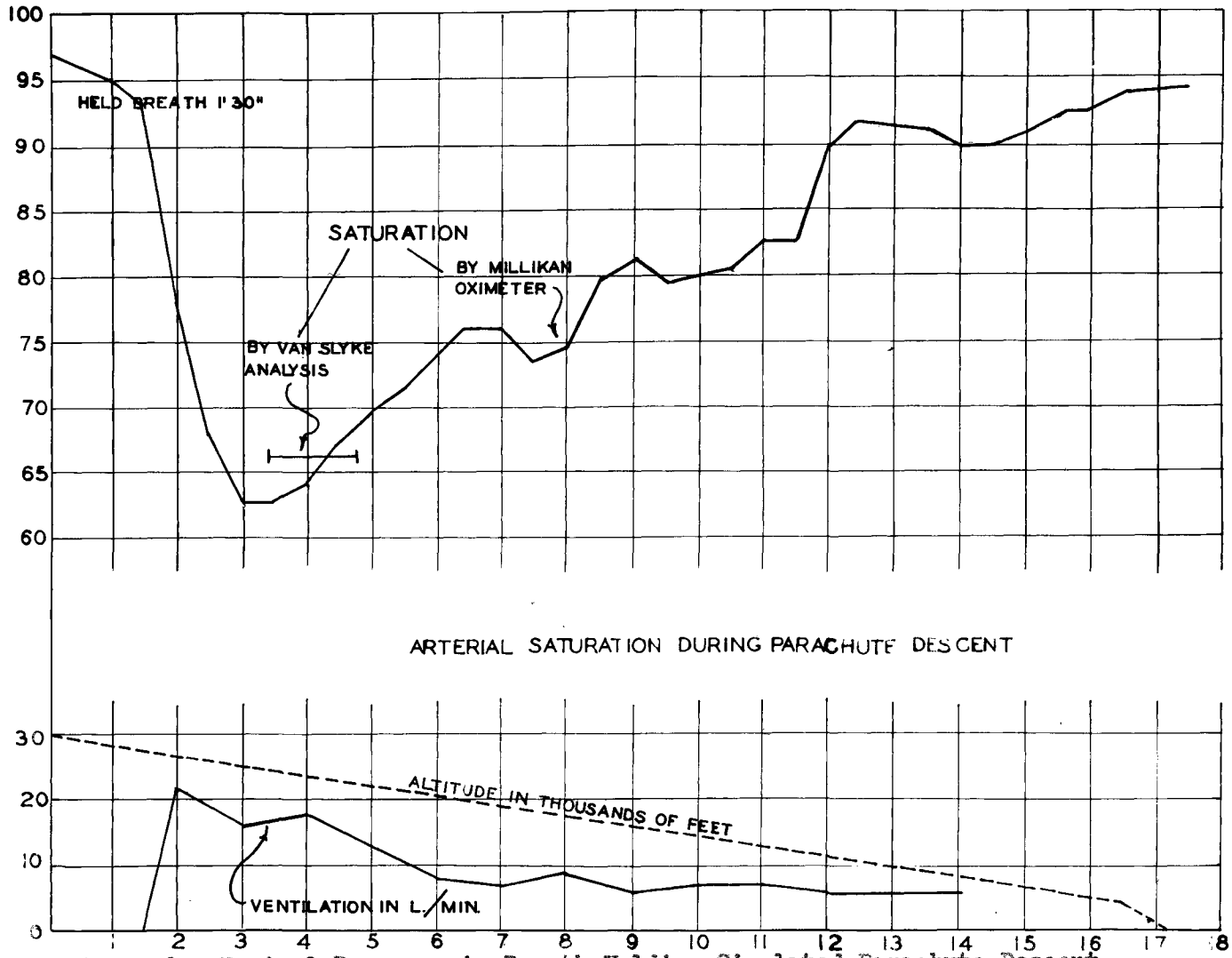

Figure 9. Typical Response in Breath Holding Simulated Parachute Descent.

whom an arterial puncture was obtained one minute and 40 seconds after the resumption of breathing and the pH of this blood was 7.48. The stimulus of anoxia apparently substitutes immediately for the initial stimulus of increased CO_2 and lowered pH with no reflection in the breathing.

A longer apnea entails a greater accumulation of CO_2, hence a stronger stimulus to the respiratory center. However, in this type of experiment, the increased pO_2, as a consequence of the lower altitude, experienced when breathing is resumed makes the stimulus of oxygen lack less. If the apnea is short the CO_2 stimulus should not be so great, but the stimulus of anoxia will be greater. Our results tend to bear out this contention. In the following table we have listed our subjects in order of the length of time the breath was held.

TABLE 8. VENTILATION AFTER HOLDING BREATH IN PARACHUTE DESCENT.

(L./min. 37°, saturated and at ambient pressure)

Subject	Time breath was held	First minute ventilation	Third minute ventilation
	seconds	l./min.	l./min.
L	30	23	18
J	42	21	19
F	47	20	15
S	50	21	16
H	68	22	14
D	102	41	31
P	120	28	15
G	130	29	14
A	149	30	11
W	160	42	10

The trend is toward a larger ventilation the first minute after breathing is resumed if the breath is held longer. This can be ascribed to the accumulated CO_2. The trend of the third minute, however, is toward decreasing ventilation if the breath has been held longer. This is easily explained on the basis of an increased pO_2 of outside air when the breathing was resumed.

For testing the altitude at which hyperventilation begins when supplementary oxygen is not breathed, five subjects were subjected to five minute exposures to 5,000, 10,000, 15,000 and 20,000 feet in the low pressure chamber. The mean results of the ventilation measurements are presented in the following table:

TABLE 9. RESPIRATION VOLUME AT ALTITUDES

(L./min. 37°, saturated, ambient pressure)

Ground	5,000 ft.	10,000 ft.	15,000 ft.	20,000 ft.
		Breathing air		
8.4	8.7	9.4	9.8	12.0
		Breathing oxygen		
8.2	8.9	8.3	8.7	8.1

It is evident from these results that no appreciable hyperventilation is experienced on short exposures to altitudes below 10,000 feet. Above this altitude some hyper-

ventilation is experienced even on short exposures. At 20,000 feet this increase amounts to nearly 50 per cent. However, from the degree of anoxia attained, which at 20,000 feet amounts to approximately 65 per cent arterial oxygen saturation, this degree of hyperventilation appears quite small. It is recognized that the length of exposure has a great deal to do with the respiratory response.

To escape the superimposed hyperpnea of exercise, necessitated by the incidence of aeroembolism at high altitudes, special modifications of the plan of ascent to 44,800 feet had to be made. By resting after exercise until the pre-exercise ground level of respiratory volume had returned, a comparative picture of the effect of altitude on respiration was obtained. The following table shows the volume of respiration at ground level before and after exercise, and at each of four altitudes at which 15 minutes were spent.

TABLE 10. VOLUME OF RESPIRATION AT VARIOUS ALTITUDES

(L./min. 37°, saturated and ambient pressure)

Ground level					
before exer.	after exer.	25,000	30,000	40,000	44,800
8.1	8.2	7.4	9.7	11.9	15.5

In this case 100 per cent oxygen was breathed throughout the entire experiment. The slight increase observed at

30,000 feet can be attributed to the lessened resistance of the oxygen regulator to breathing. However, the very definite rise at 40,000 feet and its continuation to 44,800 feet cannot be explained on this basis, but must be attributed to the stimulus of oxygen lack. Evidence for this contention is supplied in the following table complied from analyses of arterial blood drawn from eight subjects at 44,800 feet.

TABLE 11. ANALYSES OF ARTERIAL BLOOD OF SUBJECTS AT 44,800 FEET

Subject	Arterial O_2 saturation	pO_2 (mm. Hg)	pCO_2 (mm. Hg)	pH
P	62.3	31	33.7	7.45
D	66.5	30	28.7	7.51
J	58.1	27	30.3	7.51
G	69.3	29	24.3	7.61
W	62.7	27	24.7	7.55
S	60.4	29	28.3	7.53
H	67.9	29	23.5	7.59
F*	83.9	37	11.5	7.76

*This subject was consciously hyperventilating to the extent of 39.6 liters per minute.

It is of interest to note that in the case of the last subject it was possible to maintain a relatively high arterial oxygen saturation by excessive conscious hyperventilation. The pCO_2 in this case was, however, lowered nearly to the point of alkalosis tetanus. The automatic control of respiration would never compensate to this extent.

The continuous oxygen saturation, pulse rates and ventilation averages for one subject are pictured graphically in Fig. 10. The decline of saturation and incline of pulse rate and ventilation above 40,000 feet are quite apparent.

Extremely high altitudes add materially to the difficulty of completing a difficult work task. Table 12 shows the difference in response of one subject at ground level and at 38,000 feet doing the same work bout.

TABLE 12. COMPARISON OF WORK TEST AT GROUND AND 38,000 FEET

Subject: P Weight: 177 lbs. Load: 59 lbs.

	Time in minutes	Ground	38,000 ft.
Ventilation Rate (L./min. 37°, saturation, ambient pressure)	1	34.5	43.1
	2	46.5	124.0
	3	61.5	134.0
	4	67.7	123.8
	5	72.5	124.5
	6	51.4	122.0
Maximum Pulse Rate		168	176
Analysis of Blood			
Lowest O_2 Saturation		91	83
pCO_2		36.9	32.2
CO_2 Combining Capacity		31.0	32.8
pH		7.25	7.29

It is obvious from this table that the ventilation at 38,000 feet greatly exceeded that at ground level while doing the same amount of work. The analysis of the blood drawn by arterial puncture immediately after the work was stopped

(one minute 10 seconds after at 38,000 feet, two minutes after at ground level) does not reveal a great deal of difference in pH, CO_2 combining power or pCO_2 in the blood. Apparently the lactic acid production was practically the same in both cases, and sufficient to lower the pH of the blood in spite of the reduction in pCO_2.

A less severe work bout has also been attempted at altitudes. In this case the bucket weighs 40 pounds and is lifted only once every 7-1/2 seconds, or eight times a minute. The respiratory volume per minute and arterial O_2 saturation of a typical subject doing that amount of work on the ground, at 30,000 feet and at 40,000 feet is shown in Fig. 11. It will be noticed a considerable drop in arterial oxygen saturation is experienced while working at 40,000 feet. This may be interpreted as evidence of a delay in the crossing of the alveolar wall barrier by the oxygen.

Figure 10.

Arterial oxygen saturation by Millikan oximeter. Subject remained quiet throughout ascent. One-hundred per cent oxygen breathed throughout experiment, using a Krogh two-way mouthpiece. Pulse rate was recorded on a cardiotachometer.

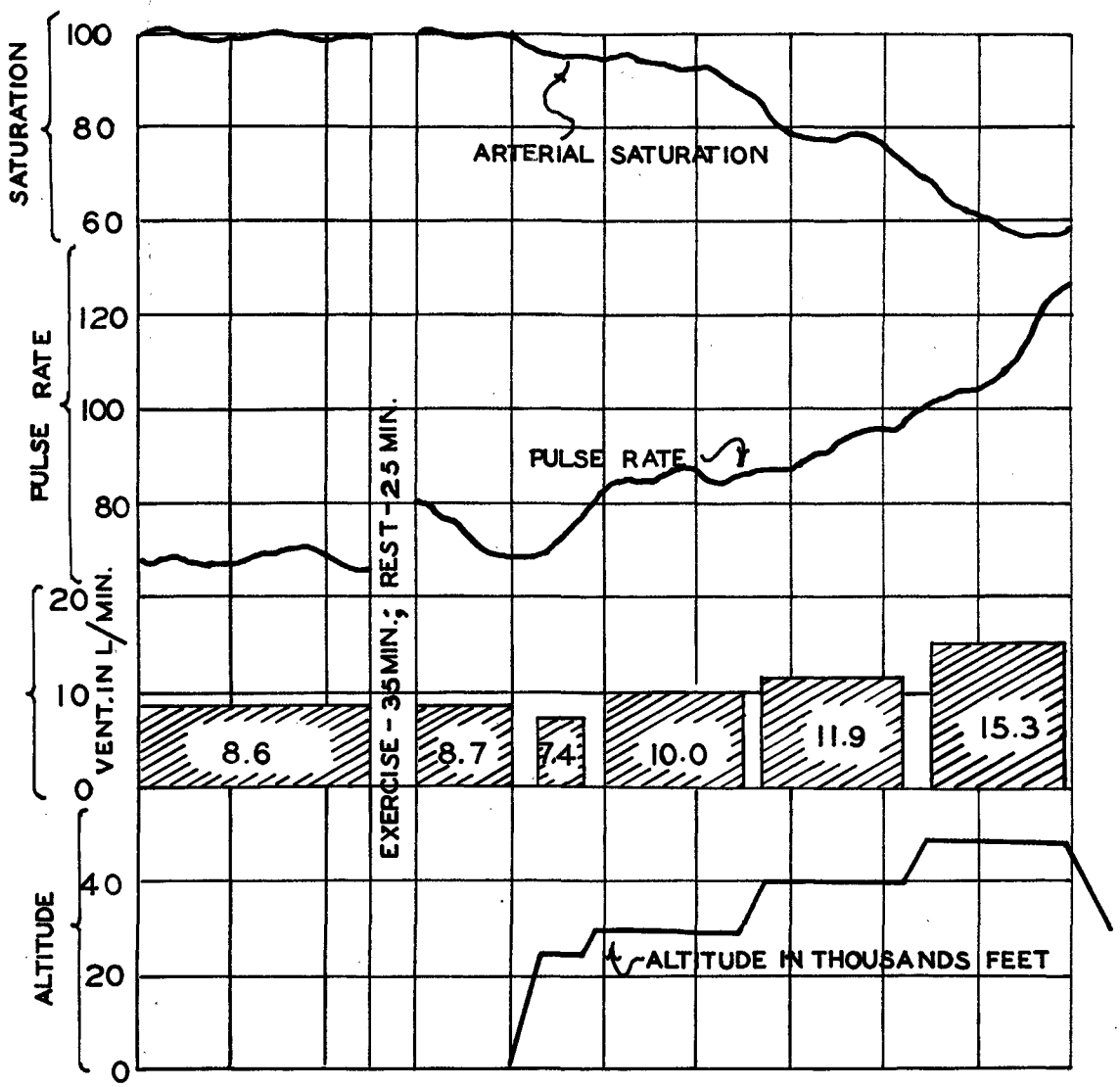

Figure 10. Work Test at High Altitudes.

Figure 11.

Arterial oxygen saturation by Millikan oximeter. Ventilation expressed as liters per minute, 37°, saturated and at ambient pressure.

The work consisted of lifting a 40-pound bucket onto a 30-inch stand and return to the floor once every 7-1/2 seconds.

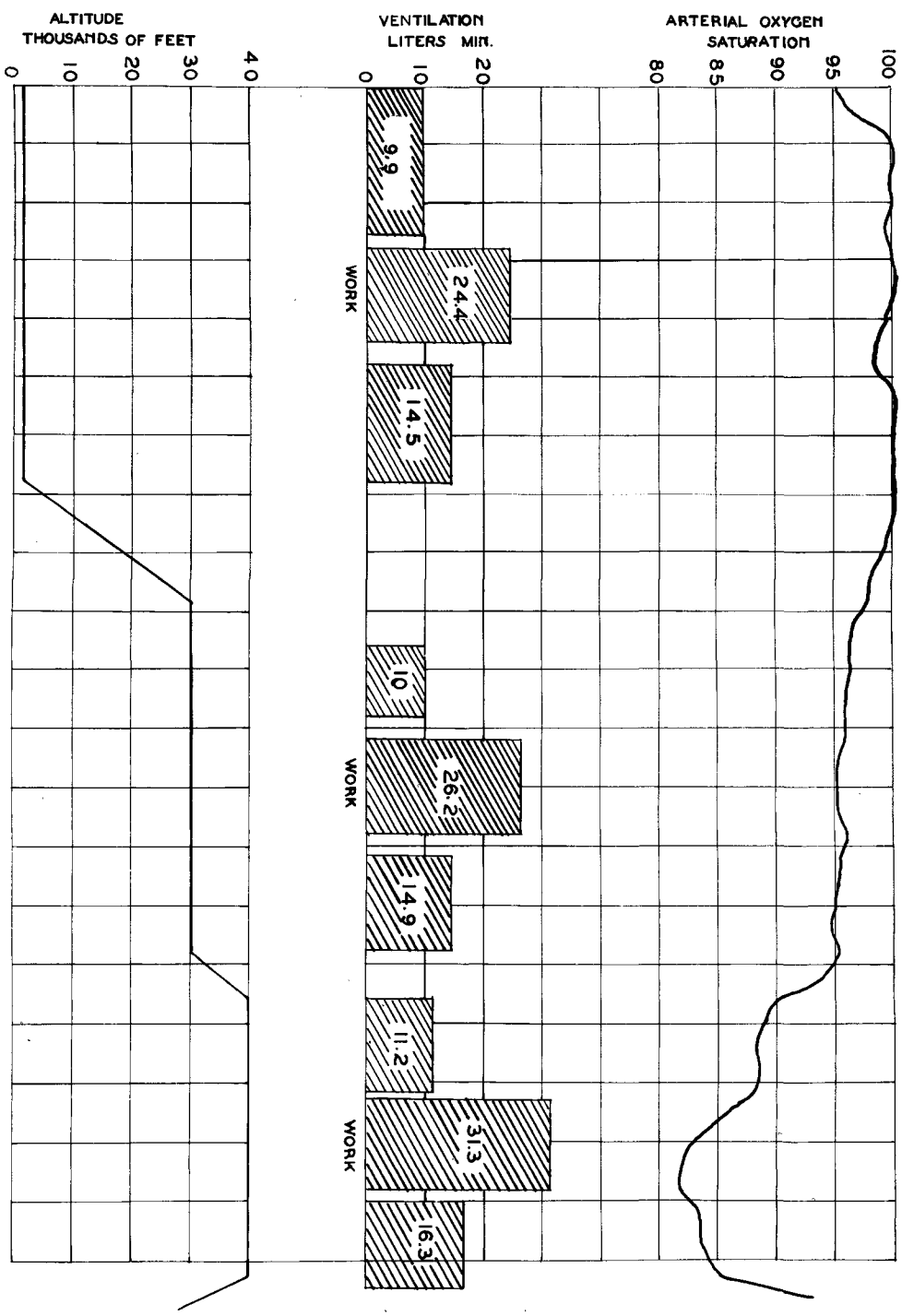

Figure 11. Effect of Moderate Work at High Altitudes.

DISCUSSION

The response of respiration to severe anoxia is a rapid one. Upon exposure to low oxygen tensions, as in a parachute descent from 30,000 feet without oxygen, the acceleration of breathing appears to go hand in hand with the decreasing arterial oxygen saturation. An interesting fact observed in these studies is the more rapid return to normal of the respiration. In these studies the ventilation had, on the average, returned to normal by the time 15,000 feet was reached, but the arterial oxygen saturation was still about 80 per cent. When ascent is made from ground level no appreciable hyperventilation is ordinarily experienced under 15,000 feet so the above mentioned fact only tends to corroborate this observation. The explanation offered for the pattern of respiration during a simulated parachute descent is as follows: At the beginning enough oxygen is in the depths of the lungs so that equilibrium between alveolar and outside air is not reached immediately. The onset of the stimulus of anoxia is thus progressive. The fall in arterial oxygen saturation is so rapid, however, that the distinct point at which hyperventilation from this cause is begun is obscured. By the time a peak stimulus is reached the altitude is about 28,000 feet or less and the pulmonary ventilation has increased nearly three times. This results in a rapid removal of the CO_2 with a resultant shift in the pH to-

ward alkalinity, which has an inhibiting influence on respiration.

As is so often seen in physiologic responses the respiratory center is apparently more responsive to sudden changes in the status quo than it is to sustained stimulus from a different level of conditions. This fact is quite evident from the work of Corwin and Horvath (16) who have pictured graphically the blood picture in response to low oxygen mixtures. Their graph is shown in Fig. 12, and it shows clearly the sharp change in pCO_2 at the beginning of each period in which a different percentage of oxygen was breathed. It is only at the beginning of such a period that the respiration is most affected, the tendency later being to settle down until another change is made.

The stimulus to respiration of the anoxia experienced is decreasing during the descent. At the same time it is opposed by an alkaline state in the body, causing the decline in stimulus to be more rapid than would otherwise be the case. As the stimulus of oxygen lack is lessened the accumulation of CO_2 brings about a more natural state of alkalinity; hence the acid-base regulation of respiration will be gradually reestablished.

The respiratory increase associated with a given low partial pressure of oxygen is apparently closely related to the degree of exercise. It seems quite clear that in low pO_2 a differential pressure of one to two mm. is sufficient to

Figure 12.

Mental patients at Metropolitan State Hospital, Waltham, Massachusetts, were subjected to low oxygen-nitrogen mixtures. Arterial oxygen saturation was determined by arterial puncture, the needle being left in the artery and the syringe changed so that periodic samples could be drawn and analyzed on the Van Slyke manometer.

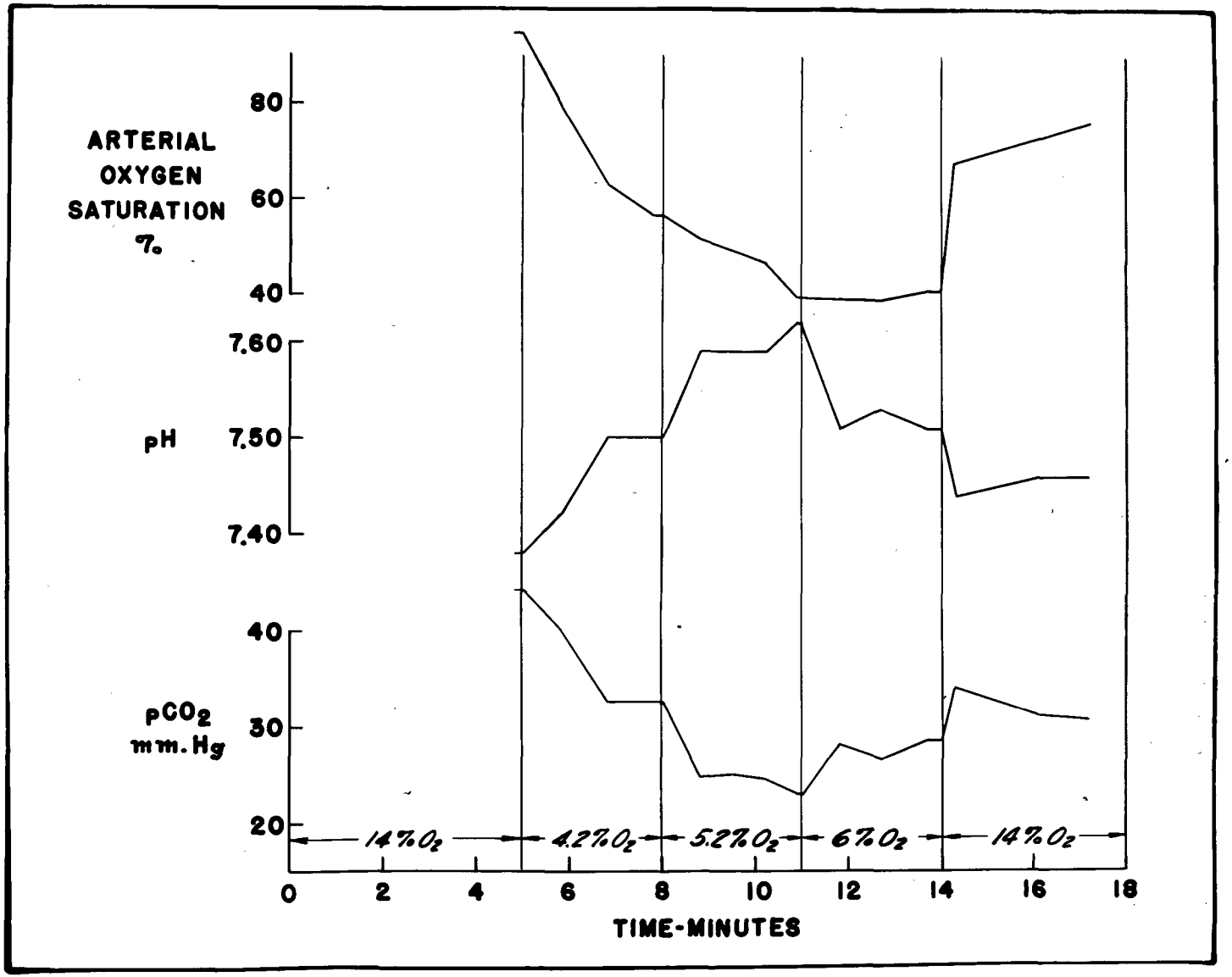

Figure 12. Response to Low Oxygen.

adequately maintain an individual while at rest, at least up to 44,800 feet, but is not enough when the oxygen consumption has been increased, as pointed out by Dill and Hall (22). More evidence to substantiate this theory has been obtained from work tests at high altitudes. It will be recalled that hyperventilation is not great at 18,000 feet while breathing air, or at 40,000 feet while breathing oxygen. No distress in breathing is noticed if one remains quiet. However, if any work is attempted the fall in arterial oxygen saturation is rapid and is accompanied by a hyperventilation.

The question of the transport of oxygen across the living lung membrane to the blood is an old one. Haldane advanced a theory of active secretion by the lungs (43) but Bancroft vigorously denied this (4). In more recent work Dill and Hall (19, O.161) (22) tend to substantiate Bancroft. Their data, together with recent supplementary measurements are shown in Table 13. Here the sum of the partial pressures of water vapor, carbon dioxide, and oxygen in the blood, hereinafter called summated pressures, is compared with the total outside chamber pressure. Since the subjects were all breathing 100 per cent oxygen at the time of the measurements these are the only partial pressures which need to be considered. Although the number of subjects in some cases is small, it is readily seen from the proximity of the two values there is no need for any assumption of an active secretion.

At the same time these data clearly indicate there is no

TABLE 13. ARTERIAL BLOOD ANALYSES AT HIGH ALTITUDE

No. Subjects	Altitude	Arterial O_2 Saturation	pCO_2	pO_2	pH_2O	Sum	Barometric Pressure
2	35,000	95.1	42.3	92	47	185.3	178.7
4	37,500	94.0	41.4	75.8	47	164.2	158.7
2	38,000	82.8	38.4	56.5	47	141.9	154.9
3	39,000	88.8	37.1	63.3	47	147.4	147.6
9	40,000	87.7	34.9	54.4	47	136.3	140.7
3	41,000	86.4	38.1	53.7	47	138.8	134.2
3	42,000	83.0	39.9	49.3	47	136.2	127.9
4	43,000	78.5	31.3	40.2	47	118.5	122
3	44,000	72.3	33.2	35.7	47	115.9	116.3
8	44,800	66.9	25.6	29.9	47	102.5	112

necessity for a large pressure gradient of oxygen between the lungs and blood. Even though a gradient of something like 25 mm. does exist under ordinary conditions it is obvious the blood pO_2 does not reflect the disappearance of this differential pressure. The total summated pressure approximates the external chamber pressure very well until the borderline of tolerable pressures is reached. Thus at 44,800 feet, where the barometer reads 112, full equilibrium apparently is not attained. Evidence that the equilibrium is in some manner associated with the degree of hyperventilation is supplied by further observations on the experiment at 44,800 feet. The subject who most nearly attained equilibrium with a summated pressure of 111.7 obviously hyperventilated the least, as evidenced by the fact that his pCO_2 was highest, 33.7. On the other hand, the subject who hyperventilated most, 39.6 liters per minute, had a pCO_2 of 11.5 and a summated pressure of only 95.5. This would indicate that even though more room is made for oxygen in the blood by removing CO_2 faster, and even though the affinity of hemoglobin for oxygen is increased by the alkaline shift of the dissociation curve, the rate at which oxygen can move into the blood in these low pO_2 values is definitely limited. The logical assumption is then that the movement of oxygen from the lungs to the blood is not wholly dependent upon a pressure gradient, at least in extreme pO_2's. It would seem logical to assume that this factor plays an important part in bringing about lessened activity of the respiratory center with

very low values of oxygen.

The response of the factors affecting respiration to anoxia is a complicated one. Some of the changes appear to be an aid to respiration while others are not. Above 15,000 feet breathing air and above 38,000 feet breathing oxygen it appears the stimulus of oxygen-want becomes a factor in the control of breathing. The tendency is toward greater ventilation with its consequent increased elimination of CO_2. This effect is beneficial in the sense that the increased alkalinity increases the affinity of hemoglobin for oxygen and, above 40,000 feet, in the sense that a reduction in pCO_2 allows an increase in pO_2 when breathing oxygen. The increased alkalinity of the blood has an opposite effect, however, that being a tendency to counteract the stimulatory effects of anoxia on the respiratory center.

It would appear that in most individuals the stimulus of oxygen-lack is adequate to maintain respiration at a sufficiently protective level up to an altitude of 18,000 feet breathing air and to 44,800 feet breathing oxygen. These observations apply to the unacclimated individual who is exposed to low oxygen tensions intermittently rather than to the fully acclimated person who presents a vastly different blood picture.

The difference in response of various subjects to the stresses of very high altitudes substantiated the observations made on individual ceilings by Henderson and Pierce during the last war (53 p.61). They found, by testing flight candidates

on the rebreather from which CO_2 was absorbed, that there exists a wide variation in ability to withstand low oxygen tensions. By noting the percentage of oxygen remaining in the tank at the time the subject showed signs of unconsciousness it was revealed that considerable difference existed in the final percentage. It would appear that the extent to which oxygen-lack will maintain fully adequate ventilation in very low oxygen differs with individuals.

At 44,800 feet the person who responded the least in ventilation also showed the most symptoms from the experience. He suffered from rather severe headache the remainder of the day. Other observations on response to altitudes point to the sensivity of the respiration to low oxygen as being a limiting factor in the ability to tolerate high altitudes.

SUMMARY

Tracings of the respiratory pattern were obtained during three levels of activity at ground level, exercising at 20,000 and 35,000 feet and while shivering in the cold. From these tracings the instantaneous rate of flow of the air into and out of the lungs was calculated. The per-minute rate of ventilation and the maximum instantaneous rate of inspiration and expiration do not appear to be significantly altered in mild degree of work at these altitudes or when shivering.

Using a low pressure chamber open parachute descent from 30,000 feet has been simulated. The degree of anoxia reached, which is considerable, increases the ventilation rate about two and one-half times. This stimulation is opposed by an alkaline condition brought on by a reduced carbon dioxide tension in the blood.

Hyperventilation while resting begins at approximately 15,000 feet breathing air, and about 38,000 feet breathing 100 per cent oxygen. At about 37,000 feet the arterial oxygen saturation of the blood begins to fall below normal in spite of the inhalation of 100 per cent oxygen. At 44,800 feet the partial pressure of oxygen in the alveolar air is at a critically low level.

Although a virtual equilibrium exists between the barometric pressure and the sum of the partial pressures of oxygen,

carbon dioxide and water vapor at extremely high altitudes while breathing 100 per cent oxygen if at rest, it is concluded from work tests at 38,000 and 40,000 feet that this equilibrium breaks down in exercise. The transfer of oxygen from the lungs to the blood appears to depend on more than simple diffusion.

It is concluded that the adequacy with which the anoxia is capable of stimulating respiration determines in a large measure a man's "ceiling". Anoxia in most cases is capable of maintaining adequate respiration at least to an altitude of 44,800 feet.

CONCLUSIONS

1. Altitudes of 20,000 and 35,000 feet and shivering in temperatures of -40° C. do not alter the inherent respiratory pattern. The maximum rate at which air is taken into the lungs and pushed out for a given respiratory cycle bears approximately the same relation to the per-minute ventilation that it does at ground level.

2. When sitting quietly hyperventilation begins at about 15,000 feet when breathing air. If hyperventilation has been produced at higher altitudes respiration will return to normal upon descent to approximately 15,000 feet. The arterial oxygen saturation at this time is roughly 80 per cent of capacity.

3. The respiratory stimulus of anoxia is very rapid and is capable of assuming control with no reflection in the respiration. If the breath is held and the subject is then exposed to a low partial pressure of oxygen the accumulated CO_2 strongly stimulates respiration. Then, in a few breaths the CO_2 content of the blood is lowered, but the oxygen saturation will be sharply lowered and the stimulus of anoxia replaces the stimulus of CO_2.

4. If 100 per cent oxygen is breathed hyperventilation begins at about 38,000 feet. The increase is roughly proportional up to 44,000 feet, but then a rather sharp rise is

noted between there and 44,800 feet, which is calculated to be the upper limit compatible with consciousness if pressure is not used.

5. Exercise puts an added strain on the forces responsible for the transport of oxygen from the lungs to the blood at altitudes. At 38,000 feet the ventilation is increased nearly twice as much as at ground level for the same amount of work. The arterial oxygen saturation and the pCO_2 are lower at 38,000 feet. The pH is nearly the same since the CO_2 combining capacity is held nearly constant by virtue of the accumulated lactic acid in both cases.

6. The completeness with which the portion of the respiratory mechanism sensitive to oxygen-lack can maintain adequate ventilation probably determines the tolerable altitude of the individual. Hyperventilation is a distinct aid in very low partial pressures of oxygen.

7. The conception of L. J. Henderson, i.e. that blood as a whole--amount of oxygen, amount of CO_2, pH, etc.--is the stimulus for respiration appears to be highly tenable in the light of our observations of respiration in the cold and at high altitudes.

ACKNOWLEDGEMENT

The writer wishes to express his appreciation for the aid and encouragement rendered by Dr. Erma Smith whose interest and stimulation prompted the work in this field. Appreciation is further expressed for the great amount of stimulation and assistance received from Major David B. Dill, who suggested the problem and guided the research. His untiring technical assistance and willingness to discuss problems has been a great inspiration.

To the entire personnel of the Aero Medical Research Laboratory, Wright Field, and to its director, Lt. Col. O. O. Benson, Jr., the writer wishes to express gratitude for the assistance they have given and for making possible this work. Especial acknowledgement is made for the assistance of Miss Margaret Jackson, technician, for aid in the analyses of blood and air; of Corporal Ralph Stacy and Private First Class Charles Saunders for the thesis plates and of Miss Clara Zuern, stenographer, for aid in the preparation of the manuscript.

LITERATURE CITED

(1) Adrian, E. D. Vagal potentials related to the filling of the lungs. J. Physiol. 79: 332-340, 1933.

(2) Armstrong, Harry G. Principles and practice of aviation medicine. Williams and Wilkins Co. Baltimore. 1939.

(3) Asmussen, Erling and Hugo Chiodi. The effect of hypoxemia on ventilation and circulation in man. Amer. J. Physiol. 132: 426-436, 1941.

(4) Barcroft, Joseph. The respiratory function of the blood. Part I. Lessons from high altitudes. Cambridge University Press. London. 1925.

(5) Bert, Paul. La pression barométrique. G. Masson, Paris. 1978.

(6) Bouckaert, J. J., L. Dautrebande and C. Heymans. Dissociation anatomo-physiologique dis deux sensibilités du sinus carotidien: sensibilité à la pression et sensibilité chemique. Annal. de Physiol. 7: 207-210, 1931.

(7) Bouckaert, J. J., K. S. Grimson, C. Heymans and A. Samaan. Mechanism of influence of hypoxemia on respiration and arterial blood pressure. Arch. Internat. Pharmacodyn. et de Therap. 65: 63-100, 1941.

(8) Boycott, A. E. and J. S. Haldane. The effects of low atmospheric pressures on respiration. J. Physiol. 37: 355-377. 1908.

(9) Boyd, T. E. Mechanism of vagal effect of pulmonary ventilation. Amer. J. Physiol. 132: 571-578, 1941.

(10) Boyle, R. New experiments physico-mechanical, touching the spring of the air. Oxford. 1666.

(11) Campbell, J. A. Diet and resistance to oxygen want. Quart. J. Exper. Physiol. 29: 259-267, 1939.

(12) Chiodi, H., D. B. Dill, F. Consolazio and S. M. Horvath. Respiratory and circulatory response to acute CO poisoning. Amer. J. Physiol. 134: 683-689, 1941.

(13) Collip, J. B. On the respiratory stimulation of carbon dioxide. J. Physiol. 54: 58-66, 1920.

(14) Comroe, J. H., Jr. Localization of the carotid chemoreceptors. Amer. J. Physiol. 127: 176-180, 1939.

(15) Comroe, J. H. and C. F. Schmidt. Part played by reflexes in dogs. Amer. J. Physiol. 121: 75-81, 1938.

(16) Corwin, William and S. M. Horvath. Physiological effects on man of severe anoxia. Metropolitan State Hospital, Waltham, Mass. Restricted report. Division of Medical Sciences, National Research Council, 1942.

(17) Courtice, F. C. The effect of oxygen lack on the cerebral circulation. J. Physiol. 100: 198-203, 1941.

(18) Dill, D. B. Effects of physical strain and of high altitudes on the heart and circulation. Amer. Heart J. 23: 441-454, 1942.

(19) Dill, D. B. Life, heat and altitude. Harvard University Press. Cambridge. 1938.

(20) Dill, D. B. and W. H. Forbes. Respiratory and metabolic effects of hypothermia. Amer. J. Physiol. 132: 685-697, 1941.

(21) Dill, D. B. and Norman Zamcheck. Respiratory adjustments to oxygen lack in the presence of carbon dioxide. Amer. J. Physiol. 129: 47-52, 1940.

(22) Dill, D. B. and F. G. Hall. Gas exchange in the lungs at high altitudes. J. Aero. Sc. 9: 220-223, 1942.

(23) Douglas, C. G. and J. S. Haldane. The regulation of normal breathing. J. Physiol. 38: 420-440. 1909.

(24) Drinker, Cecil K. Carbon monoxide asphixia. Oxford University Press. London. 1938. p. 19.

(25) Dumke, Paul and R. Dripps. Influence of anesthetics on balance between chemoreceptor and central control of respiration. Proceedings of The Federation of American Societies for Experimental Biology. Baltimore. Part II. 1: 150, 1942.

(26) Dumke, P. R., C. F. Schmidt and H. P. Chiodi. Part played by carotid body reflexes in respiratory response of dog to anoxemia with and without simultaneous hypercapnia. Amer. J. Physiol. 133: 1-20, 1941.

(27) Ege, R. and V. Henriques. Untersuchungen über die Bedeutung der Blutreaktion für die Lungenventilation. Biochem. Z. 176: 441-466, 1926.

(28) Fredericq, L. Sur la cause de l'apnée. Arch. Biol. 17: 561-580, 1901.

(29) Gellhorn, E. Fundamental principles in adjustment reactions of organism to anoxia. Ann. Inter. Med. 14 (9): 1518-1532, 1941.

(30) Gellhorn, E., R. Cortell and H. B. Carlson. Fundamental differences in excitability of somatic and autonomic centers in response to anoxia. Amer. J. Physiol. 135: 641-648, 1942.

(31) Geppert, J. and N. Zuntz. Ueber die Regulation der Athmung. Pflügers Arch. ges. Physiol. 42: 189-245, 1888.

(32) Gesell, Robert Forces driving the respiratory act. Science 91 (2358): 229-233, 1940.

(33) Gesell, Robert Respiration and its adjustments. Ann. Rev. Physiol. Vol. I, 1939. Annual Reviews, Inc. Stanford University P. O., California. PP 185-216.

(34) Gesell, Robert, A. K. Atkinson and R. C. Brown. Graduation of intensity of inspiratory contractions. Amer. J. Physiol. 131: 659-673, 1941.

(35) Gesell, Robert, A. K. Atkinson and R. C. Brown. Origin of respiratory activity patterns. Amer. J. Physiol. 128: 629-634, 1940.

(36) Gesell, Robert, and Mary Alice Hamilton. Reflexogenic components of breathing. Amer. J. Physiol. 133: 694-719, 1941.

(37) Gesell, R., J. Lapides and M. Levin. Interaction of central and peripheral chemical control of breathing. Amer. J. Physiol. 130: 155-170, 1940.

(38) Gesell, R. and C. Moyer. Changes in balance of respiratory drives resulting from open pneumothorax. Amer. J. Physiol. 135: 539-549, 1942.

(39) Gesell, R. and C. Moyer. Dual excitatory action of vagal stretch reflex. Amer. J. Physiol. 131: 674-689, 1941.

(40) Gollwitzer-Meier, K. L. and E. Lerche. Carotiskörper und die Regulierung der Atmung durch das Blut. Pflügers Arch. ges. Physiol. 244 (2): 145-156, 1940.

(41) Graham, J. D. P. Respiratory reflexes in the fowl. J. Physiol. 97: 525-532, 1940.

(42) Haggard, H. W. and Yandell Henderson. The transport of CO_2 in the blood. J. Biol. Chem. 33: 333-351, 1918.

(43) Haldane, J. S. and J. G. Priestley. Respiration. New Edition. Yale University Press. New Haven. 1935.

(44) Haldane, J. S. and J. G. Priestley. The regulation of the lung ventilation. J. Physiol. 32: 225-266, 1905.

(45) Haldane, J. S. and E. A. Mavrogordata. The effect of nerve impulses from higher centers on the respiratory center. J. Physiol. 50: 41-53, 1916.

(46) Hall, F. G. The effect of altitude on hemoglobin in man. J. Biol. Chem. 115: 486-495, 1936.

(47) Haney, H. F. Chemical control of respiration. Diseases of the Chest. 7: 236-241, 1941.

(48) Hasselbalch, K. A. Neutralitätsregulation und Reizbarkeit des Atemyentrums in ihren Wirkungen auf die Kohlen-säurespannung des Blutes. Biochem. Z. 46: 403-439, 1912.

(49) Head, H. On the regulation of respiration. J. Physiol. 10: 1-70, 1889.

(50) Henderson, Lawrence J. Blood, a study in general physiology. Yale University Press. New Haven. 1928.

(51) Henderson, Yandell Adventures in respiration. The Williams and Wilkins Co. Baltimore. 1938.

(52) Henderson, Yandell Respiration. Physiol. Rev. 5: 131, 1925.

(53) Henderson, Yandell et al. Medical studies in aviation (7 papers) J. Amer. Med. Asso. 71: 1382-1400, 1918.

(54) Hering, E. and J. Brewer. Die Selbststeuerung der Athmung durch den Nervus vagus. S. B. Akad. Wiss. Wien. 57: Abt. II. 672-677, 1868.

(55) Herrlich, H. C., J. F. Fazekas and H. E. Himwich. Survival of infant and adult rats at high altitudes. Proc. Soc. Exper. Biol. and Med. 48: 446-450, 1941.

(56) Heymans, C. and J. J. Bouckaert. Les Chemo-récepteurs du Sinus Carotidien. Ergebn. d. Physiol. 41: 28-52, 1939.

(57) Heymans, C., J. J. Bouckaert, and L. Dautrebande. Rôle Réflexogène Respiratoire Des Zoues Vaso-Sensibles Cardio-Aortique Et Sino-Carotidiennes. Ion Hydrogène, CO^2, Sinus Carotidiens Et Réflexes Respiratoires. C. R. Soc. Biol. Paris. 105: 881-910, 1930.

(58) Heymans, C., J. J. Bouckaert, and L. Dautrebande. Sinus Carotidien Et Réflexes Respiratoires. Arch. Internat. de Pharmacodyn. et de Therap. 39: 400-448, 1930.

(59) Heymans, C., J. J. Bouckaert and L. Dautrebande. Automatisme Du Centre Respiratoire De La Tête Isolee. Arch. Internat. de. Pharmacodyn. et Therap. 65: 63-98, 1941.

(60) Heymans, C. and J. F. Heymans. Sur Les Modifications Directes Et Sur La Régulation Réflexe De l'activite Du Centre Respiratoire De La Tête Isolée Du Chien. Arch. Internat. de Pharmacodyn. et de Therap. 33: 273-369.

(61) Hooke, R. Philosophical Translations II. P. 539. 1667. Original not seen; cited in Haldane (43) p. 2.

(62) Jacobs, M. H. The relation of carbonic and other acids in the stimulation of respiration. Amer. J. Physiol. 51: 321, 1920.

(63) Johnson, R. E., W. H. Forbes, D. B. Dill and L. J. Henderson. Respiration. Ann. Rev. Physiol. Vol. II. 1940. Annual Reviews Inc. Stanford Univ. P.O., California. pp. 21-44.

(64) Keys, Ancel, Paul M. Stapp and Antonio Violante. Response of the human cardio-vascular system to acute alterations in the composition of inspired air. Dept. Physiological Hygiene, Univ. of Minnesota. Restricted report, Division of Medical Sciences, National Research Council, 1942.

(65) Kramer, K. and O. Ganer. Zur Frage der Entstehung eines atmungserregenden Stoffes wahren der Muskelarbeit. Klin. Wchnschr. 20: 309-310, 1941.

(66) Kussmaul, A. and A. Tener. Untersuchungen über Ursprung und Wesen der fallsuchtartigen Zuckungen bei der Verblutung. Untersuch. Naturl. Mensch. Tiere 3: 1, 1857.

(67) Lacquer, E. and F. Verzar. Die spezifische Wirkung der Kohlensäure auf das atemzentrum. Pflügers Arch. ges. Physiol. 143: 395-427, 1912.

(68) Lernox, W. G., F. A. Gibbs and E. L. Gibbs. Brain function and its relation to the oxygen supply. Arch. Neurol. Psychiat. Chicago 34: 1001, 1935.

(69) Lindsay, E. B. and H. W. Magoun. Localization of the medullary respiratory centers in the monkey. Amer. J. Physiol. 134: 177, 1941.

(70) Lower, R. Tractatus de corde, London. p. 86. 1669. Original not seen; cited in Haldane (43) p. 1.

(71) Magoun, H. W. Evidence for a functional division of the respiratory center. Amer. J. Physiol. 134: 185-190, 1941.

(72) Main, R. J. Effects of epinephrine and amphetamine on respiration and blood pressure in different postures. Proc. Soc. Exper. Biol. and Med. 45: 776-780, 1940.

(73) Mayow, J. Tractatus quinque medico-physici. Oxford, 1673. Original not seen; cited in Haldane (43) p. 1.

(74) McDonough, F. K. Homeostasis in the sympathectomized dog. Amer. J. Physiol. 125: 530-539, 1939.

(75) Mellanby, J. Hydrogen-ion effects on the respiratory center. J. Physiol. 56: 38, 1922.

(76) Miescher-Rusch, F. Der Carotiakörper und die Wirkung von Säurestoffmangel. Arch. Anat. Physiol. Leipzig. p. 355. 1885.

(77) Monge, Carlos Life in the Andes and chronic mountain sickness. Science 95 (2456): 79-84, 1942.

(78) Moyer, C. A. and H. K. Beecher. Variability of Hering-Brewer reflexes in the dog under sodium evipal anesthesia. Amer. J. Physiol. 136: 7-13, 1942.

(79) Moyer, C. A. and H. K. Beecher. Central stimulation of respiration during hypoxia. Amer. J. Physiol. 136: 13-21, 1942.

(80) Nielsen, M. The means of stimulation by carbon dioxide. Skandinav. Arch. Physiol. 74: Suppl. 10, 87-94, 1936.

(81) Peters, J. P. and D. D. Van Slyke. Quantitative clinical chemistry. Vol. II. Methods. Williams and Wilkins Co. 1932. p. 324.

(82) Pflüger, E. F. W. and K. Dohmen. Ueber die Ursache der Athembewegungen sowie der Dyspnoë und Apnoë. Pflügers Arch. ges. Physiol. 1: 61-106, 1868.

(83) Pitts, R. F. Differentiation of respiratory centers. Amer. J. Physiol. 134: 192-201, 1941.

(84) Pitts, R. F., H. W. Magoun, and S. W. Ranson. Localization of medullary centers in cat. Amer. J. Physiol. 126: 673-688, 1939.

(85) Pitts, R. F. and G. Stella. Differentiation of respiratory centers by electrical potentials. J. Physiol. 95: 365-371, 1939.

(86) Rosenthal, J. Die Athembewegungen. Berlin. 1862. Original not seen; cited by Haldane (43) p. 11.

(87) Rudberg, T. Wirkung der Sauerstoffatmung auf die Atmungssteigerung bei Carotisabklemmung. Acta. Physiol. Scand. 1: 89-92, 1940.

(88) Schmidt, C. F. The chemoreceptors of the carotid body and their affect on the respiratory center. Amer. J. Physiol. 102: 94-102, 1932.

(89) Schmidt, C. F. and J. H. Comroe, Jr. Annual Rev. of Physiol. Vol. III, 1941. Annual Reviews, Inc., Stanford University P.O., California.

(90) Schmidt, C. F. and J. H. Comroe, Jr. Functions of the carotid and aortic bodies. Physiol. Rev. 20 (1): 115-157, 1940.

(91) Schmidt, C. F., P. R. Dumke, and R. D. Dripps. Part played by carotid body reflexes in respiratory response of dog to small changes in CO_2 tension in arterial blood. Amer. J. Physiol. 128: 1-9, 1939.

(92) Shaw, L. A., A. R. Behnke, and A. C. Messer. The role of carbon dioxide in producing the symptoms of oxygen poisoning. Amer. J. Physiol. 108: 652-660, 1934.

(93) Shock, N. W. Age changes and sex differences in alveolar carbon dioxide tension. Amer. J. Physiol. 133: 610-616, 1941.

(94) Stadie, W. V., and K. A. Martin. Carbon monoxide poisoning: a biochemical study. J. Clin. Invest. 2: 77, 1925-26. Original not seen; cited by Chiodi et al. (12) p. 685.

(95) Ter Braak, J. W. G. and D. G. W. Van Voorthuysen. Weitere Beobachtungen über den tonischen Vaguseinfluss bei verschiedenen Konstanten Lungenvolum. Pflügers Arch. ges. Physiol. 243: 724-732, 1940.

(96) Variation of air temperature with altitude. Report No. PC-20-R. Airsearch Mfg. Co., Inglewood, California. Oct. 1, 1941.

(97) Van Liere, Edward J. Anoxia, its effect on the body. The University of Chicago Press, Chicago, Illinois. 1942.

(98) Verduzio, Rodolfo Il paracudute parte I and II. Rivista Aeronautica. 14: 283-303, 1938. 14: 564-586, 1938.

(99) Von Euler, U. S., and G. Liljestrand. Chemical stimulation of carotid sinus and regulation of respiration. Skandinav. Arch. f. Physiol. 74: 101-128, 1936.

(100) Von Euler, U. S., G. Liljestrand, and Y. Zotterman. Excitation mechanism of chemoreceptors of carotid body. Skandinav. Arch. f. Physiol. 83: 132-152, 1939.

(101) Von Euler, U. S., and G. Liljestrand. Effect of carotid sinus denervation on respiration during rest. Acta. Physiol. Scand. 1: 93-104, 1940.

(102) Walter, F. Untersuchungen über die Wirkung der Säuren auf den thierischen Organismns. Arch. Exper. Path. Pharmak. 7: 148-178, 1877.

(103) Willmon, T. L., and A. R. Behnke. Nitrogen elimination and oxygen absorption at high barometric pressures. Amer. J. Physiol. 131: 633-639, 1941.

(104) Winterstein, H. Die Regulierung der Atmung durch das Blut. Pflügers Arch. ges. Physiol. 138: 167, 1911.

(105) Wyss, O. A. M. Ein weiterer Beitrag zur Kenntnis vom Mechanismus der vagalen Atmungssteuerung. Pflugers Arch. ges. Physiol. 243: 457-467, 1940.

(106) Zaeper, G. New theory on quantitative regulation of respiration. English Summary. Klin. Wochenschr. 19: 850-853, 1940.

(107) Directions for operating Millikan A-1 and Coleman Model A oximeters. Coleman Elec. Co., Inc., Maywood, Illinois.