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HYPOXIA

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PREFACE

Scientists, especially physiologists, have manifested an interest in the effects of oxygen deprivation on the animal organism for many years. Lavoisier (1743-94), the brilliant French chemist, first demonstrated the importance of oxygen want to animal life.

World War I (1914-18) aroused an active interest in researches dealing with hypoxia, doubtless because of the use of aircraft. World War II (1939-45) gave still more impetus to investigations on low oxygen tension. During and shortly after the latter war, a great deal of literature was published on hypoxia, especially that produced by high altitudes, anoxic hypoxia. More recently, the exigencies of space medicine have renewed interest in oxygen want.

It is to be remembered that many people in the world dwell at high altitudes. In the United States there are many thousands of people, especially in the Southwest, living at altitudes from 5,000 to over 8,000 feet. In the Andean Mountains there are several millions of native inhabitants born, raised, and living in regions at altitudes over 10,000 feet. Indeed, not far from Lima, Peru, there are about five thousand people (natives and foreign inhabitants, including former residents of the United States) living at an altitude of 14,900 feet, at an average barometric pressure of 446 mm. Hg.

Tibet, the highest country in the world, has a population of approximately four million people. The average elevation is given as 16,000 feet, but this, of course, includes the high peaks. Nevertheless, the capital city, Lhasa, with a population of about fifty thousand, lies at an altitude of somewhat over 12,000 feet.

Not only high altitudes, but, more important, many diseases are associated with some form of hypoxia. In fact, diseases of the heart, circulation, the blood, and the lungs may all cause a condition of oxygen want.

While, as previously mentioned, there has been a tremendous amount of research done in the field of hypoxia, many problems still remain unsolved. The authors hope that this monograph will stimu-

late further research in this extremely important area. It is hoped further that these researches will add not only to knowledge but to the alleviation of suffering caused by disease.

The authors are under obligation to a number of their colleagues for valuable suggestions and constructive criticism. We wish to thank especially Hugh A. Lindsay and David W. Northup of the Department of Physiology of the West Virginia University School of Medicine for critically reading the manuscript and Wilbert E. Gladfelter of the same department for advising on the section dealing with the nervous system. We appreciate, also, the help of Reginald F. Krause and Daniel T. Watts for consulting in areas concerning biological chemistry and pharmacology, respectively. These men, however, are in no way to be held responsible for errors of commission or omission. The authors alone are responsible for these.

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CHAPTER XVIII

EFFECT OF HYPOXIA ON THE NERVOUS SYSTEM

Of all the tissues in the body, nervous tissue is the least capable of withstanding oxygen want. Whereas cartilage tissue, for example, may withstand total deprivation of oxygen for several hours without suffering any apparent deleterious effects, nervous tissue can withstand deprivation of oxygen for only a few minutes. Since nervous tissue is so sensitive to oxygen want, it is obvious that the effect of hypoxia on the central nervous system of the intact organism is of paramount importance.

BLOOD SUPPLY TO THE BRAIN

The literature on cerebral circulation was reviewed by Wolff (109) in 1936. In 1943 Schmidt (86) published a monograph on cerebral circulation. The effect of hypoxia on cerebral circulation was reviewed by Opitz (76) in 1950, by Kety (62) in 1958, and by Lassen (65) in 1959. The reader is referred to these reviews for details of this important subject.

Schmidt (85) and Schmidt and Pierson (87) showed that oxygen deficiency produces vasodilatation and an increased volume of blood flow to the medulla oblongata and hypothalamus. A number of investigators in the early 1930's (20, 67, 110) also demonstrated that hypoxia produces dilatation of the pial vessels. These findings have been confirmed by later workers (65) .

Wolff (109) stated that inhalation of carbon dioxide produces a more marked vasodilatation of the vessels which supply the brain than does oxygen want. If this were true, there would be a greater dilatation of the cerebral vessels during asphyxia than during anoxic hypoxia. On the other hand, Dumke and Schmidt (31) in 1943 observed that both hypoxia and hypercapnia increased cerebral blood flow but that the effect of hypoxia was more striking than that produced by carbon dioxide.

The consensus is that slight variations of oxygen tensions do not affect cerebral blood flow; however, a moderate decrease in oxygen tension may produce a significant increase. Courtice (23) in 1941, working with chloralosed cats, found that there was no increase in cerebral circulation until the inspired air contains less than 15 per cent oxygen. Kety and Schmidt (63) in 1948 reported that in subjects breathing 10-13 per cent oxygen the cerebral blood flow increased about 35 per cent. Lassen (65) reported similar findings. The latter worker has emphasized that the pronounced vasodilatory response to oxygen lack means that a greater degree of arterial oxygen unsaturation can be tolerated than would be the case if this response did not occur.

Opitz and Schneider (76) reported in 1950 that cerebral blood flow increased by anemia and that vasodilatation commences when the pO_2 of the cerebral venous blood falls to about 28 mm. Hg.

Although there is sound evidence that anoxic hypoxia and probably hemic hypoxia cause an increased blood supply to the brain, it is likely that in spite of this the diminished oxygen tension during hypoxia produces a deficient oxygen supply to the brain. It is generally conceded that during anoxic hypoxia the brain is one of the first organs to be affected.

SURVIVAL TIME OF DIFFERENT NERVE TISSUES DEPRIVED OF BLOOD

It has been known for a long time that different parts of the nervous system are more sensitive to deprivation of blood supply, that is, stagnant and hemic hypoxia, than are others. According to Heymans[1] (49), Stenon (93) in 1667 and Legallois (66) more than a century and a half later, were the first to investigate this important problem.

Many workers have experimentally produced anemia of the brain by occluding the arterial supply; among the early investigators were: Cooper (22) in 1836; Hill (51) in 1896 and in 1900 (52); Crile and Dolley (25) in 1908; and Pike, Guthrie, and Stewart (78) also in 1908. Others have reported studies on the effect of acute anemia on nervous centers (4, 16, 17, 25, 28, 39, 43, 50, 60, 61, 72, 77, 94, 95, 103).

Cannon and Burkett (19) in 1913 reviewed the literature of the

[1]C. Heymans in 1950 reviewed the literature concerning survival and revival of nervous tissues after arrest of circulation. The reader is referred to this extensive review which lists 246 references. (C. Heymans, *Physiol. Rev.*, 30 [1950], 395.)

effect of anemia on nerve cells of different classes. Table 10, was compiled by Drinker (30) from the literature cited by Cannon and Burkett, shows the survival time of different nerve tissues when completely deprived of blood.

TABLE 10

SURVIVAL TIME OF DIFFERENT NERVE TISSUES COMPLETELY DEPRIVED OF BLOOD*

Tissue	Survival Time (Minutes)
Cerebrum, small pyramidal cells	8
Cerebellum, Purkinje's cells	13
Medullary centers	20–30
Spinal cord	45–60
Sympathetic ganglia	60
Myenteric plexus	180

* From W. P. Drinker, *Carbon Monoxide Asphyxia* (New York: Oxford University Press, 1938), p. 133.

Drinker, interestingly enough, has pointed out that Table 10 indicates that individuals who have suffered from severe hypoxia, such as may be produced by carbon monoxide poisoning, may be practically decerebrated.

Heymans *et al.* (50) in 1937 studied the effect of acute anemia on the nerve centers by perfusion of the isolated head of the dog. The circulation was interrupted for varying periods of time, and the ability of the centers to revive after the circulation had been completely interrupted was noted.

Table 11 shows that the cortical regions are the most sensitive to oxygen want. It is of interest that Davies and Bronk (26a), in studies

TABLE 11

ABILITY OF CENTERS AT VARIOUS LEVELS OF THE NERVOUS SYSTEM TO WITHSTAND COMPLETE INTERRUPTION OF BLOOD SUPPLY*

Interruption of Central Circulation up to	Cortical	Palpebral Pupillary	Cardio-regulatory	Vaso-motor	Respiratory
1–5 min.	+	+	+	+	+
5–10	−	+	+	+	+
10–15	−	−	+	+	+
15–30	−	−	+	+	+
30	−	−	−	−	−

* From W. P. Drinker, *Carbon Monoxide Asphyxia* (New York: Oxford University Press, 1938), p. 134.

on oxygen tension in the mammalian brain, reported that the cortex (at least locally) is on the verge of oxygen insufficiency even in its normal state. Actually the cortex has but a small reserve of dissolved oxygen should the circulation fail completely. Their experiments suggest, however, that the cortex ought to function normally as long as its oxygen tension is well above 5 mm. Hg.

It is of especial interest (Table 11) that the respiratory center, which is generally regarded as being extremely sensitive to oxygen want, may be revived after it has been deprived of its circulation for a considerable time. Heymans *et al.* (50) pointed out that their experiments demonstrated that the respiratory and circulatory centers possessed great resistance to hypoxia and could be revived after the circulation had been arrested for as long as thirty minutes. They stated, however, that certain centers, which probably were situated in the cerebrum, were more sensitive to anemia and were irreparably damaged if the circulation were arrested for more than five minutes.

Arrest of circulation in spinal cord.—As early as 1667 Stenon (93) reported that anemia of the spinal cord produces paralysis at the end of one minute and suppression of sensitivity and motor functions after three minutes. Legallois (see 66) in 1830 reported that ligation of the abdominal aorta produced paralysis of motor spinal functions but that the spinal centers may recover their function if the circulation has not been obstructed too long.

Since this early work a number of investigators (12, 13, 14, 15, 21, 36, 69, 84, 92, 97, 100) have reported the effects of interruption of the circulation of the spinal cord. Many of these studies were made following obstruction of the abdominal aorta.

HISTOLOGIC STUDIES OF STRUCTURAL CHANGES

Anoxic hypoxia.Thorner and Lewy (96) in 1940 reported experiments performed on guinea pigs and cats which had been subjected to complete hypoxia by being placed in an environment of pure nitrogen for various periods of time. These workers found that exposures to sublethal periods of pure hypoxia produced vascular and degenerative changes in the central nervous system. It was emphasized that some of these changes were irreversible and became summated in animals repeatedly subjected to hypoxia.

Following fatal cases of nitrous oxide-oxygen anesthesia, lesions of the brain, especially in the cortex and basal ganglia, have been observed (41, 70). These changes have been attributed to anoxic hypoxia.

It has been suggested by van der Molen (98) that cortical cell changes occur at partial pressures of oxygen equivalent to an altitude of 28,000 feet (8,535 meters) and, moreover, that some of these changes might be irreversible. It will be remembered, however, that the average unacclimatized individual cannot live much beyond an

altitude of 25,000 feet (7,620 meters) . Only individuals thoroughly acclimated could withstand an altitude of 28,000 feet; it is known, of course, that several members of the various Mount Everest expeditions were reasonably well acclimated to this great height.

Windle and his co-workers (105, 106, 107, 108), during the early 1940's, carried out extensive researches on the central nervous system of full-term guinea pig fetuses which had been subjected to severe grades of hypoxia (and of asphyxia). (Some of these animals were resuscitated and later subjected to learning tests.) Controlled histopathologic studies were made. Neuropathologic changes of various degrees of severity were observed, which were not necessarily related to the duration of the hypoxia. Among the changes noted were capillary hemorrhages, clouding of Nissl substances, shrinkage of the neuron, and loss of stainability. In some instances, there was a generalized necrosis of the brain and spinal cord with chromatolysis and edema. Glial proliferation and loss of nerve cells, especially in the pyramidal layers of the cerebral cortex, were also found.

Morrison (74) in 1946 made comprehensive histologic observations on twenty-five dogs and ten monkeys which had been subjected to various degrees of hypoxia. He observed that a single exposure to a simulated altitude of 32,000 feet (9,755 meters) for twenty-five minutes produced extensive lamina necrosis in the cortex of the monkey.

Repeated exposures of moderate hypoxia (12—13 volumes per cent of oxygen in the blood) showed that the first histologic changes occurred in the cell bodies of the cortical gray matter. When 10 volumes per cent oxygen were used, and the animals subjected to repeated exposures, the white matter became involved, demyelinization appearing in the corpus callosum and centrum semiovale.

It was observed further that during severe hypoxia the frontal lobe was most often, and the temporal lobe least often, involved. The cerebellum was more often affected than the basal ganglion. The spinal cord and medulla were not affected by hypoxia compatible with life.

In 1945 HofE, Grenell, and Fulton (57), working with guinea pigs, reported that hypoxia caused marked changes in the cell, which involved the cytoplasm, nuclei, and Nissl substance. Damaged cells were found in various locations of the brain, but those in the medulla and cerebellar cortex were especially involved.

Metz (73) in 1949, after subjecting several different species of vertebrates (goldfish, frogs, turtles, pigeons, and rats) to severe grades of hypoxia, commented on the fact that he did not see much histologic nerve damage. He emphasized the possibility that the changes which may have occurred were not morphologic in nature but rather were biochemical phenomena at a submicroscopic level. This is an interesting observation and suggests further researches along this line.

Recently Hager *et al.* (46) studied electron-microscopic changes in brain tissue of hamsters following acute hypoxia. The studies suggested that there is a rise of intracellular osmotic pressure and disintegration in both the perikaryon and the mitochondria.

Gerard (38), from his studies on hypoxia and neural metabolism, has concluded that one of the functions of oxygen is to keep the cell membrane polarized and, further, that proteolytic processes are initiated by complete hypoxia. It is thought that the accumulation of lactic acid in severe degrees of hypoxia may be partially responsible for this reaction.

Gellhorn *et al.* (37) have suggested that hypoxia and hypoglycemia have a similar physiologic action on the central nervous system and that they act synergistically in the production of convulsive seizures. Sugar and Gerard (95) have also suggested that hypoglycemia acts much like hypoxia on the function of the brain, since it leads to interference with oxidation in that organ.

Hemic and stagnant hypoxia.—Histologic studies of nervous tissue have been made on the differential effects of hypoxia following anemia. Gomez and Pike (41) in 1909, working with cats, reported histologic changes in nerve cells brought about by total anemia of the central nervous system. The order of susceptibility of the cells of the central nervous system to oxygen want, as shown by histological studies, was as follows: small pyramidal cells, Purkinje cells, cells of the medulla oblongata, cells of retina, cells of cervical cord, cells in lumbar cord, and sympathetic ganglionic cells.

Gildea and Cobb (39) in 1930, studying pathologic effects of cerebral anemia, observed nonspecific cortical lesions, such as focal areas of necrosis and swollen and shrunken ganglion cells. The most pronounced effect was noted in the cells of lamina III and IV of the cortex.

In 1938 Greenfield (42) reviewed previous work on neuronal damage from stagnant and anoxic hypoxia. He emphasized that there are considerable differences in the responses of different nerve cells.

Weinberger *et al.* (101) in 1940, working with cats, produced temporary anemia by occluding the pulmonary artery. At the end of three minutes and ten seconds, permanent and severe pathologic changes were found in the cerebral cortex. Longer periods of hemic

hypoxia produced lesions in the Purkinje cells of the cerebellum and in nerve cells in the basal ganglion.

Effect of anemia on cells of spinal cord: A number of investigators (34, 47, 81, 92, 99) have made histologic studies of certain nerve cells after the circulation of the spinal cord had been partially or totally arrested. For the most part, severe anemia (ischemia) produced grave damage to the cells, and in some instances necrosis and destruction occurred. The amount of damage, of course, depended upon the severity and duration of the anemia. Some cells—for example, those of the spinal ganglia—withstood anemia much better than others.

These studies on the cells of the spinal cord have important clinical significance. They are especially pertinent in surgical operations involving important blood vessels, particularly the aorta. Recently, however, the use of extracorporeal circulation has removed many dangers in this area.

As might be expected, arrest of circulation produces grave organic changes in the cells of the central nervous system within a relatively short time. It has been emphasized by Sugar and Gerard (95), however, that while the damages which follow sudden anemia are primarily clue to hypoxia, there are other important contributing factors. Those which they mention are hypoglycemia, hypercapnia, and the increased extracellular potassium.

Carbon monoxide poisoning.—The effect of carbon monoxide on the nervous system has engaged the attention of numerous workers (53, 54, 58, 75, 91, 96, 111) . Not only has necrosis of nerve fibers in the brain been observed, but necrosis in the peripheral nerves, as well (58, 91).

In 1934 Yant *et al.* (111) made extensive investigations of histologic changes produced in the central nervous system of dogs following administration of carbon monoxide; various pronounced lesions were found.

In 1946 Lhermitte and De Ajuriaguerra (68) reported that if death rapidly followed carbon monoxide poisoning, hemorrhages, necrosis, and edema occurred. These changes primarily involved the lenticular nuclei; but the subcortical white matter, the hippocampus, the substantia nigra, and the cerebellum also were affected. If carbon monoxide poisoning is continued for long, changes appear in the vascular network with infiltration of the walls by neutral lipids and other substances, such as ferric salts and calcium.

These authors suggest that a toxic factor in addition to the anoxic factor in carbon monoxide poisoning affects the neuroglia and the vascular network with specific involvement of the basilar region and

the white fibers of the centrum ovale. In this connection, Thorner and Lewy (96) in 1940 raised the interesting question whether the cerebral changes in carbon monoxide poisoning are actually typical of hypoxia or are caused by other factors.

Dutra (32) in 1952, studying the brain of man, reported that cerebral lesions which occur as residua of carbon monoxide poisoning consist essentially of dilatation of blood vessels, edema, perivascular hemorrhages, degeneration and death of ganglionic cells, focal demyelinization, and foci of necrosis. He felt that these lesions were either directly or indirectly caused by diminution of the supply of oxygen.

Obviously, carbon monoxide poisoning is capable of producing severe damage to nervous tissue. Some of the histologic changes following severe poisoning are irreversible, so that permanent damage has been done, and as Drinker has pointed out, individuals may be practically decerebrated.

CHEMISTRY OF THE BRAIN

During the past two decades or so, considerable research has been done on the chemistry of the brain during hypoxia. Several investigators (6, 7, 44, 45) have found an increase in lactic acid during anoxic hypoxia. Gurdjian *et al.* (44, 45) in 1944 reported that cerebral lactic acid rose when the oxygen content of inspired air fell to 10-13 per cent. Criscuolo and Biddulph (26) in 1958, working with rats, found that adrenalectomy prevented an increase in lactic acid of the brain during hypoxia. If, however, epinephrine were administered, the usual rise of lactic acid during hypoxia was observed. The authors felt that this finding suggested that blood sugar is the substrate for lactic acid.

There is evidence that hypoxia causes a decrease in phosphocreatine. Gurdjian *et al.* (44) reported a decrease of phosohocreatine when animals breathed 7 per cent oxygen. No change, however, was noted in cerebral adenosine triphosphate. In 1953 Albaum *et al.* (2), working with rabbits, subjected them to progressive stages of hypoxia and correlated the chemical changes in the brain with electrical measurement of function. Moderate decreases of adenosine triphosphate, creatine phosphate, and glycogen were observed. These decreases, however, were not noted until the stage of inexcitability had been reached.

Welsh (102) subjected rats to anoxic hypoxia (200-100 mm. Hg

barometric pressure) for One to two hours and observed that the acetylcholine in the brain was decreased by approximately one-third to one-half. Insulin hypoglycemia was found to cause a greater decrease in acetylcholine than anoxic hypoxia. It was suggested that the decline in free acetylcholine might account for the decrease in excitability of the cortex under conditions of hypoxia and of hypoglycemia.

Dixon (29) in 1949 studied changes in the concentration of potassium in slices of rabbit cerebral cortex, which were bathed in a bicarbonate-Ringer's solution. In the absence of glucose a loss of potassium from the tissues was noted. With active utilization of glucose, however, there was an increase in the uptake of potassium. In this respect brain tissue resembles other tissues of the body.

The chemistry of the brain during hypoxic states obviously needs further investigation. Studies which correlate the chemical changes with electrical activity of the brain are especially needed.

ABILITY OF YOUNG ANIMALS TO WITHSTAND ASPHYXIA AND HYPOXIA

It has been known for well over two centuries that young animals are considerably less susceptible to asphyxia than adults. As early as 1725 Robert Boyle (10) commented on the resistance of kittens to asphyxia, and Paul Bert (5) in 1870 called attention to the fact that newborn animals were capable of withstanding prolonged asphyxia. Since that time many observers have reported studies on asphyxia and also on hypoxia in young animals and have confirmed and extended the earlier work.

Studies have been made on rats (1, 8, 9, 11, 18, 27, 35, 48, 55, 83, 88, 89, 90, 104), on dogs (33, 35, 40, 55, 61, 64, 88, 90, 104), on guinea pigs (18, 35, 40, 104), on rabbits (35, 40, 88, 90, 104), on cats (35, 64, 90, 104), and on mice (3, 59, 79, 80) . A few observations have also been made on chicks and ducklings (82) and on the opossum (64) . Newborn human infants, too, are capable of withstanding considerable periods of hypoxia; several workers have emphasized this (24, 71, 104).

Space does not permit giving details concerning all these experiments. Suffice it to say that the problem has been approached in numerous ways, and various grades and different types of hypoxia were used; the length of exposure was also varied. A few typical experiments may be cited.

Rabat (60) in 1940, studying resistance of very young puppies to arrest of brain circulation, found they were much more resistant to acute hypoxia than adult animals. The respiratory center in the newborn animal continued to function seventeen times as long as in the adult. The newborn also achieved complete functional recovery much more quickly than did the adult animal. At the age of four months, the resistance was diminished to the adult level.

Fazekas, Alexander, and Himwich (35) in 1941 studied the tolerance of the adult and infant of various species (rat, dog, cat, rabbit, and guinea pig) to hypoxia. The newborn exhibited a much greater tolerance to hypoxia than adults. Tolerance varied in the different species; for example, tolerance was longest in the physiologically immature newborn rats and shortest in the comparatively mature guinea pig. The authors suggested that in the newborn puppy and rat the factor permitting survival was poikilothermia, the fall of temperature diminishing the metabolic demands. It has also been demonstrated that in these two animals there is a lower cerebral metabolic rate.

Glass, Snyder, and Webster (40) in 1944, working with dogs, rabbits, and guinea pigs, subjected to pure nitrogen, concluded that tolerance to hypoxia is related to the stage of development rather than to environment. Interesting results were obtained with suckling rabbits breathing pure nitrogen. The survival period at one week was ten minutes; at two weeks, four minutes; and at three weeks, one and a half minutes, the last value being the same as that of the matured animal. These authors emphasized that the defense of the fetus against asphyxia is important because of the increased hazard of respiratory failure during the terminal phase of intrauterine life and the early neonatal period.

Selle (89) has pointed out that the increased tolerance of young animals to hypoxia is apparently due to several factors: (a) a low metabolic rate of the central nervous system, *(b)* poikilothermia, and *(c)* an anaerobic source of energy. Kabat (60) and Jelinek (59) also feel that the newborn can obtain anaerobic energy from glycolysis to a greater extent than adults. It has been shown by Himwich and his associates (55) that insulin reduces, and glucose increases, the survival of young animals placed in pure nitrogen. He and his coworkers (56), studying the survival of young animals which had been given sodium cyanide (which inhibits the cytochrome system), demonstrated clearly that anaerobic energy is available to young animals.

De Haan and Field (27) in 1959, working with rats, felt that young

animals can withstand hypoxia better than adults because of high glycogen levels and the infant's ability to metabolize lactic and pyruvic acids to lipids.

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CEREBROSPINAL FLUID

PRESSURE

In 1960 Small *et al.* (20) reported the effect on anesthetized dogs of the inspiration of 8 per cent oxygen in nitrogen mixtures. Cerebrospinal fluid, arterial blood, and central venous pressures were all measured simultaneously with modern pressure transducers. The peak increase in cerebrospinal fluid pressure, occurring at four minutes on the average, was 108 per cent over the control. Mean arterial blood pressure increased 31 per cent and venous pressure 69 per cent at the same time. Vasodilation in the brain as well as increased blood pressures, both arterial and venous, were suggested as the causes of the rise in cerebrospinal fluid pressure. Earlier experimenters have reported similar findings in both dogs and cats. Most have found an early rise in short bouts of severe hypoxia (2, 15, 17). With longer exposures the terminal increase may be lessed marked or absent (1,7, 23, 25). Edstrom and Essex (3) found the rise occurring for thirteen to thirty-three minutes following the breathing of pure nitrogen gas until near collapse.

According to present concepts (10, 21), hypoxia can cause cerebral vasodilation and increased cerebral blood flow. Since brain and cerebrospinal fluid are incompressible, in order for the cranium to accommodate the extra volume of blood there must be a shift of fluid from the cranial cavity. In the process cerebrospinal fluid pressure is apparently elevated, and cerebrospinal fluid absorption into the venous outflow is probably increased temporarily until a new equilibrium is reached.

Not all of the points in the above explanation have been directly substantiated in experiment. However, both Edstrom and Essex (3) and Loehning *et al.* (13) have seen the brain volume of anesthetized dogs increase during or after hypoxia (0—10 per cent oxygen mixtures) . White *et al.* (23) found increased cranial volume in anesthetized cats even when the brains were exsanguinated following the experimental period. The latter result suggests increased cerebral intercellular fluid, increased extracellular fluid, or both. Most workers have not found the frank edema that this would entail, nor has the reversal of intracranial changes been as difficult as this would suggest.

Changes in cerebrospinal fluid pressure similar to those in anoxic hypoxia have been observed under conditions of toxic hypoxia brought on by carbon monoxide poisoning. In anesthetized dogs and cats Forbes *et al.* (4) found abrupt rises in pressure when the concentrations of carbon monoxide in inspired air were increased. Maurer (15) also saw pressures increased 170 per cent over the control in anesthetized cats. Sjostrand (18) placed windows in the cranium of anesthetized cats for observations during exposure to carbon monoxide. He found increases in brain volume and vasodilation in the pial circulation accompanying the elevations of intracranial pressure. All of these changes were readily reversible.

Observations of human subjects exposed to atmospheres containing carbon monoxide have shown increased pressures in the cerebrospinal fluid and increased dilation of retinal vessels (4, 14, 16) .

BLOOD-CEREBROSPINAL FLUID BARRIER

It has been observed by several workers (5, 6, 8, 12) that the pH of the cerebrospinal fluid in anoxic hypoxia is increased. The increase has been attributed to the parallel increase in the blood pH directly due to the hypocapnia induced by the hypoxic hyperpnea. Several workers (5, 6, 9) have reported a paradoxical rise in pH of the cerebrospinal fluid accompanying a hypoxia not entailing hyperpnea (chemoreceptor denervation or artificial respiration) . Furthermore, Stone *et al.* (22) have shown that the rise in cerebral pH is attended by an increased lactic acid concentration in the cerebral tissue which may regress in recovery without a further change in the pH. Gokhan and Winterstein (6) suggested the phenomenon to be due to increased clearance of the cerebral tissues of acid metabolites occurring during the hypoxic increase in cerebral blood flow. This interesting explanation has yet to be verified by further research.

The penetration into the cerebrospinal fluid of tissue constituents not normally present there or of artificially tagged components of the blood plasma during hypoxia has been studied. Wiemers *et al.* (24) in 1950 found that radioactive thorium does not readily enter the cerebrospinal fluid either normally or as a result of extreme hypoxia in rats and kittens (10,000-11,000 meters, or 33,000-36,000 feet). On the other hand, Slobody *et al.* (19) have found in dogs that the slope of the curve relating concentration of albumin (tagged with radioactive iodine) to time in hypoxia to be five times that during the control periods. The hypoxia was severe: breathing oxygen-nitrogen mixtures having 3-5 per cent oxygen or decompression to simulated altitude between 25,000 and 35,000 feet (7,600 and 10,700 meters) . Similar penetration has been found by Lending *et al.* (11) by glutamic oxalacetic transaminase and lactic dehydrogenase during exposure to simulated altitudes of 27,000-37,000 feet (8,200-11,300 meters) in puppies. Obviously the degree of hypoxia has been extreme in these experiments, and caution should be used in applying the results to the milder forms of hypoxia usually seen.

In carbon monoxide poisoning the increased penetration of the blood-cerebrospinal fluid barrier has been signaled mainly by increases in protein concentration in the cerebrospinal fluid (14, 16) in some instances.

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THE AUTONOMIC NERVOUS SYSTEM

A comparatively limited amount of work has been reported on the effect of hypoxia on the autonomic nervous system. Much more work is needed. It was held by Cannon[2] for many years that the sympathetico-adrenal system played an important role in the adaptation of an animal to hypoxia; a part of his "emergency theory" was built on this concept. Cannon felt that hypoxia was capable of producing an increase in the flow of epinephrine and explained many of the phenomena produced by hypoxia by this mechanism. He suggested (personal communication), for example, that the retardation of gastric emptying produced by hypoxia (p. 213) could be accounted for by an increased release of epinephrine.

According to Sawyer *et al.* (11), if normal cats are exposed to an oxygen tension of 6 per cent, they will withstand this degree of hypoxia for at least an hour without collapsing. Cats which have had the greater part of their autonomic nervous system removed, however, will collapse within 15-38 minutes. McDonough (6) found that sympathectomized dogs breathing 4 per cent oxygen suffered respiratory failure in 102 minutes, whereas control animals continued to

[2] The reader is referred to the sections which deal with the effect of hypoxia on the adrenals (p. 244) and on the blood sugar (p. 65) .

breathe up to 145 minutes. These findings support Cannon's early views.

Gellhorn and his associates have made a number of studies on the autonomic nervous system during hypoxia. Ury and Gellhorn (12), working with rabbits, reported that 6—8 per cent oxygen raised the threshold for pupillary reflex dilatation produced by weak stimulation of the sciatic nerve. They suggested the possibility that this might have been produced by inhibition of the parasympathetics and pointed out that, if this were true, both excitatory and inhibitory processes in the central nervous system would be diminished under the influence of hypoxia.

In 1940 Feldman, Cortell, and Gellhorn (4) studied the effect of hypoxia on the parasympathetic and on the sympathetic centers. Evidence was presented (from results obtained by work on the vago-insulin and sympathetico-adrenal system) that under the influence of hypoxia both parasympathetic and sympathetic centers are excited. Two years later Gellhorn, Cortell, and Carlson (2), studying the effect of hypoxia (oxygen-nitrogen mixtures between 4.5-8.1 per cent oxygen) on autonomic and somatic responses elicited by stimulation of the hypothalamus, medulla, and spinal cord in narcotized cats, found that the autonomic centers in the central nervous system are less sensitive to hypoxia than are somatic centers.

Safford and Gellhorn (10) in 1945, working with rats on age and autonomic balance, found a diminished excitability of the sympathetico-adrenal system with increased age.

In 1959 Woods and Richardson (13), studying the effects of acute hypoxia on cardiac contractility in anesthetized and vagotomized dogs, observed that breathing 100 per cent nitrogen produced a marked increase in heart force and in blood pressure. Experiments with dogs after bilateral adrenalectomy, thoracic sympathectomy, and a total preganglionic blocking indicated that the responses to acute hypoxia are mainly due to sympathetic nerves.

Studies have been made of the effect of total sympathectomy on red blood cell formation, on hemoglobin production, and on polycythemic response to hypoxia. Orahovats and Root (9) in 1953 studied the effect of total sympathectomy on red blood cell formation and on hemoglobin production in six normal and six totally sympathectomized dogs. The experimental group produced red blood cells and hemoglobin at approximately the same rates as did the control group. It was concluded that the sympathetic nervous system is not essential for regeneration of red blood cells or hemoglobin in the anemic dog.

In similar experimentation, Grant and Root (3) studied the polycythemic response of completely sympathectomized dogs to discontinuous hypoxia (twenty-seven to seventy-three days). The polycythemic response did not differ from that of the control animals. They also concluded that the peripheral sympathetic nervous system of the dog is not essential for the polycythemic response to anoxic hypoxia.

Some clinical investigations have been made of the effect of altitude on the autonomic nervous system. It is believed by Monge (8) and by Aste (1) that residents of high altitudes show a hypertonus of the autonomic nervous system. Monge, after stimulation of the oculocardiac reflex, observed an increased tonus of the vagus nerve. Compression of the solar plexus gave a similar response of the sympathetic nerve. Aste, by intravenous injection of atropine in twenty-five soldiers who lived in the high Andes, also demonstrated a hypertonus of the vegetative nervous system. According to McFarland (7), Dr. Crane, then chief surgeon at the Cerro de Pasco Mines in Peru, found that in order to produce an effect on the circulation equal to that seen at lower levels it is necessary to inject twice the amount of atropine.

Keys *et al.* (5) have pointed out that hypoxia disturbs the stability of the balance between the sympathetic and parasympathetic nervous systems. There is an initial tendency for the sympathetic system to dominate, but this gives way to parasympathetic dominance, which is well marked.

In summary, it may be said that hypoxia is capable of producing a wide-spread influence on the autonomic nervous system. The effects of hypoxia on the alimentary tract, on the kidneys, on the sphincter pupillae of the eye, and, perhaps, on the other tissues probably can be explained, in part at least, by its effect on the nerve supply to these various organs.

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MEDULLARY CENTERS

According to Gasser and Loevenhart (4), the views which have been held regarding the effect of decreased oxidation on the activity of the medullary centers may be classified as follows: *(a)* Stimulation cannot be produced by decreased oxidation, *(b)* Stimulation may be produced by decreased oxidation, but only indirectly—as by increasing the stimulating effect of carbon dioxide or by causing formation or accumulation of acid metabolic products, *(c)* Decreased oxidation itself, under proper conditions, may stimulate the medullary centers.

The third view was first advanced by Rosenthal (17) in 1882. Gasser and Loevenhart (4) felt that they had proved definitely that this view was correct. Their work was done in 1914, and since that time, of course, the function of the carotid bodies has been discovered.

It was shown by Kussmaul and Terrer (10), as early as 1857, that when the blood supply to the brain is completely suppressed, the respiratory center is first stimulated and then depressed. Grove and Loevenhart (8) in 1911 reported that the respiratory center is more sensitive to hydrocyanic acid than the vasomotor center and that the latter is apparently more sensitive than the cardioinhibitory center.

In 1914 Gasser and Loevenhart (4), reporting studies on the effect of oxygen want on medullary centers, pointed out that stimulation of these centers by hypoxia depends upon three factors: *(a)* the suddenness of the oxygen want, (&) the extent to which the oxygen was decreased, and *(c)* the condition of the center. Hypoxia was produced by the administration of carbon monoxide and by sodium

cyanide, and the latent periods of the stimulation of the medullary centers were determined. The latent periods were found to be so short that the stimulation could not be attributed to the accumulation of acid products. They concluded that oxygen want itself is a stimulus to the medullary centers.

The hypoxia produced by carbon monoxide first stimulated the centers and then depressed them. They were stimulated and then depressed in the following order: respiratory center, vasomotor center, and Cardioinhibitory center. Their work also gave support to the theory that the activity of the medullary centers depends on the condition of their oxidative processes.

Gasser and Loevenhart (4) pointed out that if cerebral anemia is produced by clamping the cerebral arteries (19), the medullary centers respond in the same manner as they do when subjected to anoxic hypoxia and, further, that the same relative irritability of the centers has been shown by investigators working on the effect of increased intracranial pressure (3, 15).

In 1919 Lutz and Schneider (11) reported that oxygen want stimulates the respiratory center in man, and in the same year Haldane *et al.* (9) also came to the conclusion that oxygen want per se can act as a stimulus to this center. These reports were made before the function of the carotid bodies was discovered. It is now thought that oxygen want stimulates the respiratory center indirectly through the chemoreceptors. It is known, then, that oxygen want, either directly or indirectly, is capable of stimulating the medullary centers. It should be emphasized, however, that the medulla oblongata as a whole is much less sensitive to lack of oxygen than are the phylogenetically younger parts of the central nervous system, such as the cerebral and cerebellar cortices.

It is in order to consider briefly the effect of hypoxia on each center:

Respiratory center.—The effect of hypoxia on this center has been discussed in some detail in the section which deals with hypoxia and respiration, and it need not be repeated here. (See chapter viii, p. 129.)

Vasomotor center.—It has been known for a long time that if an animal is subjected to hypoxia the vasomotor center is stimulated and that if the hypoxia is severe a considerable rise of blood pressure may occur. Mathison (14) in 1911 showed that not only oxygen want but also an excess of carbon dioxide in the arterial blood causes stimulation of the vasomotor center. Hypoxia presumably acts either by direct stimulation of the center or reflexly through the sinoaortic

nerves (2) . When these nerves are severed (and the vagi cut), hypoxia produces a fall in systemic blood pressure. The work of Loevenhart and his associates on this center has been mentioned previously.

Gellhorn and Lambert (6) have pointed out that the present concept of the mode of action of oxygen deficiency and carbon dioxide excess is the same for both respiration and circulation. Carbon dioxide causes stimulation of the "isolated" respiratory and vasomotor centers. These authors call attention to the fact that the reactions of these centers to carbon dioxide is, however, different from that of other nerve centers.

Bernthai and Woodcock (1) in 1951 reported experiments on dogs with denervated carotid and aortic bodies. They concluded that oxygen want simultaneously exerts two separate and opposite influences upon vasomotor neurons, one excitatory and the other depressant and, further, that the activity of the center during hypoxia reflects the algebraic sum of the opposing influences.

Cardioinhibitory center.—In 1910 Mathison (13) observed that irregular cardiac slowing occurred frequently during asphyxia in animals with intact vagi. He felt this was caused by stimulation of the Cardioinhibitory center. Gasser and Loevenhart, as previously mentioned, also found that this center was stimulated by oxygen want.

Cardioaccelerator center.—It will be assumed for the sake of convenience in this discussion that there is an accelerator center, although its existence has not been conclusively proved. Nolf and Plumier (16), after work with dogs, believed that they had obtained some evidence of increased tonus in the accelerator cardiac nerves during asphyxia. Mathison (12), on the other hand, showed that during asphyxia the acceleration which immediately preceded the heart block was not due to stimulation of the accelerator center.

Some evidence has been presented by Sands and De Graff (18) that in progressive anoxic hypoxia the stimulating effects, up to the period of the crisis (which they found to be produced by 9 per cent oxygen), can be accounted for by the fact that hypoxia either depresses the vagi or stimulates the accelerator mechanism. In progressive hypoxia, when the vagi are cut, cardiac acceleration is often, although not always, absent; this indicates that the accelerator mechanism may be stimulated. The effect is much the same as that obtained if small doses of epinephrine are administered.

Lutz and Schneider (11), having produced hypoxia in man by use of both low pressures and low percentages of oxygen, believed they had evidence that hypoxia stimulated the accelerator center and that

this took place before the cardioinhibitory center was stimulated. They admitted, however, that they could offer no real experimental proof.

It must be emphasized that it is often difficult to interpret experimental results when working on the centers regulating heart rate, since it is known that the heart may be accelerated in at least four different ways: (a) by stimulation of accelerator nerves (or center), *(b)* by decreasing vagal tone, (c) by secretion of epinephrine, and *(d)* by an increase in the temperature of the blood (5). Since cardiac acceleration may be produced by several factors, conclusions from experimental procedures must be drawn with special care.

Vomiting center.—It has been known for many years that anoxic hypoxia may produce vomiting; for example, many, although not all, individuals who ascend to high altitudes may vomit. There are many factors (some psychic) which seem to cause vomiting, and it is difficult to prove by exactly what mechanism hypoxia stimulates it.

Mechanism of medullary center effects.—The mechanism by which oxygen want affects medullary centers is as yet unknown. The extensive researches during the past few years on the functions of the aortic and carotid bodies have thrown a good deal of light on this problem, but more work is still needed. There is considerable controversy regarding the relative importance of the various factors which are known to influence the chemoreceptors.

Not only are the chemoreceptors influenced by oxygen want, but the nerve cells of the centers, too, may be affected. Gesell (7) presented evidence many years ago that the cells of the respiratory center could be directly influenced by changes in the hydrogen-ion concentration of the blood. Moreover, Gellhorn and his associates (6) have shown that carbon dioxide may influence certain centers in the medulla. It has also been demonstrated, beyond much doubt, that anoxic hypoxia causes a depression of the isolated respiratory center and perhaps other centers as well.

Finally, these vital medullary centers may be affected by oxygen want, either reflexly through the chemoreceptors or by direct action of the cells of the centers, in ways which at present are not recognized.

Since, normally, the medullary centers are under strict control of higher neural organizations—for example, the hypothalamic and pontine autonomic centers—it would be of interest to repeat, on the bulbospinal animal, much of the work reported on the effect of hypoxia on the medullary centers.

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PSYCHOLOGICAL PROCESSES

The mind.— *(a)* Acute hypoxia: Under certain conditions, the grade of hypoxia may be so acute that loss of consciousness can occur without any warning. This could happen, for example, when an individual is overwhelmed by a noxious gas, such as when a miner walks into a pocket of methane or carbon monoxide gas. Unless a person is removed promptly from such an atmosphere, he will, of course, die. These circumstances are fortunately rather rare.

It is in order to discuss somewhat less severe grades of hypoxia. It has been said (6) that acute hypoxia resembles alcoholic intoxication;

the symptoms are headache, mental confusion, drowsiness, and muscular weakness and inco-ordination. A person exposed to a low-oxygen tension often passes through an initial stage of euphoria, accompanied by a feeling of self-satisfaction and a sense of power. The oxygen want stimulates the central nervous system so that the subject may become hilarious and sing or shout, and manifest other emotional disturbances.

After a certain length of time this initial stimulation is followed by depression; emotional outbursts of a different nature appear; and the personality frequently changes for the worse. Hilarity gives way to moroseness and quarrelsomeness, and the person may become pugnacious or dangerously violent. These latter symptoms are especially likely to occur in hypoxia produced by carbon monoxide poisoning. A striking example of this is given by Haldane (27), who relates that an inspector of mines who had been affected by carbon monoxide gas came out of the mine and shook hands cordially with the bystanders; but when the doctor in attendance offered him his arm, he regarded this as an insult and challenged him to a fight.

Hypoxia quickly affects the higher centers, causing a blunting of the finer sensibilities and a loss of sense of judgment and of self-criticism. The subject feels, however, that his mind is not only quite clear but unusually keen. He develops a fixity of purpose and continues to do what he was doing when hypoxia first began to affect him, in spite of the fact that it may lead to disaster. This fixity of purpose is highly dangerous, especially when such an individual is responsible for the lives or others, such as is true of an airplane pilot.

Individuals who surfer from oxygen want and manifest a fixity of purpose often make no effort to remove themselves from the zone of danger. This is well illustrated by a report of Foster and Haldane (24). Sir Clement le Neve Foster, who was chief government inspector of mines in Great Britain, inspected a mine in which a disaster had occurred and became himself a victim of carbon monoxide poisoning. He has given a dramatic account of his experience. He could have walked away from the danger zone, which he himself knew; but he lost his initiative, so that instead he sat down and wrote farewell messages, in which he repeated the word "good-bye" a number of times. It is of further interest that once or twice he was inconsistent in spelling the word.

Another example which shows, among other things, loss of interest and initiative is that of Longstaff (43) . The purpose of his expedition to the Himalyas was to find the highest point by ascertaining the height of the various peaks by means of the theodolite. He lost interest in his observations and failed to check his results carefully and critically when he was at great heights, so that his figures were of no value upon his return. He missed, therefore, the main object of his expedition.

Barcroft himself experienced, and relates a third incident in his monograph (7) . He had planned to incarcerate himself for a week in a low-pressure chamber. On the fifth day his wife called to see him and asked him about the barometric pressure. He stated that he had been at a simulated altitude of 18,000 feet (5,485 meters) and was now at 15,000 feet (4,570 meters) but, "after all, it made no difference." His wife realized at once that his judgment of what was important had vanished, and the experiment was ended at that point.

The experience of Haldane *et al.* (28) in a low-pressure chamber at about 22,000 feet (6,705 meters) is instructive in showing the workings of the mind under conditions of acute hypoxia. Kellas was an experienced mountaineer and was better acclimated than Haldane. At a simulated altitude of 22,000 feet, Haldane, who found that he could no longer write or make observations, handed his notebook to Kellas. Haldane insisted that the low pressure be maintained, although later he had absolutely no remembrance of it. At a barometric pressure corresponding to 20,000 feet (6,095 meters), he was handed a mirror and for some time peered at the back of it. Finally, Haldane consented that the pressure be raised, and at 14,000 feet (4,270 meters) , his mind became clear and he noticed the power return to his legs. Haldane admitted himself that his insistence upon keeping the pressure so low was irrational and that he had not intended to do so at the beginning of the experiment.

Birley (12) has reported several interesting examples of altered senses of judgment of British aviators during the war of 1914-18. One pilot who had been flying at great height found later that he had taken eighteen photographs on the same plate. In another instance, a pilot at 19,000 feet (5,790 meters) cordially waved to an enemy craft and took no further action, although his observer vehemently protested.

Pugh and Ward (57) relate a more recent instance of the peculiar behavior which may be manifested at high altitudes. One individual, having returned from a climb to 28,700 feet (8,744 meters), collapsed and lay exhausted on the ground. The comment made by one of his companions was, "Poor old Tom, he's had it." No sympathy was shown him nor any help offered. Surely this callousness would not have been shown at lower levels.

These dramatic instances give an understanding of the effects of

hypoxia on the mind which is clearer than any long or technical discussion could be. They particularly emphasize the fact that under conditions of oxygen want critical judgment is quite likely to be lost and that initiative, too, may entirely disappear.

b) Aftereffects of acute hypoxia: If the exposure to acute hypoxia has not been too long or too severe, the aftereffects, although often producing unpleasant symptoms, are transient in nature and of no especial consequence. The most common complaint is that of headache; this may come on during the time the subject is actually exposed to hypoxia or may develop a few hours later. It may be rather intractable and not alleviated by the ordinary analgesic drugs, but after a few hours it subsides of its own accord. Besides headache, other symptoms referable to the central nervous system—such as nausea, muscular weakness, and emotional disturbances—may manifest themselves after return to sea level.

It is generally thought that repeated exposure to oxygen want can have a cumulative effect. Armstrong (2) has stressed this and has described a condition which develops in airplane pilots only, which he has termed "aeroneurosis." He has defined this as a chronic functional disorder characterized by gastric disturbances, nervous irritability, mental fatigue, and increased motor activity. The exact etiology of this condition is unknown, and oxygen want might be only one factor in its production.

If the subject has been exposed to severe hypoxia for too long a time, the aftereffects are often of a formidable nature and may end in death. If death does not ensue, the hypoxia may cause changes in the brain resulting in permanent disability. There are instances on record which indicate that this has happened after prolonged administration of nitrous oxide anesthesia (17, 70).

Thompson and Corwin (67) in 1938 reported an interesting and heroic study on the posthypoxic period. Thompson subjected himself to acute hypoxia in a chamber for several hours; for the most part, he was kept at a simulated altitude which ranged from about 11,500 feet (3,500 meters) to 17,000 feet (5,180 meters) . After his removal from the chamber, he was in a stuporous or semicomatose state and showed rather alarming posthypoxic symptoms. When his respiration failed and artificial respiration became necessary, no concern was expressed, although he was quite aware of its significance. His motor responses were slow, and activity required a great amount of effort; still greater effort was needed for initiation of effort. There were no delusional or hallucinatory experiences. He stated that it was difficult to tell when the symptoms actually disappeared, but it was several

days; and, as a matter of fact, a week or more following the exposure he was still making mistakes in routine laboratory experiments. His observations agreed with those of Haldane, that mental and physical aberrations may appear after exposure to hypoxia.

c) Aftereffects of carbon monoxide poisoning: Grave aftereffects are not uncommon following exposures to carbon monoxide. Whether this is due to the fact that it produces both hemic and histotoxic hypoxia is unknown. The patient does not recover at once, as he does following short exposures to anoxic hypoxia; or, if he does recover, he may regain only partial consciousness and then lapse again into unconsciousness. Marked spastic conditions of the muscles and an occasional epileptiform seizure have been described. The patient may linger on for days in a semicomatose condition with spastic muscles and, occasionally, opisthotonus. When consciousness supervenes, loss of memory, mental incapacity, or even mania sometimes occur. If the patient survives the first few days, the symptoms will generally pass away, and he will recover, except in those instances where organic changes have taken place within the central nervous system. Following severe exposure to carbon monoxide poisoning, the patient may act as if he were practically decerebrated, as has been pointed out by Drinker (19).

d) Chronic hypoxia: While the effect of acute hypoxia on the body resembles alcoholic intoxication, that of chronic hypoxic simulates fatigue, both mental and physical (6). Since the effect of oxygen want on psychologic processes is under consideration, our discussion will be limited chiefly to the effects on the mind.

People living at high altitudes for long periods become acclimated. The matter of acclimatization has been discussed in a separate section (see p. 162). During acclimatization certain compensatory factors greatly aid the body in withstanding low partial pressures of oxygen, so that the subject can live with a greater degree of comfort and do his work more easily. These compensatory factors, however, are not equally effective in all individuals. The mental and physical health of some individuals often remains indifferent; they become irritable and do not get along with their fellow men; they may show a mild mental depression and often lack the ability to concentrate. Mental tasks are harder under conditions of oxygen want, and mistakes are more frequent. Recovery from mental fatigue, too, is slower than it is at lower altitudes. Many of these people, furthermore, are unable to obtain a refreshing sleep; their nights are often restless and disturbed by unpleasant dreams. This lack of restful sleep tends also to keep their health constantly under par. A return to lower altitudes,

of course, will restore normal health to these people, and, indeed, they often find it necessary to take periodic sojourns at sea level.

Miscellaneous studies.—Within the limits of this monograph it is not feasible to discuss in detail the wealth of work which has been reported on various psychological studies made during oxygen want. Many of these have been made on aviators, but miscellaneous experimental studies not necessarily in the interests of aviation have been made on other human subjects. In the discussion which follows, the studies made on aviators will be considered first.

1. Studies made on aviators[3]: Until the year 1914, little work had been reported on the effect of hypoxia on psychologic processes, but during the war of 1914—18 numerous psychologic studies were made on aviators by a number of workers (1, 3, 4, 12, 16, 18, 21, 23, 32, 38, 47, 56, 65, 68, 71).

Dunlap (21) has summarized the findings of these early studies on pilots as follows: (a) The primary and important psychologic effects of oxygen want are on voluntary co-ordination and attention. (6) Sensitivity and perception remain efficient until hypoxia curtails the ability of the subject to attend to stimuli, *(c)* There is no reduction in speed of simple reactions, *(d)* There is no falling-off of rapidity in discrimination except that due to deficiency of motor control, *(e)* Memory and other higher mental processes are not affected until muscular inco-ordination produces distractibility or until the ability to attend to details of learning is decreased. Finally, it is suggested that the effects of hypoxia produce a change in the integrative action of the nervous system rather than any change in the irritability or efficiency of any part.

Bagby (4) in 1921 reported some of the significant results of the work done in the Medical Research Laboratory of the United States Army. The subjects used in these experiments were exposed to hypoxia by the use of the Henderson rebreathing apparatus. He summarized the findings as follows:

a) Motor performance: Progressive hypoxia caused muscular tremor, inco-ordination, and overdischarge. These became worse as rebreathing proceeded, because of a loss of integration of the central nervous system.

b) Attention phenomenon: Hypoxia increased the subject's distractibility, so that a marked reduction developed in the ability to simultaneously carry on a number of discrete tasks. When the hypoxia

[3] Reports of the early work done on aviators may be found in *Air Service Medical* (Washington, D.C.: U.S. Government Printing Office, 1919), Part II, chap, vii, "Psychology Department," pp. 293-330.

became severe, the subject was unable to concentrate on any task in a normal manner.

c) Condition of resting muscles: The observations were made on the left hand; the muscles first relaxed, then became tense, and finally became twitchy.

d) Removal of inhibitions: The subjects often manifested uncontrolled anger, but in milder forms they showed an attitude of resentment. The type of reactions varied, since some of them became silly and even went into fits of uncontrollable laughter.

e) Self observation: Many subjects stated that they could "pull themselves together" for a short time but then they "wanted to rest."

The various psychologic studies made on airplane pilots have been of both academic, and of practical, value. Some of these tests have demonstrated the importance of the factors of fatigue, staleness, and ill-health in these individuals. Certain psychologic tests, moreover, can be used as an aid in the selection of airplane personnel. It is true, of course, that nowadays these airmen are not subjected to hypoxia as they were, for example, during the war of 1914—18. Now either they are equipped with oxygen masks or the cabin of their aircraft is pressurized. However, equipment failure could, of course, cause these men to be subjected to severe grades of hypoxia.

2. Miscellaneous studies: Barcroft (8) relates that a few mental tests were given to the members of his South American party (1921-22) at Cerro de Pasco, which lies at an altitude of 14,200 feet (4,330 meters) . The conclusion was that the tests were too simple to be of real value. It was observed, however, that the amount of mental effort necessary to do the tests was more pronounced than the loss of accuracy with which they were done.

Kingston (34), medical officer to the 1924 Mount Everest Expedition, gave simple mathematical tests to members of the party at 7,000 feet (2,130 meters), 14,000 feet (4,270 meters), 16,000 feet (4,875 meters), and 21,000 feet (6,400 meters) . Apparently by making increased effort, the men did very well on these tests. McFarland believes that the tests probably were too simple to show subtle incapacities. It is to be remembered also that the tests were made on fairly well-acclimated subjects.

Lowson (44) in 1923 reported some studies made on the effect of oxygen want on certain psychologic processes. He concluded that until the diminution of oxygen reached 50 per cent of the normal no significant alteration in behavior occurred in the average subject; beyond this, however, the changes were rapid and great.

Tanaka (66) in 1928, working with a low-pressure chamber under

Haldane's direction at Oxford, reported work done on six subjects. He tested speed in simple and complex sorting, addition, memory, and strength of grip at different altitudes up to 21,000 feet (6,400 meters). He concluded: *(a)* that hypoxia caused a deficiency in both mental and physical work; *(b)* that there was considerable difference as to the altitude at which changes occurred; (c) that hypoxia caused a greater deficiency in mental than in physical work; *(d)* that hypoxia affected especially the quality of work; and *(e)* that the usual critical point where sudden changes occurred was 428 mm. Hg, which corresponds to an altitude of about 15,000 feet (4,570 meters) .

McFarland (48) in 1932 made exhaustive studies of oxygen want on psychologic processes. In this work he used a spirometer and oxygen mixtures ranging from 11.43 (about 17,000 feet—5,180 meters) to 7.68 per cent (about 28,000 feet—8,535 meters) . He came to the following conclusions: (a) Simple sensory and motor responses were not seriously impaired until the oxygen want was so severe that the subject approached collapse—about 24,000 feet (7,135 meters) or an oxygen percentage of 8.87. Vision and kinesthesis (muscle sense) were the first to be affected, and hearing, the last, (fe) Choice reactions appeared to be impaired before simple reactions, (c) Neuromuscular control was impaired before the loss of capacity in more highly organized functions, such as choice reactions, *(d)* There was a loss of memory with oxygen percentages as low as 9.05. *(e)* Concerning the effect on attention, hypoxia apparently both facilitates attention by eliminating extraneous factors and handicaps it by undermining voluntary co-ordination. (/) Hypoxia impairs higher mental powers, (g) Hypoxia affects feelings or moods; depending on the length of time the individual is subjected to hypoxia and other factors, it may stimulate or depress, *(h)* It was concluded, also, that significant data relative to the basic patterns of personality could be obtained under severe oxygen want.

McFarland (49) in 1937 reported observations on psychological studies made during sudden ascents to 15,000 feet (4,570 meters) and 16,500 feet (5,025 meters) on trans-Andean planes and during slower ascents by train, also in the Andes, to somewhat lower altitudes. From his observations he concluded that the rate of ascent was an important variable and that there was a significant impairment of both simple and complex psychological functions at these altitudes. He found that the mental tests which involved complex reactions were most affected by high altitudes; the motor tests were affected less; and the sensory tests least of all.

3. Studies made on subjects undergoing acclimatization: In a subsequent paper McFarland (50) reported sensory and motor tests on ten subjects undergoing acclimatization during a three-month period at various levels up to an altitude of 20,140 feet (9,135 meters). The following sensory and motor tests were given: *(a)* auditory thresholds—for eight frequencies, (&) phoria test for ocular muscle balance, *(c)* fatigue of accommodation and convergence, *(d)* measurement of after images, *(e)* color-naming test, (/) simple and choice reaction time, (g) dotting test of neuromuscular co-ordination, and *(h)* mirror test. He found a variability of response for both the individual and the group at 15,440 feet (4,700 meters) and above and a significant difference in the means for the group at 17,500 feet (5,330 meters) and above.

He also reported (51) on the following psychologic tests, using the same subjects and the same altitudes: *(a)* speed of apprehension for words, *(b)* judgments of duration, *(c)* repetition of auditory patterns, *(d)* perseveration tests, *(e)* memory tests, (/) code transliteration, and (g) Thorndike C.A.V.D. intelligence test.

At 15,440 feet differences in the means and variabilities of the mental tests were observed; these became more marked at higher altitudes. There was a close parallel between the periods of greatest discomfort in adaptation to the altitude and the psychosomatic changes or psychologic complaints.

It appears from the observations of McFarland that in fairly well-acclimated subjects psychologic processes, for practical purposes, are not affected until an altitude of approximately 15,440 feet (4,700 meters) is attained. It will be recalled in this connection that Barcroft stated that at Cerro de Pasco (14,200 feet—4,330 meters) mental tests gave indeterminate results. Any psychologic tests made, moreover, on acclimated subjects on Pike's Peak (14,100 feet—4,300 meters) probably would not show any positive results.

4. Most common alterations in psychologic behavior: It is of distinct interest to call attention to the ten most common alterations in psychologic behavior which McFarland reported. These observations were made on members of the International High Altitude Expedition to Chile. In order of frequency, they were as follows: *(a)* greater effort to carry out tasks, *(b)* more critical attitude toward other people, *(c)* mental laziness, *(d)* heightened sensory irritability, *(e)* sensitivity on certain subjects, (/) dislike of being told how to do things, (g) difficulty in concentrating, *(h)* slowness in reasoning, *(f)* frequent recurrence of ideas, and (;') difficulty in remembering.

These alterations in behavior reported by McFarland coincide with the early observations of Barcroft, Haldane, and others. It must be

remembered, however, that McFarland's observations were made on ten rather highly selected subjects. The identical alterations in behavior in the same order of frequency might not be found in an unselected group of subjects.

McFarland reported that no significant correlations between mental tests and biochemical determinations were found. The correlation between mental tests and physiological measurements at high altitude, however, revealed a number of positive relationships.

Pugh and Ward (57) have reported observations made on mental activity during one of the more recent Mount Everest expeditions. They relate that at about 21,000 feet (6,400 meters) some members of the expedition did not experience noticeable impairment of mental activity. For example, one individual solved crossword puzzles readily, and Pugh himself relates that he did gas analysis for six hours and made few errors. All of these individuals were, of course, well acclimated to great heights.

At altitudes over 22,500 feet (6,855 meters), however, considerable impairment of mental faculties was apparent. At 26,000 feet (7,925 meters), mental and physical depression were noted. There was retardation of thought and action, and a noticeable diminution of excellence of insight and judgment.

Barach (5) in 1943 made observations on impairment of emotional control caused by hypoxia. He reported that the affective response may be depressive in nature or may take the form of exhilaration, the mood varying with the nature of the individual. In a rather small series, he found euphoria in 50 per cent of his subjects, but about the same number showed a dullness. Von Tavel (69) in the same year noted a predominantly euphoric reaction in only 10—20 per cent of his subjects. Obviously more work is needed in the field of emotional control during hypoxic states. The problem is of distinct practical interest, since depressive states are so often found in a number of clinical conditions.

Useful consciousness.—Hall (29) has defined useful consciousness during hypoxia as that state in which the individual remains attentive and is able to perform useful or purposeful acts. He has pointed out that the end point of useful consciousness can be determined with greater definiteness than can that of total loss of consciousness. Cell (25) has defined it slightly differently. He states that useful consciousness is a term expressing the length of time between the period when the subject's oxygen supply is totally deprived (at various altitudes) and the onset of physical or mental deterioration. Gell points out that it is determined primarily by altitude but is influenced somewhat by the inherent tolerance of the individual and markedly affected by the amount of physical activity.

The interval of useful consciousness at great altitudes is very short. Cell (25) states that at 40,000 feet (12,190 meters) useful consciousness lasts thirty seconds or less; at 35,000 feet (10,670 meters), from forty-five to sixty seconds; at 30,000 feet (9,145 meters), from twenty to ninety seconds; and at 25,000 feet (7,620 meters), from two to three minutes.

Under conditions of explosive decompression, such as might be produced by a meteor piercing a pressurized cabin, the interval of useful consciousness in the range of altitude between 25,000 feet and 65,000 feet (19,810 meters) is greatly diminished. According to Luft (45) at an altitude of 45,000 feet (13,715 meters), the interval would be about fifteen seconds. The reason for this is that during decompression the oxygen reverses its direction of flow; that is, it passes from the blood back into the lungs. This process continues until equilibrium is reached with the oxygen of the atmosphere.

The three workers previously mentioned, Hall, Cell and Luft, have all emphasized the practical importance to aviation of accurate appraisal of the factors which influence useful consciousness in flyers under the stress of hypoxia. Mackenzie *et al.* (46) have also stressed the significance of such studies, and Ruff and Strughold (60), too, have recognized their extreme importance.

Several workers (31, 35, 36, 46) have used writing tests to determine the end point of useful consciousness. Hemingway (31) in 1944 subjected thirty-one individuals, who wore oxygen masks, to a simulated altitude of 35,000 feet (10,670 meters). At this altitude, the oxygen supply line was disconnected, and air was breathed. The subjects started writing immediately but were unable to write longer than from fifty-five to eighty seconds (average of 72.6 seconds) . The average arterial oxygen saturation was 56.6 per cent. The author felt that there was practically no danger in performing this test.

Ivy (36) in 1946 used a similar technic; that is, he cut off the oxygen supply of subjects at different altitudes and observed how long they continued to write. He stated that 26,000 feet (7,925 meters) was the critical altitude in that none of the forty-nine subjects at this altitude was able to continue writing longer than fifteen minutes. He obtained the following results: Useful consciousness was present for 3.0 minutes at 28,000 feet (8,535 meters) ; 2.4 minutes at 30,000 feet (9,145 meters) ; 1.8 minutes at 32,000 feet (9,755 meters) ; 1.4 minutes at 36,000 feet (19,975 meters) . These periods are somewhat longer than those given by Cell. Ability to write persisted at arterial

oxygen saturation greater than 66 per cent. Ivy felt that an arterial oxygen saturation of 75 per cent was the lowest safe limit for voluntary directed movement.

In the same year, Hoffman *et al.* (35) studied the interval of useful consciousness by using a simple task, namely, card-sorting. The time of useful consciousness was determined by the appearance of the first error made in the sorting. The average time of useful consciousness was 110 seconds at 28,000 feet (8,535 meters) ; 73 seconds at 30,000 feet (9,145 meters) ; 46 seconds at 35,000 feet (10,670 meters) ; and 35 seconds at 38,000 feet (11,580 meters). The period of useful consciousness was found to be approximately three-fourths of the total time that consciousness was retained. On the average, the arterial oxygen saturation was 64 per cent at the appearance of the first error.

Hall (29) in 1949 used the interval of useful consciousness (by the subjects' response to signals) to determine tolerance to altitude. Ten healthy young men while breathing air were subjected to the following altitudes: 30,000, 35,000, 37,000, 40,000, and 42,000 feet, corresponding to 9,100, 10,700, 11,300, 12,300, and 12,900 meters, respectively. Four subjects were bled, so that the oxygen capacities of the blood were lowered from an average of 15.3 gm. to 13.3 gm. of hemoglobin per 100 ml. of blood. In five subjects, the oxygen capacities of the blood were increased from 15.6 to 17.0 gm. of hemoglobin per 100 ml. of blood by blood transfusion. The interval of useful consciousness while breathing air at 35,000 feet (10,700 meters) was determined on each subject. It was concluded that changes induced in the oxygen capacity of the blood modified tolerance to altitude when useful consciousness was used as the index.

In 1951 Hall and his collaborator (30), working with human subjects, found that the addition of certain amounts of carbon dioxide to ambient air at low barometric pressures of 225 mm. Hg and 179 mm. Hg increased the duration of useful consciousness. It is of interest, too, that the interval of useful consciousness may be significantly improved by the ingestion of glucose. Riesin *et al.* (59) found that thirty-nine control subjects lost useful consciousness, on an average, at the end of 185.7 seconds at a simulated altitude of 27,000 feet (8,200 meters). In contrast, thirty-eight volunteers who had ingested glucose previous to the experiment retained effective consciousness, on an average, for 261 seconds.

Acclimatization and useful consciousness: In 1945 Mackenzie *et al.* (46), using a writing test, determined the interval of useful consciousness in fifty-five men, the majority of whom had been partially acclimatized. Simulated altitudes from 25,000 feet (7,600

meters) to 36,000 feet (11,000 meters) were used. The non-acclimatized group at 30,000 feet (9,100 meters) did not do as well as the partially acclimatized group at 33,000 feet (10,000 meters). In the former group the period of useful consciousness was 94 seconds, whereas in the latter it was 106 seconds. It has been shown (11,33) that a few-weeks stay at the moderate altitudes of 6,600 and 10,200 feet (2,000 and 3,100 meters, respectively) may cause a lengthening of the time of useful consciousness in man at extreme altitudes of 25,000 feet (7,600 meters) and 26,200 feet (8,100 meters).

It should be pointed out that the interval of useful consciousness depends in a large measure upon the type of test used. Most of the tests employed have been of extremely simple nature, such as writing or simple card-sorting. It seems to the authors that more challenging tests should be used, for example, problems in mental arithmetic.

While considerable work has been done on determining the interval of useful consciousness in unacclimatized individuals, more studies are needed on subjects who are well-acclimatized to reasonably high altitudes.

Memory and learning ability.—During the past two decades or so, studies have been made on memory and on learning ability of animals which had been subjected to severe grades of hypoxia (and asphyxia) for varying periods of time previous to tests for these psychologic functions.

1. Studies on animals: In 1944 Becker and Windle (10) asphyxiated guinea pigs at birth, resuscitated them, and, at four to six weeks of age, subjected them to learning tests. Twenty-three of the thirty-six experimental animals used showed definite pathologic changes; nineteen showed inferior maze-learning ability. Jensen, Becker, and Windle (37), four years later, subjected fifteen young adult male guinea pigs daily (except Sundays) to a simulated altitude of 30,000 feet (9,145 meters) . After 100 hours of exposure, the animals were tested for retention of learning; no significant differences were found. They were tested also after 150, 200, and 250 hours of exposure. The most pronounced changes in learning occurred after 250 hours of exposure. Four experimental animals were unable to relearn the problem in twenty trials, although some experimental animals, after 200 hours of exposure, had relearned the problem after ten trials. It should be remarked that a simulated altitude of 30,000 feet represents a very severe grade of hypoxia.

Bunch (14) in 1952 reported observations made on a large group of rats of the effects of pre- and postnatal hypoxia upon memory and learning ability at maturity. Pregnant animals were exposed to a

simulated altitude of 30,000 feet (9,145 meters) for two hours. One hundred of the offspring learned the maze (multiple-T-14 unit water maze) problem as adults and were compared with 100 control animals. The hypoxic rats were significantly inferior to their controls in the measure of learning.

Richardson (58) in 1954 produced asphyxia in rats for periods from one to twenty minutes by preventing initiation of respiration before removing full-term fetuses from the uterus. Beginning at sixty-five days of age, they were tested on the Hebb-Williams closed maze; the experimental animals made more errors than the controls. It was concluded that oxygen deprivation at the time of birth tends to reduce the rat's ability to transfer prior learning to new situations.

In 1957 Cassin and Fregly (15) subjected newborn dogs (less than twenty-four hours old) to pure nitrogen for periods varying from eleven to eighty-one minutes. The animals were revived by artificial respiration, and oxygen was given under positive pressure. They all showed some degree of central nervous system insult lasting from five to forty-eight hours, but from one to six months later, no gross motor or behavioral aberrations were observed. Nevertheless, psychologic tests, problem-solving (open-field maze) and auditory discrimination (shuttle box), showed subtle behavioral differences.

2. Studies on man: Dougal and Fiset (20) in 1950 performed psychologic tests on men who had been subjected repeatedly to a simulated altitude of 10,000 feet (3,050 meters) . The authors concluded that the relative deficit of oxygen at that altitude inhibits partly the normal functioning of the higher centers, especially the learning process.

Kossmann (41) in 1947 reported a case history of a flyer who experienced severe anoxic hypoxia during a bombing mission. His nervous system apparently was physiologically damaged, for even three weeks following the episode, he showed impairment of memory and slowing of cerebration. However, eighteen and a half months later, he presumably had made a complete recovery, for his memory and intelligence tests appeared normal.

Pugh and Ward (57) have commented on possible aftereffects in human beings who have been exposed to great heights for an appreciable period. The authors called attention to eight mountain climbers who had climbed to an altitude of 28,000 feet (8,535 meters) without oxygen. They pointed out that all these individuals later enjoyed careers of distinction and occupied positions that could not have been attained by men who suffered any significant degree of mental deterioration. There was one possible exception; one individual who had spent five nights at an altitude of 25,000 feet (7,620 meters) complained of some loss of memory.

Obviously, studies of memory and learning ability made on both man and animals following exposure to hypoxia or asphyxia are of great practical importance. It is known, for example, that the human fetus, either *in utero* or during birth, may be subjected to asphyxia or hypoxia or both. It is known, also, that hypoxia produced by carbon monoxide poisoning may cause permanent brain injury and that nitrous oxide given in high concentrations during anesthesia may do likewise. It is not in the province of this monograph to pursue further these interesting and important clinical problems. Suffice it to say that more studies should be made on animals. It would be highly desirable if such experiments could be made on the higher apes.

Dreams.—Since dreams are deemed important by psychoanalysts and since they are often mentioned in the literature which deals with high altitudes, the effect of hypoxia on dreams will be considered briefly.

Most writers emphasize the disturbances of sleep experienced by unacclimatized subjects at high altitudes. It has been pointed out by Monge (53) that native Andeans accustomed to living at great heights complain of restless sleep and disturbing dreams when they suffer an attack of chronic mountain sickness (Monge's disease). Dr. Crane, who served as medical officer for the Cerro de Pasco Copper Corporation, observed that newcomers to Cerro de Pasco, at altitudes from 12,000 to 14,200 feet (3,660 to 4,330 meters), experienced restless sleep and fantastic dreams, which were often apprehensive in character.

Probably the most comprehensive observations on the effect of high altitudes on dreams are those made by McFarland (51) . He has presented in some detail the dream experiences of members of the International High Altitude Expedition to Chile. He relates that, prior to the ascent to the high-plateau region, dreams of the members were generally associated with home situations and with vivid experiences close at hand; they were also concerned with sexual or anxiety situations.

When the members of the expedition first ascended high altitudes, that is, before acclimatization took place, they experienced dreams which were fantastic and illusory in nature—they presumably had the usual experience of newcomers to high altitudes. When they reached their high-altitude stations (from 17,500 feet—5,330 meters to 21,140 feet—6,440 meters), and were by this time presumably fairly

well acclimated, they dreamed infrequently, and there was little consciousness of sex.

An interesting observation was that dreams which accompanied the greatest physiological disabilities were usually the most vivid and fantastic. McFarland has expressed it thus: "Variations in the general physiological state, therefore, appeared to be equally as important as inner conflicts or motives, considered by many to be the basic course of dreams." The psychoanalysts probably would find it hard to reconcile this with their concept of the significance of dreams. It is pertinent to mention that several illnesses, especially those associated with gastrointestinal disorders of any kind, may produce disturbing dreams. Sufferers from migraine often experience unpleasant dreams the night preceding an acute attack. This lends evidence to the statement made by McFarland.

Reaction time.—It is necessary to distinguish between "simple-reaction time" and "choice-reaction time." The former designates the time which elapses from the moment the stimulus is given until the response occurs. Choice-reaction time, however, requires judgment; since the subject must choose whether or not he is to respond to a given stimulus, more synapses are involved, and the time is normally longer than simple-reaction time.

A number of studies have shown (9) that anoxic hypoxia produces only slight retardation of simple-reaction time until an altitude of about 20,000 feet (6,095 meters) is reached; this is about the point of collapse in the unacclimatized subject. In 1911 Durig and Reichel (22), performing experiments on Monte Rosa (altitude of 15,000 feet—4,570 meters) on subjects who had been there eight days, and again after sixteen-days sojourn, reported a possible loss in auditory-reaction time, although they admitted their results were indeterminate. In 1893 Mosso (54) had reported somewhat similar results. In 1935 Jongbloed (40), using a low-pressure chamber, found that at a simulated altitude of about 16,404 feet (5,000 meters) choice-reaction times were significantly lengthened. Stern (64) in 1926 found that newcomers at Davos, at altitudes of 5,100 feet (1,585 meters) and 8,400 feet (2,560 meters), showed a prolonged reaction time, which was shortened by oxygen inhalation.

Tanaka (66) in 1928, using a low-pressure chamber, and McFarland (48) in 1932, using a Douglas bag, observed a significant loss in speed and accuracy in choice-reaction time above 15,000 feet (4,570 meters) and 18,000 feet (5,485 meters). However, Bonnardel and Liberson (13) in 1932 at an altitude on the Jungfraujoch of 11,333 feet (3,454 meters) found no significant changes in either visual or auditory reaction time.

McFarland (50) feels that slow reaction times which have been reported below 14,000 feet (4,270 meters) probably have been observed following a rapid ascent, so that the element of fatigue is added. In 1937 he (49) reported determinations of choice-reaction times of six subjects at Lima, Peru (about sea level), and Morococha (altitude 14,890 feet—4,540 meters) . Expressed in hundredths of a second, the mean for the six subjects at Lima was 53.7 and at Morococha, 60.3.

Studies made on acclimatized subjects: In a later paper McFarland (51) reported studies made of sensory and motor responses in subjects during acclimatization in the Chilean Andes. No significant differences were observed in the simple-reaction tests until an altitude of about 20,140 feet (6,135 meters) was reached. Variability of responses was, however, reliably increased at 17,500 feet (5,330 meters). Choice-reaction time was significantly impaired at 17,500 feet.

In a subsequent paper (52), studies made of simple- and choice-reaction time on native miners in the Chilean Andes at an altitude of 17,500 feet were reported. The reaction time was prolonged, and the responses were more variable in these men than in workmen at sea level. The differences were statistically significant.

Neuromuscular control.—Kingston (34), medical officer to the 1924 Mount Everest Expedition, reported mild tremor of eyelids and fingers at 14,000 feet (4,270 meters) in one subject and at 21,000 feet (6,400 meters) in another. In 1925 Stern (63) found an increase in hand tremor at Davos, at altitudes of 5,100 feet (1,585 meters) and 8,400 feet (2,560 meters) . Loewy and Wittkower (42) in 1933 described an increased reflex irritability in seven of nine subjects at similar altitudes and also noted unusually active responses to Chvostek's sign and Trousseau's phenomenon. It would seem that the findings of these latter workers should be rechecked, since the altitude was so moderate.

Jongbloed (39) found that at a barometric pressure of 150 mm. Hg (about 39,000 feet—11,880 meters) animals showed catatonic reactions similar to those produced by bulbocapnine. McFarland (48), using a Douglas bag, observed, at a simulated altitude of 17,500 feet (5,330 meters), increased muscular tremors and a loss of neuromuscular control in handwriting tests. He reported, further, that at a simulated altitude beyond 19,500 feet (5,940 meters) the loss of efficiency was sudden and great. Goralewski (26) in 1935, using a low-pressure chamber and requiring the subjects to reproduce geometrical figures and sentences, noticed an impairment in this ability in a number of subjects at oxygen percentages of 14-18 (about

10,000-3,000 feet—3,050-910 meters) ; this impairment was increased at lower oxygen pressures.

In 1946 Muido (55) studied the effect of hypoxia on eye-hand co-ordination by use of the pursuit meter (apparatus *ad modium* Abramson). Three individuals were subjected to a simulated altitude of about 19,500 feet (6,000 meters) in a low-pressure chamber. An appreciable deterioration of co-ordination was found. Russell (61) in 1948, also using the low-pressure chamber, studied the effect of mild hypoxia for thirty-five minutes on simple psychomotor skills, namely, finger dexterity and arm-hand co-ordination. He found: *(a)* a decrease in level of performance which appeared immediately after the introduction of mild hypoxia; *(b)* a rapid adjustment following this decrement as the period under mild hypoxia increased; and (c) following this adjustment, an improvement with continued practice under the mild hypoxic conditions.

More recently, Shepard (62) subjected ten normal individuals to a simulated altitude of 20,000 feet (6,095 meters) for ten minutes. All subjects showed significant changes in psychomotor performance.

In summary: appreciable degrees of acute hypoxia may produce deleterious effects on neuromuscular control. These effects, in a measure at least, resemble those produced by alcohol.

Acclimatization and neuromuscular control: McFarland (50), working with subjects during acclimatization, found that in the dotting test for neuromuscular co-ordination there was no sign of loss of efficiency until an altitude of 15,440 feet (4,700 meters) was attained.

Observations made on natives at high altitudes: McFarland (52) used the dotting test for determination of neuromuscular co-ordination on natives of the Chilean Andes residing at an altitude of about 17,000 feet (5,180 meters) . The difference between the means of men working at sea level and those of the natives at high altitudes on this test of neuromuscular co-ordination was not statistically significant. Responses of the natives of high altitudes, however, were more variable.

Effect of hypoxia on handwriting: Many investigators have studied this problem, since it is a practical and easy method of studying muscular control. In general, it may be said that the more severe the hypoxia, the greater the loss of the ability to write normally. Figure 11 shows specimens of handwriting at different oxygen percentages up to 7.68, approximate altitude of 28,000 feet (8,535 meters) . It is readily seen that as the hypoxia progresses in severity the handwriting becomes less and less legible (48).

Type of paralysis produced by hypoxia: In severe hypoxia, an ascending type of paralysis is produced. The legs first lose their power, so that the subject is unable to stand; as the paralysis ascends, the arm muscles soon become affected; the neck muscles are the last of all to be involved. That hypoxia produces an ascending type of paralysis was dramatically illustrated by Coxwell when he made his famous balloon ascent with Glashier. Coxwell's muscles, except those of his neck, were, for the most part, paralyzed; he could still move his head and so was able to grasp the rope valves with his teeth. By so doing, he saved his life and that of his companion.

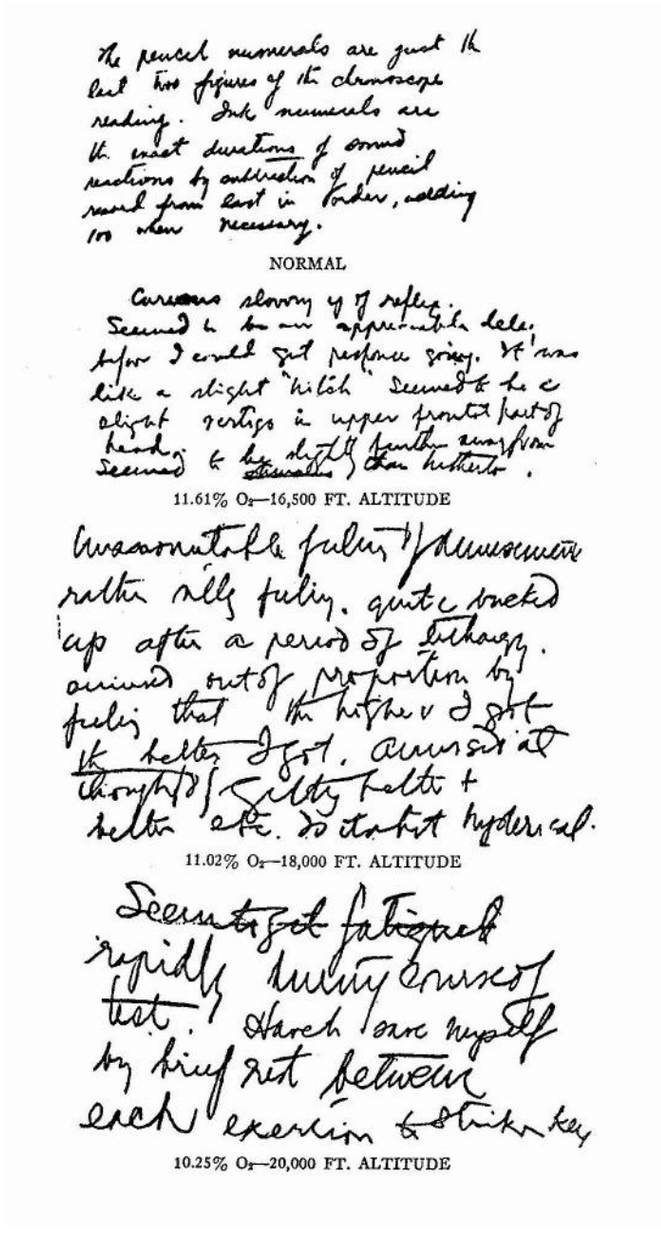
Another dramatic instance of muscular paralysis due to oxygen want is the experience of Tissandier, sole survivor of the three-man ascent in the balloon "Zenith." At great heights he realized that he needed oxygen but could not husband the strength to raise the mouthpiece of the oxygen container to his lips.

Finally, it may be mentioned that individuals suffering from carbon monoxide poisoning often become paralyzed, so that although they are conscious and wish to leave the zone of danger, they are physically unable to do so.

Resume of effect of hypoxia on psychologic processes.—Since a brief review has been presented of many of the observations made on psychologic processes during hypoxia, little need be said by way of summary. The various psychologic tests are presumably of most practical importance for airplane pilots. One important finding is the great individual variation which may occur. This indicates, of course, the need for careful selection of pilots.

There was a time when psychologic tests for pilots were probably more important than they are now, since most planes, both military and commercial, have pressurized cabins. There are situations, however, in which hypoxia of varying degree may occur, for example, in case of failure of the mechanism which controls the pressure in the plane. Under these conditions, both pilots and passengers would be subjected to hypoxia—the degree, of course, depending upon the height at which the plane was flying. If failure occurs at extreme altitudes, the length of the period of useful consciousness becomes a very important matter. It is true that at times not much can be done to avert disaster, but often every second of consciousness will help. However, in the event of explosive decompression at high altitudes, the period of useful consciousness is perhaps only about fifteen seconds.

It has been pointed out previously, nerve tissue is the least capable of withstanding hypoxia, and the nerve cells of the cerebrum are the



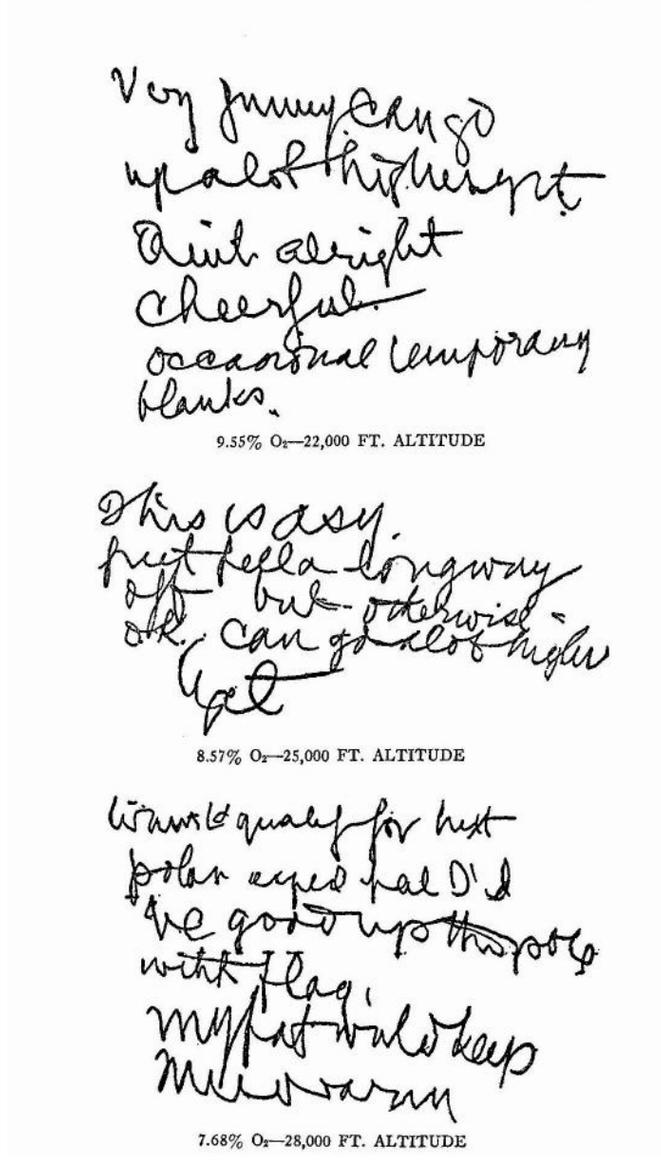


FIG. 11.—Specimen of handwriting at the oxygen percentages and corresponding altitudes indicated. (From R. A. McFarland, "The Psychological Effects of Oxygen Deprivation on Human Behavior," *Arch. Psychol.* [N.Y.], 145 [1932], 110-11.)

first to be affected in oxygen deprivation. The effect of severe grades of anoxic and hemic hypoxia on the mind is a matter of cogent importance. It is known that high grades of hypoxia or asphyxia at birth may produce irreparable damage to the infant brain. Hypoxia, too, may affect the brain of the adult; this is especially true of carbon monoxide poisoning. Unfortunately some individuals never recover, and indeed, some lead a vegatative existence the remainder of their lives. Nitrous oxide, when given in heavy concentrations for a relatively prolonged period, may also produce irreparable damage to the brain. There is evidence that severe hemorrhages, such as may be produced by accidents, may also cause brain damage due to the prolonged anemia.

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THE FUNCTIONING OF SMALL UNITS OF THE NERVOUS SYSTEM

Nerve fiber.—A number of studies have been made on the survival time of nerves during hypoxia (and asphyxia) in cats, dogs, rabbits, and frogs (36, 37, 53, 86) .

In 1930 Gerard (36) reported experiments on the response of the nerve fiber to oxygen lack. He found that in the course of asphyxia action potentials led from the exposed region first rise and then fall to zero. He concluded from his experiments that asphyxia initially causes prolongation of action potentials, followed later by a depression of potential magnitude, a prolongation of refractory period, and fiber block. The time required for asphyxiation of a nerve depends on the temperature and the type of nerve; the higher the metabolism, the faster the block. When oxygen was readmitted to an asphyxiated nerve, the action potential rose rapidly within five to ten minutes to high values. The maximum response for fast stimulation may be five to six times as great as the pre-asphyxial ones, but for slow stimulation, as much as twelve times as great.

Lehmann (53) in 1937, working with excised nerves (peroneal, phrenic, and saphenous) of the cat under controlled conditions of hydrogen-ion concentration, found that when they were immersed in pure nitrogen, a typical sequence of irritability changes occurred. There was a lowering of the threshold of excitability first, followed by a progressive failure of irritability of the nerve fiber. The after-potentials disappeared before the spike—ten minutes on the average for the former, and thirty minutes for the latter. The normal functional state was restored if the hypoxia did not last too long.

Wright (86) found that the average survival times of twenty-eight rabbit nerves, ten cat nerves, and three dog nerves were 24, 33, and 33 minutes, respectively. He pointed out that the survival time of a nerve is a constant for each species. A number of workers (1, 8, 10, 27, 32, 34, 88) have experimented on various animals to determine the length of time a nerve functions after ischemia. On the whole, it was found that the time varies in different animals. It has been shown by Wright (87) and others (3) that hypoxia causes progressive depolarization and blocking of impulses in nerve tissue when a critical degree of depolarization is reached.

In 1931 Lewis, Pickering, and Rothschild (57) produced ischemic blocking of human nerves and reported that anesthesia always starts in the distal part and spreads proximally. They found, also, that the nerve is more sensitive to asphyxia in its proximal, than its distal, part and, further, that long nerves are affected earlier than short ones. A number of investigators have confirmed these findings (6, 41, 48, 73, 88), but some workers have questioned them (10, 68, 84). It was shown by Thorner and Brink (74) in 1940 that if the human ulnar nerve is deprived of its circulation for a period not exceeding thirty minutes, a succession of events occur similar to those outlined by Lehmann (53), that is, first a lowering of the threshold of excitability and then a progressive failure of irritability.

In 1948 Grandjean and his co-workers (39, 40) and Zwahlen and Grandjean (89) investigated the effect of altitude on nervous excitability. The studies showed that, in general, the threshold of

sensory structures was increased; motor nerves, however, were unaffected.

Hypoxia and asphyxia and synaptic conduction.—Most of the studies reported on the effect of hypoxia on the synapses have involved stagnant hypoxia; that is, the circulation was arrested. Under this condition, there is, of course, considerable accumulation of carbon dioxide in the tissues.

As early as 1905 Tuckett (75), by producing anemia of the superior cervical ganglion, observed that the ganglion cells possessed greater resistance than those of the spinal cord. Schroder (66), however, was one of the first to study systematically the effects of anemia on sympathetic ganglia. In 1913 Cannon and Burket (22) pointed out that cells of the mesenteric plexus had a high resistance to complete anemia. Eccles (31), studying electric responses of the superior cervical ganglion, observed that a very small minute-blood supply is sufficient to maintain functional ganglionic activity.

Sugar and Gerard (71) have emphasized that synaptic conduction through the cervical sympathetic ganglion can withstand considerable hypoxia. In support of this view, they cite their own histochemical researches (70), the work of Bronk and Larrabee (19), and that of Bargeton (5). Bronk and Larrabee (19), working with the stellate ganglion, reported that it could be deprived of its circulation for about thirty minutes before it began to lose its capacity to respond. Deprivation of its circulation for approximately sixty minutes, however, caused cessation of its functioning.

In a subsequent study, Bronk *et al.* (18,20) investigated the effect of hypoxia on conduction of impulses along axons and on transmission of impulses through synapses. Arresting the circulation of the ganglion caused transmission through it to fail in about thirty to forty minutes. Within two minutes after stopping the circulation, the oxygen tension fell to less than 5 per cent of its initial value, as shown by placing an oxygen electrode on the ganglion. However, even with a very small rate of oxygen consumption or with virtually none, transmission of the impulse was maintained for some time—in some pathways for as long as thirty minutes. This observation was in agreement with the work of Eccles. Indeed, it was shown that even after seven and a half hours of interruption of the circulation, one fourth, or more, of the synaptic pathways transmitted impulses.

Bargeton (5) in 1938, working with the superior cervical ganglion of the cat, found that in striking contrast to the cells of the central nervous system, the sympathetic ganglion cells showed a marked resistance to deprivation of blood. He showed that complete suppression of blood supply resulted in gradual disappearance of activity of the ganglion; within ten or fifteen minutes, there was total disappearance of activity, but a large degree of functional recovery returned after the ganglion had been completely deprived of blood for as long as seventy minutes.

Working with isolated, perfused heads of dogs, Heymans (42) in 1947 found that stimulation of the pre-ganglionic fibers of the superior cervical ganglion induced mydriasis during complete arrest of the circulation of the head up to forty-five minutes.

It is obvious that sympathetic ganglia show a marked resistance to oxygen deprivation.

Asphyxiation and synaptic potentials: Bonnet and Bremer (14), studying synaptic potentials in the frog's spinal cord during reflex activity, found that the potentials were depressed by asphyxiation. This work was confirmed by Brooks and Eccles (21). Van Harreveld (78), working on central synaptic conduction and asphyxia, reported that the cells in the spinal cord showed considerable resistance to asphyxia.

Tendon reflexes.—It was shown by Porter (62) in 1912 that hypoxia may abolish the flexor reflex in spinal cats. In 1932 King *et al.* (47) demonstrated that hypoxia inhibits the knee jerk. Jokl (44) in 1939 studied tendon reflexes at altitude. He reported that reflexes were normal until an altitude of 6,000 feet (1,800 meters) was reached. Beyond this height, they became diminished and remained so up to an approximate altitude of 15,000 feet (4,500 meters) . It seems that this altitude represents a critical level, for above it tendon reflexes become increased, which, according to Jokl, indicates an early disturbance of nervous control. The author also stated that a second critical level exists at about 29,000 feet (8,840 meters) ; at this altitude, loss of consciousness, muscular cramps, paralysis, and death may occur. It is generally believed, however, that the symptoms described by Jokl frequently occur at 25,000 feet (7,620 meters) or less in unacclimatized individuals.

Van Harreveld and his colleagues have published a number of studies on the effect of asphyxiation of the spinal cord. In 1939 Van Harreveld and Marmont (82) produced asphyxiation in the spinal cords of cats by raising the dural pressure above the arterial. After fifty-five minutes of asphyxiation, the tendon reflexes returned for forty-eight hours and then disappeared.

In subsequent papers (76, 78), Van Harreveld concluded that to abolish all reflex activity in spinal cats an average of three minutes and twenty-two seconds of asphyxia is needed. In later papers (79, 80),

he reported that reflex activity is increased at the beginning of asphyxia of the cord and that a flexion reflex persists longer than the knee jerk. Van Harreveld and Tyler (83) studied the metabolism of spinal cord tissue after asphyxiation and found that the metabolic changes paralleled the temporary return of reflex function.

The chronaxie.—Not many physiologists would concede that the chronaxie is a true measure of excitability of tissues. The term is becoming obsolete. The consensus now is that only the determination of the strength-duration curve gives an accurate measurement of the excitability of tissues. Be that as it may, the term "chronaxie" is still found in the literature.

A number of studies have been made on the effect of hemic hypoxia on the excitability of the different areas of the cerebral cortex.

Rizzolo (65) in 1927 ligated both carotid and both vertebral arteries in a series of dogs and determined the effect of stagnant hypoxia so produced on the chronaxie of the cortex of the brain. He subjected another group of animals to repeated hemorrhages (hemic hypoxia) and made similar studies. He concluded that in neither group was there any modification of the chronaxie. This was true even in animals which had suffered a pronounced hemorrhage (withdrawal of 200-300 cc. of blood from dogs, weighing 6-12 kg.) . Occasionally (in two cases out of ten), however, he observed a definite prolongation of the chronaxie following a small hemorrhage (50-100 cc.) in a medium-sized dog. Richard (64), a few years later, using virtually the same technique, confirmed Rizzolo's work.

In 1936 the Chauchards (24) repeated the work of Rizzolo and that of Richard and reached the same conclusion, namely, that there was no change in the chronaxie of the cerebral cortex following ligation of both carotid and both vertebral vessels. These authors stressed the fact that, even after ligation of these four vessels, the cerebral hemispheres still received considerable blood; they felt that this explained absence of change in the chronaxie. They pointed out that local anemia of the cortex produced by compression of the brain caused a prolongation of the chronaxie; if the pressure was reduced, however, and it had not been acting too long, the chronaxie returned to normal. They emphasized that complete interruption of the circulation always produced a decreased excitability of the cerebral cortex. If the circulation had been interrupted for only one and a half minutes, the chronaxie quickly returned to normal; but after two and a half minutes of complete ischemia of the cortex, the alteration of the chronaxie persisted.

Apparently all workers agree that the blood supply to the cortex

may be diminished considerably before there is any change in the excitability of tissues as measured by the chronaxie. One can only speculate about the relationship between the excitability of the cortex and the normal physiologic processes which occur in the cells of the cerebrum. It would be expected, however, that there is some definite relationship.

In this connection, the interesting work of Lennox and the Gibbses (54) may be mentioned. These investigators found that unconsciousness supervenes in man if the oxygen supply to the brain is suddenly reduced so that the oxygen saturation of the blood in the internal jugular vein falls to 24 per cent or less. The subject does remain conscious, however, as long as the oxygen saturation does not fall below 30 per cent.

Studies have also been made on the effect of anoxic hypoxia on the cortical chronaxie. The Chauchards (26) in 1940, using guinea pigs, observed that a simulated altitude between about 16,400 feet (5,000 meters) and 19,700 feet (6,000 meters) produced an increase of 80 per cent in the cortical chronaxie.

Beyne *et al.* (12) in 1948 studied the cortical chronaxie in man. At a simulated altitude of over 19,700 feet (6,000 meters), a shortening of the chronaxie was noted. They also made observations on guinea pigs; using simulated altitudes from about 13,000 feet (about 4,000 meters) to 16,500 feet (5,000 meters), an increase in the chronaxie was observed. Their results with the guinea pig agreed with those reported by the Chauchards.

Boeles (13) in 1954 reported observations on the chronaxie of the first motor neuron and the motor units in pentobarbitalized cats. The excitability of the sciatic nerve and the gastrocnemius muscle showed no changes until the duration of cardiac arrest had exceeded fifteen minutes, after which reanimation was no longer possible. The excitation time of the motor area of the cortex decreased one to three minutes after the onset of hypoxia, after which it increased; within fifteen to twenty seconds, the motor area became inexcitable. When respiratory arrest persisted for more than five minutes, the inexcitability was irreversible.

Several workers (25, 72, 85) have made studies on the chronaxie of the nerve fiber. The Chauchards (25), working with guinea pigs, found a diminution in the chronaxie at a simulated altitude of about 15,000 feet (4,500 meters). The chronaxie of the extensors of the hindleg decreased much less than those of the flexors.

Asphyxiation and reciprocal innervation.—It was shown in 1939 by Van Harreveld and Marmont (82), working with cats whose

spinal cords had been asphyxiated for various periods of time, that after recovery the hind legs showed an exaggerated extensor tone; this usually lasted until death (about three weeks later). The conclusion was that the high extensor tone was caused by a selective damage to the inhibiting system which normally keeps the tone in check.

Van Harreveld (77, 76) studied the problem further and found that asphyxiation was capable of abolishing reciprocal innervation. He felt that this strongly supported the assumption that asphyxia damages the inhibitory neurones more severely than the excitatory ones.

As far as the authors are aware, no studies have been reported of the effect of anoxic hypoxia on reciprocal innervation.

Conditioned reflexes.—A paucity of experiments have been reported in the literature of the effect of hypoxia on conditioned reflexes.

Andreyev (2) in 1935 ligated both common carotids and both vertebral arteries in dogs and studied the changes in higher nervous activity by the method of conditioned reflexes. He observed that during the first ten to twelve days following the operation the temporary disturbances were most marked and were manifested in the complete disappearance of the conditioned reflexes. Later these were often restored. The more delicate functions of the cortex, however, as represented by the formation of long-delayed conditioned reflexes, were eliminated either permanently or for a long time.

In evaluating the effects of anemic hypoxia on conditioned reflexes, it will be remembered that, while anemia produces its effects primarily by hypoxia, it produces other changes as well.

Gantt *et al.* (33) in 1949 studied the effects of hypoxia on conditioned reflexes of two dogs, one aged eleven years and the other four years. They were exposed four hours (five or six times) to 18,000 feet (5,500 meters) and 25,000 feet (7,600 meters), by either reducing oxygen pressure or lowering the oxygen content. The responses measured were based on food or on pain. Both animals showed a marked impairment at a simulated altitude of 25,000 feet, but no change occurred at 18,000 feet in the younger dog.

The authors felt that conditional-reflex measurements can be useful in evaluating efficacy of therapy for altitude tolerance. They pointed out that conditional-reflex impairment appears when there is no other observable change.

Brain potentials.—Observations made on animals: The influence of hypoxia and asphyxia on potentials of specific brain regions has been studied in animals by a number of workers (4, 7, 9, 16, 17, 23, 30, 35, 63, 67, 71) . All investigators generally agree that effective degrees of hypoxia either diminish or eliminate brain potentials. Hypoxia often produces some initial stimulation of brain potentials, but this is quickly followed by a depression.

Prawdicz-Neminski (63) in 1925 studied brain waves from the motor and visual cortices of curarized dogs and followed them after artificial respiration was suspended. No change during the dyspneic phase of asphyxia was observed, but the potentials increased through the convulsive phase and finally disappeared, although the heart was still beating. Bartley and Bishop (7) in 1933 reported that the potentials disappeared three to five minutes after ligating a superficial artery, which supplied the area of the cortex under observation. Simpson and Derbyshire (67) reported that bilateral carotid occlusion abolished potentials from the cat's motor cortex in twenty seconds. Gate and Horsten (23) in 1951, however, reported that total disappearance of the electrical activity of the brain was seen only after occlusion of all the arterial blood supply (common carotid, vertebral, and anterior spinal artery).

Sugar and Gerard (71) in 1938, studying brain potentials in cats in which an abrupt and functionally complete anemia of the brain had been produced, reported noticeable differences in the "survival time" (duration of occlusion necessary to abolish electrical activity) and the "recovery time" (interval between restoration of circulation and return of potentials) in various parts of the brain. For example, they found that following complete anemia it took fourteen to fifteen seconds for the disappearance of potentials in the cerebral cortex, whereas it took from thirty to forty seconds to make them disappear from the region of the medulla.

Van Harreveld (81) in 1947, using cats, described the EEC after ten to thirty minutes of asphyxia. After the shorter period of asphyxiation, the EEG was characterized by short (one to two seconds duration) bursts of activity with a wave frequency of 7-12 per second, repeated ten to twenty times per minute. After longer asphyxiation, the EEG was characterized by spindles of activity of longer (ten to twenty seconds) duration with a wave frequency of 12-16 per second, which were repeated with intervals varying from a few seconds to about one minute.

Gellhorn and Kessler (35) in 1942 showed that in cats and rats the effect of hypoxia on brain potentials is greatly aggravated during hypoglycemia. This action on brain potentials can be offset by the inhalation of pure oxygen.

Kessler and Gellhorn and their associate (46) a year later studied

the effect of hypoxia on the EEG of unanesthetized rats during rapid ascent. When a level of 190 mm. Hg was reached, a period of temporary silence of the cortex ensued. During the period of recovery, the appearance of large spindles of a frequency of 8-10 per second occurred. If the ascent was not rapid, the period of temporary silence was not always manifested, although the spindles might be found. The authors observed that the occurrence of spindles was confined mostly to barometric pressures varying between 280 and 160 mm. Hg. When the pressure was lowered to 110-140 mm. Hg, a period of electrical silence occurred; the animals did not recover.

It is of interest that thyroid preparations lower the threshold during hypoxia. Kessler and Gellhorn (45) found no significant changes in the EEG in normal rats exposed to 7 per cent oxygen. When a thyroid preparation (thyroid powder or thyroxin) was administered, profound changes in the EEG occurred.

Lubin and Price (58) reported that the minimal amount of acid (hydrochloric) or alkali (sodium carbonate) injected intravenously necessary to produce changes in the respiratory rate in anesthetized cats had no effect on the cortical potentials. Although in most cases intravenous injection of acid causes dilatation of the pial vessels, and and intravenous injection of alkali causes constriction, these changes are not obviously related to the alterations of cortical potentials.

Observations made on human beings: It has been shown by several workers that breathing mixtures low in oxygen can abolish brain potentials in man.

In 1934 Berger (11), working with human beings, reported that the electroencephalogram became more irregular and that larger waves were seen after about seven minutes of rebreathing from a closed bag with carbon dioxide absorbed.

Gibbs and Davis (38) in 1935 obtained electroencephalograms from subjects who became unconscious after breathing pure nitrogen. It had been previously established in resting subjects that frequencies from 10 to 20 per second normally occurred and attained a maximum of 60 microvolts. Breathing pure nitrogen caused the frequency of the predominant waves to decrease to between 1 and 5 per second but caused the amplitude to increase to about 100 microvolts. These changes occurred gradually and began before the subject lost consciousness. It was also observed that overventilation of the lungs up to the point of clouding of consciousness produced similar alterations in the electroencephalogram. When the subject was allowed to breathe room air after he had breathed pure nitrogen, a decrease in

all electrical activity was noted, followed by a gradual return of the normal waves.

Davis *et al.* (29) in 1938 allowed human beings to breathe gas mixtures containing 7.8-11.4 per cent oxygen while simultaneous electroencephalograms were recorded. The average voltage increased slightly; but later it decreased, and shorter trains of alpha waves occurred. Irregular delta waves appeared at the time cyanosis was first noticed; and just before consciousness was lost, large delta waves dominated the record. These delta waves disappeared with the first breath of room air, and the normal pattern was restored in about two minutes.

Hoaglund (43) in 1938 reported that a fall in oxygen tension decreased the alpha frequency. In the same year Lennox *et al.* (56) concluded from their work that hypoxia causes a significant slowing of frequency of waves of cortical activity only when the hypoxia is so extreme that unconsciousness impends. The following year Davis and Davis (28) described the effects on patients who breathed 8 per cent oxygen until consciousness was lost. With the increase of the hypoxia, the delta waves replaced the alpha waves.

Brazier (15) in 1948, studying changes in the wave frequency of the EEG in human subjects under conditions of progressive hypoxia, reported that there occurred a progressive slowing of the alpha rhythm. More recently Luft and Noell (59) studied the cerebral manifestations of hypoxia during and after exposure to a barometric pressure of 68-70 mm. Hg, approximately 54,000 feet (16,600 meters) . During what they termed a period of "failing posture," the electroencephalogram deteriorated progressively until finally there occurred an absence of brain activity.

It is apparent that the electrical activity of the cerebral cortex of man is relatively resistant to the effects of hypoxia, as witnessed by the fact that most investigators have had to use severe degrees of hypoxia before significant changes in electrical activity occurred. This is also apparently true in animals.

Carbon dioxide and brain potentials.—It has been shown by Lennox *et al.* (55) that carbon dioxide accumulation increases fast waves, and it is thought that it may, in part, contribute to the augmented high-frequency potentials seen early in hypoxia. If there is sufficient excess of carbon dioxide, however, the brain potentials may be abolished, as they are during severe hypoxia. Pollock (61) in 1949, working with cats, found that high concentrations of carbon dioxide (15 per cent carbon dioxide and 85 per cent oxygen) in-

crease the frequency, but lower the amplitude, of the cat's normal EEG. Higher concentrations (30 per cent carbon dioxide and 70 per cent oxygen) decrease the frequency and may cause reversible irregularities to appear. In evaluating the effect of carbon dioxide on brain potentials, it must be remembered that carbon dioxide at a concentration of about 15 per cent has an anesthetic action.

Spreading cortical depression (SD) of Leao.—Leao (49, 50) described a decrease in the amplitude of cortical activity as a consequence of stimulation (electrical, chemical, mechanical, or thermal). A characteristic of this depression is its slow spread at a rate of only 1 to 3 mm. per minute. It was suggested by Leao and Morison (52) that it did not require neuronal pathways for its propagation, but that it was propagated along the blood vessels. Sloan and Jasper (69), however, concluded from their work that the disturbance must spread along the neurons by contiguity.

Leao (51) reported that acute anemia (produced by arterial occlusion) is followed by SD in 2.5—5 minutes. It is believed by Marshall (60) that hypoxia, whether produced by severe blood-pressure depression or by breathing air low in oxygen content, may trigger the reaction. He believes, further, that during asphyxia, hypoxia, or rebreathing the swelling of the brain and the marked changes in thoracic pressure may bring about a spreading cortical depression by mechanical stimulation and also increase the sensitivity of the brain to initiation of SD.

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EFFECT OF HYPOXIA ON SENSE ORGANS

THE EYE

McFarland, Evans, and Halperin (48) in 1941; Weaver (74) in 1943; and Gellhorn and Mailman (24) also in 1943 have reviewed the literature concerning the effect of hypoxia on vision. Of the three reviews, that of McFarland *et al.* is the most extensive.

McFarland *et al.* (48) have pointed out that the retina is closely related to the brain, embryologically, morphologically, and physiologically. Furthermore, Krause (37) has shown that because the retina is anatomically a part of the brain, it has a similar metabolism. Since nervous tissue, as previously mentioned, is particularly sensitive to oxygen want, it would follow that certain functions involving the retina would be similarly affected.

Balloonists first called attention to the fact that accomodation was affected at high altitudes and further reported that they experienced difficulty in reading the mercury column, although distant vision was unaltered.

Wilmer and Berens (76), making quantitative studies of vision as early as 1918, found that judgment of distance, range of visual fields, accomodation, convergence, and retinal sensitivity were impaired at an oxygen pressure corresponding to an altitude of 20,000 feet (6,095 meters) . Slight differences at 15,000 feet (4,570 meters) were noted, but none at 10,000 feet (3,050 meters) . Goldman and Schubert (29) and Sauer (59) obtained similar results. Barcroft (4) relates that several members of his South American party experienced visual disturbances at Cerro de Pasco, altitude of 14,200 feet (4,325 meters) .

Discrimination of light intensity.—Many observers have noticed an increase in the threshold for brightness produced by hypoxia. Bert (6) called attention to this many years ago, and reports of balloonists also emphasized it.

It has been shown by a number of workers (9, 18, 46, 47, 73) that during hypoxia the threshold for light is raised both for light-adapted and dark-adapted eyes. It was demonstrated by McFarland and Evans (47) that there is a diminution in sensitivity to light at a

simulated altitude of only 7,400 feet (2,255 meters). By determining the absolute light threshold during hypoxia, these workers found that at a simulated altitude of 15,000 feet (4,570 meters) a light intensity 2.5 times greater than normal was required in order for it to be seen.

It has also been shown that the threshold for discrimination of light intensities increases during hypoxia (23, 62, 63) . Gellhorn and Spiesman (26) in 1935, using oxygen mixtures from 11 to 9 per cent, corresponding to altitudes from 17,000 feet (5,182 meters) to 22,000 feet (6,705 meters), observed a decrease in visual intensity and discrimination. Schubert (62, 63) in the same year also reported a considerable increase in the threshold for brightness in experiments performed in a low-pressure chamber at simulated altitudes above 21,000 feet (6,400 meters).

Visual acuity is also lessened by hypoxia (5) . McFarland and Halperin (50) have emphasized the importance of light intensity when studying visual acuity. At low-light intensities, visual acuity is greatly decreased during hypoxia; whereas, at high intensities, the effect is slight.

In what Monge (53) termed "subacute mountain sickness," he found a diminution of visual acuity and a cloudiness of vision.

Peripheral field of vision.—Wilmer and Berens (76) in 1918 found a contraction of the peripheral field of vision at about 15,000 feet (4,500 meters) ; more severe degrees of hypoxia intensified the contraction. Goldman and Schubert (29) in 1933 made similar investigations, using both a low-pressure chamber and low-oxygen mixtures. They also found a shrinkage of peripheral vision noticeable at about 14,000 feet (4,200 meters). Four years later, Furuya (22), working with a low-pressure chamber, obtained somewhat similar results. He noted that changes began at about 16,400 feet (5,000 meters) . Kyrieleis (38), on the other hand, could not find any contraction in the peripheral field of vision at simulated altitudes as high as 26,000 feet (7,925 meters). He felt that the results obtained by some of the other workers could be explained as due to weakness of attention of their subjects, and he also criticized their methods.

Halstead (30) in 1945, subjected twenty males to a simulated altitude of 10,000 feet (3,050 meters) for five or six hours daily, six days a week for a period of from four to six weeks. About the fourth week of exposure, thirteen of the twenty subjects developed a marked and progressive impairment of peripheral vision; in some subjects, central vision was also affected. In several instances, days or weeks elapsed before return to previous levels of visual efficiency.

Four additional subjects were exposed to altitudes ranging from 15,500 feet (4,720 meters) to 18,000 feet (5,485 meters). The impairment of peripheral vision appeared earlier and was more marked.

In summary, it may be said that although there is still some controversy concerning the effect of hypoxia on the peripheral field of vision, there is fairly substantial evidence that hypoxia constricts the peripheral field.

Central field of vision.—In 1938 Evans and McFarland (17) reported that central visual acuity remained unaffected even at the peak of oxygen deprivation and that except for a region from 6 to 8 degrees about the macula, the angioscotoma widened with progressive oxygen want until it obliterated the visual field. It is of interest in this connection that Cusick *et al.* (13) in 1940 showed that at an altitude of 18,000 feet (5,485 meters) to 21,000 feet (6,400 meters) the retinal vessels dilate. (See p. 338.)

Since ephedrine sulphate is often given in conditions associated with angioscotoma brought about by venous stasis, Evans and McFarland suggested that similar medication might be of benefit to individuals who suffer from visual disturbances produced by hypoxia. It is believed, however, that the changes in the size of the vessels are not alone responsible for the angioscotoma but that hypoxia also affects the functions of the ganglia of the retina.

It has also been observed that hypoxia produces a widening of the blind spot (29).

Afterimages.—Gellhorn and Spiesman (27) in 1935, using a Douglas bag, found a lengthening of the latent period of negative afterimages following inhalation of oxygen mixtures from 11 to 9 per cent, corresponding to altitudes of about 17,000 feet (5,180 meters) to 22,000 feet (6,705 meters). It was found that the effect lasted as long as twelve minutes after readmission of air.

Two years later McFarland (42), in airplane ascents, found a lengthening of the appearance and disappearance of afterimages of 43 and 46 per cent, respectively after one flight. Using a low-pressure chamber, McFarland and his co-workers (48) found a lengthening of the latent time of the afterimage; in general, a more severe degree of hypoxia produced a greater lengthening. Simulated altitudes of 11,500 feet (3,405 meters), 14,000 feet (4,270 meters), and 17,000 feet (5,180 meters) were used.

In 1943 McFarland and his collaborators (51), using a low-pressure chamber, measured the latency of the "tertiary" visual afterimage and found that hypoxia prolonged it. They noted that this effect was consistent with the apparent dimming of the visual field at altitude.

It was noted, furthermore, that inhalation of oxygen produced only a slow recovery of this function.

Experiments on acclimatized subjects.—Working with acclimatized subjects during the International High Altitude Expedition to the Chilean Andes, McFarland (43) reported a lengthening of the latent period of the afterimage, which was statistically significant at 20,100 feet (6,100 meters) . He also observed a tendency for the afterimages to persist longer.

Site of action of hypoxia on visual system.—Gellhorn and Hailman (24) point out that the retina is composed of a complex set of ganglion cells whose metabolism is probably similar to that of other parts of the central nervous system. The fact that hypoglycemia and hypoxia act synergistically on the visual threshold of the dark-adapted eye (49) bears this out.

The above authors have suggested that hypoxia could act on the visual system in one or more of three ways by affecting: *(a)* photochemical processes in the retina; (&) retinal synapses; and (c) the geniculate-striate system. They point out that the rapid recovery of light sensitivity of the dark-adapted eye following readmission of air indicates that the effect of oxygen deprivation on visual function is extraphotochemical (10, 47) . Further proof that hypoxia acts on the retinal neurons and not on the photochemical system has been demonstrated by Craik (12). He rendered the eye temporarily blind by local pressure, but when the pressure was removed, afterimages were formed. Seitz and his co-worker (65, 66) have shown that if strychnine is applied locally to one eye during hypoxia, the treated eye regains a normal critical fusion frequency (CFF) and a normal angioscotoma. This shows that the retinal synapses may be more sensitive to hypoxia than are those located in the geniculate-striate system.

Although the retinal synapses are presumably more sensitive to hypoxia, it must be remembered that the final sensation and perception is greatly influenced by the reactivity of cortical neurons. Gellhorn and Hailman state that hypoxia impairs visual processes through interference with the transmission of nervous impulses from the retina to the brain, but hypoxia also causes alteration in cortical functions.

Size of retinal vessels.—Cusick *et al.* (13), in 1940 reported studies of the effect of hypoxia on the size of retinal vessels. They found that at simulated altitudes from 16,000 to 19,000 feet (about 5,500 to 6,400 meters) the diameter of retinal vessels increased 10-20 per cent, the veins dilating more than the arteries. In 1947 Duquet *et al.* (16) subjected fourteen men between the ages of eighteen and thirty-eight

to hypoxia, using a decompression chamber. They found enlargement of the retinal vessels at altitudes as low as 13,100 feet (4,000 meters) ; the dilatation reached its maximum at 19,700 feet (6,000 meters) . Their results were in agreement with those of Cusick and his co-workers.

Hickman and Frayser (33) in 1959 reported that when the arterial blood oxygen is reduced by breathing low-oxygen mixtures (10 per cent in nitrogen for approximately five minutes), the retinal venous blood oxygen falls, but less than the arterial oxygen, so that there was a decrease in the retinal arteriovenous oxygen difference. This was presumably associated with an increased retinal blood flow, since (by photographic means) the vessels were seen to dilate.

It is of interest that Dammert (14) observed that subjects suffering from high-altitude disease showed a considerable dilatation of the capillaries of the retina.

Intraocular tension.—As early as 1918, Wilmer and Berens (76) stated that there was no correlation between the intraocular tension and various cardiovascular changes produced by high altitudes. Furuya (20) in 1936, however, reported that intraocular tension always increases at high altitudes above about 13,000 to 16,000 feet (4,000 to 4,900 meters) . He made his measurements on six subjects in a low-pressure chamber. Similar findings were reported two years later by Buscalossi (11), who also used a low-pressure chamber. He measured ocular tension with Schiotz's tonometer. On the other hand, Pinson (54) in 1940 reported that anesthetized rabbits subjected to a simulated altitude of 40,000 feet (12,200 meters) showed no appreciable alterations in intraocular pressure. The question arises whether the anesthetic agent influenced his results.

If hypoxia actually causes a rise in intraocular tension, it is of considerable clinical significance, since it might be hazardous for individuals suffering from glaucoma to subject themselves to high altitudes.

Color vision.—Wilmer and Berens (76) in 1918 could not find any changes in color sensitivity at simulated altitudes of 20,000 feet feet (6,095 meters) or more. On the other hand, Vishnevskiy and Tsyrlin (72) in 1935 found that retinal sensitivity to red, green, and blue light was somewhat decreased at altitude. They concluded that cone vision was affected to a greater extent than rod vision. McDonald and Adler (41), however, in 1939 found that rod vision and cone vision are equally affected by oxygen deprivation.

Velhagen (71) in 1935, using the anomaloscope, reported that many people who have normal color vision at sea level suffer a dis-

turbance in this function at altitude. He stated, also, that slight anomalies in color vision became accentuated under conditions of oxygen deprivation and, further, that one form of congenital anomaly may be converted into another. These changes he reported took place at about 10,000 feet (3,000 meters).

Schmidt (60) a year later, also using the anomaloscope, came to a somewhat different conclusion. He felt that if there were no color blindness at sea level, there would be none at altitude. He also believed that there was no conversion of color blindness from one form to another at altitude. He felt, however, as did Velhagen, that if color blindness were present at sea level, it would be increased by oxygen want and that this probably occurred at about 10,000 feet.

Mechanism of pupillary dilatation during hypoxia.—In 1945 Gellhorn and Levin (25) studied the size of the pupils of normal and adrenalectomized cats which had been subjected to hypoxia; later, asphyxia was also produced by clamping the trachea. Pupillary size was determined on normal, sympathectomized, and completely denervated pupils. They reported that no evidence was found that adrenalin or sympathetic excitation plays a part in the dilatation of the pupil seen either in hypoxia or asphyxia. It was suggested that the dilatation had both a neural and a non-neural component. The former is probably associated with a diminution of the tone of the third nerve center; the latter, with the formation of acid metabolites.

Hodes (35), on the other hand, felt that pupillary dilatation occurred only when the animal was moribund and the dilatation was caused by direct effects of hypoxia on the iris and not by neural factors. Hoorens (36) in 1948 emphasized that hemic hypoxia, anoxic hypoxia, and asphyxia all produced a marked mydriasis. He felt their action was due in part to a central neurogenic mechanism and in part to a purely peripheral one.

Flicker fusion frequency (FFF) .—The frequency at which an interrupted or flickering light is perceived as a steady light is known as the fusion frequency of flickering light (FFF). It may be determined by measuring the number of light and dark intervals, or cycles, per second at which fusion occurs. A number of workers have studied the effect of hypoxia on this phenomenon.

Seitz (64) in 1940 reported that hypoxia produced by breathing gas mixtures low in oxygen caused a considerable decrease in FFF. Lilienthal and Fugitt (39) studied the effects of small amounts of COHb (hemic hypoxia) on men already under conditions of anoxic hypoxia. Increments in COHb of the order of 5-10 per cent resulted in appreciable deterioriation of FFF at altitudes of 5,000 feet (1,525

meters) and 6,000 feet (1,830 meters), which alone do not affect this phenomenon. These authors stated that FFF is usually impaired at altitudes of from 9,000 feet (2,745 meters) to 12,000 feet (3,660 meters).

Simonson and Winchell (67) found that when men breathed 14 per cent oxygen, corresponding to an approximate altitude of 10,000 feet (3,050 meters), a significant decrease of FFF developed within twelve minutes in thirteen subjects. In 1954 Rokseth and Lorentzen (57) carried out experiments on twenty-five healthy human subjects ranging in age from twenty to twenty-five years. They were subjected to a simulated altitude of 10,000 feet (3,050 meters) but were also given alcohol (doses of 0.5-0.7 g/kg body weight) . In most subjects the combination of alcohol and hypoxia caused a greater decrease in FFF than did hypoxia alone. The effect appeared to be a simple additive one.

Adler and Ivy and their associates (1) in 1950 found a gradual deterioration of FFF following repeated exposure to altitude. The subjects reported an increasing "feeling of tiredness." It was felt that FFF might be used as a criterion of central nervous fatigue.

Fatigue of accommodation and of convergence.—Several workers have shown that hypoxia may cause fatigue of accommodation and of convergence. Wilmer and Berens (76), working with rebreather tests, called attention to this phenomenon in 1918; they found increased fatigability at 15,000 feet (4,500 meters). McFarland (43) in 1937 also found a significant increase in fatigue at about the same altitude in the Chilean Andes as reported by Wilmer and Berens. In the same year, Furuya (21) reported a decrease in range of accommodation which began about 16,400 feet (5,000 meters) . Giardini (28) in 1949, working with eight subjects, found that a simulated altitude of about 13,000 feet (3,900 meters) produced a significant fatigue of accommodation.

Extraocular muscles.—Considerable work has been reported on the effect of hypoxia on the phorias. The literature in this field has been reviewed by McFarland *et al.* (48). In this monograph only the effect of hypoxia on orthophoric subjects will be considered.

McFarland *et al.* (43) found that the test for 40 cm. vision revealed an increase of the average deviation from orthophoria at 20,000 feet (6,000 meters), which was usually in the direction of an insufficiency of convergence. This actually was measurable at 9,200 feet (2,800 meters). He observed similar changes in a low-oxygen chamber (45) .

Wilmer and Berens (76) reported a decrease in adduction, abduction, and sursumvergence (upward movement) at 20,000 feet (6,000

meters). They measured the field of binocular fixation in a group of men with normal muscle balance and discovered that 7 per cent of these men suffered deterioration during hypoxia. After testing the eyes with a stereoscope, they reported that there was a change in fusion ability in two of six persons.

Co-ordinated ocular movements.—In 1937 McFarland, Knehr, and Berens (52) reported the effect of oxygen deprivation on ocular movements during reading and during fixation. Photographic technics were used in this study. They found that in reading the eyes did not co-ordinate as well at 18,000 feet (5,485 meters) and that it took longer to read a given line. There was also a general tendency toward diminished precision of ocular fixation. Interestingly enough, they observed certain latent defects during periods of hypoxia in a number of subjects, who apparently had normal ocular muscle balance.

Effect of recompression on visual functions.—It is of interest that visual functions may be increased temporarily above the normal level after recompression. For example, Schubert (61) has found that recompression from about 23,000 feet (7,000 meters) to about 16,400 feet (5,000 meters) produced an increased sensitivity to visual discrimination. This probably may be regarded as a supernormal phase, a physiologic phenomenon not infrequently observed in nerve functions.

HEARING

In progressive anoxic hypoxia, the sense of hearing is the last to disappear. Henderson (32) in 1918 and Bagby (3) in 1921, using both the rebreather method for inducing hypoxia and the low-pressure chamber, could detect no change in hearing caused by oxygen want until either all the other, higher cerebral centers were impaired or just before collapse took place. In 1904 Aggazzotti (2), working with a low-pressure chamber, reported, however, a decrease in auditory sensitivity both in human beings and in guinea pigs at a barometric pressure of 420 mm. Hg, corresponding to an approximate altitude of 15,500 feet (4,720 meters) .

Barcroft (4) reported that some of the members of his expedition suffered from auditory disturbances at Cerro de Pasco, situated at an altitude of 14,200 feet (4,300 meters) ; and Richter (56), during a Himalayan expedition, also noticed alteration in hearing. Raffo (55) in 1934, too, observed a decrease in auditory sensitivity in residents of the Andes at an altitude of 13,600 feet (4,150 meters).

Using a Douglas bag for inducing hypoxia, Gellhorn and Spiesman (26) in 1935 reported that, if 10 per cent oxygen or less were inhaled for ten to thirty minutes, there was an increase in the hearing threshold, which often lasted for several hours, depending upon the severity of the hypoxia, the duration of the experiment, and the sensitivity of the subject.

McFarland (42) in 1937 reported that the auditory threshold for eight different frequencies was about twice as high at Morococha, Peru, altitude of 14,900 feet (4,540 meters), as at Lima (approximately at sea level). In a subsequent paper (43) in which he reported studies made during acclimatization, he found that at 17,500 feet (5,300 meters) the threshold for the four highest frequencies was significantly increased.

Studies made on the auditory threshold on native residents in the Chilean Andes (altitudes from 15,000 to 17,000 feet—4570 meters to 5,180 meters) by McFarland (44) showed that the threshold was six to eight decibels higher than for workmen at sea level; the results were statistically significant. The variability of response was also greater in the high-altitude group.

Cochlear potentials.—Weaver *et al.* (75) in 1949 studied the effects of oxygen deprivation upon cochlear potentials in cats. They reported that only severe grades of hypoxia (4 per cent oxygen or less), corresponding to altitudes over 40,000 feet (12,200 meters), caused deleterious effects. As the hypoxia developed, the cochlear potentials underwent a rapid initial loss and then leveled off; with extreme hypoxia, the losses amounted to forty decibels or more.

Bornschein and Krejci (7) in the same year, also using cats, found that hypoxia caused a decrease of cochlear potentials and that in severe grades of hypoxia the changes produced were not always reversible. They concluded that the effect on cochlear potentials was a primary sequel of the hypoxia and not a secondary one following a disturbed circulation.

In 1953 Wing *et al.* (77), working on cochlear microphonics, observed that they were reversibly reduced when arterial oxygen content was decreased to values roughly between the limits of 6-9 volumes per cent. Davis *et al.* (15) in 1955 reported studies on cochlear potentials in guinea pigs following intracochlear injections of certain substances (sodium cyanide and sodium azide) during hypoxia. They concluded that the summating potential was affected by hypoxia and by ionic change. In the same year, Tonndorf and his coworkers (70) studied the combined effect of sound and oxygen deprivation (10—8 per cent oxygen) upon microphonics in guinea pigs. Various combinations of sounds were produced (1,000 c.p.s., 130 db..

1 min) . There was some decrease in the cochlear microphonics, the effect depending upon the degree of oxygen deprivation and on the magnitude of the simultaneous sound. It appears, then, that a rather severe grade of hypoxia must exist before there is a significant change in cochlear potentials.

Vestibular sensations.—Little work has been reported on this phenomenon. Raffo (55) in 1934 found a heightened sensitivity to artificial stimulation of the vestibular apparatus. On the other hand, Ruff and Strughold (58) in 1942 reported that hypoxia caused a decrease in vestibular sensitivity. Gellhorn and Spiesman (26) showed that vestibular reflexes in man, measured by the number of nystagmic movements following caloric stimulation, are altered to a lesser degree than certain other sensory functions, such as hearing and vision. They reported that inhalation of 10 per cent oxygen from seven to fifty minutes caused a decrease in nystagmic responses only in some of their subjects. It would seem that more work is needed on the effect of hypoxia on vestibular sensations.

TACTUAL SENSITIVITY

The effect of altitude on tactual sensitivity was studied by Loewy and Wittkower (40) following an ascent, without physical strain, from an altitude of that of Davos—5,100 feet (1,550 meters) —to one of 8,700 feet (2,650 meters). An increased effect of the dermographic and chemical stimuli was noted. The sensitivity to pressure on the skin was slightly impaired, as was the two-point threshold. The explanation they gave for their findings was that the oxygen want stimulated the vasomotor center, causing a peripheral vasoconstriction. It seems, however, that this work needs confirmation, since it is questionable whether the vasomotor center would be stimulated at 8,700 feet.

Hartmann (31), in acclimatized subjects in the Himalayas, found that below an altitude of 23,000 feet (7,000 meters) skin sensitivity was not impaired. He felt, on the basis of experimental evidence obtained from work done in a low-pressure chamber, that in non-acclimatized subjects the critical changes in skin sensitivity occur at altitudes approximately 5,000 feet (1,525 meters) lower than they would in acclimatized subjects. According to his work, then, changes would not occur in the average person until a height of about 18,000 feet (5,485 meters) was attained. This, indeed seems more likely than the findings reported by Loewy and Wittkower (above). Furthermore, Strughold (69) in 1936 found an increased threshold of sensitivity at a simulated altitude of about 18,000 feet (5,485 meters) in non-acclimatized subjects; this also confirms the findings of Hartmann.

On the other hand, Fleisch and Grandjean (19) in 1944 observed some changes in skin sensitivity at lower levels. Working with eighteen subjects at an altitude on the Jungfraujoch of 11,500 feet (3,450 meters), they found a lowering of the threshold for pressure. This returned to normal in about a week.

TASTE AND SMELL

Little experimental work has been reported on the effect of hypoxia on taste and smell. Quantitative data are difficult to obtain. These two special senses are so closely associated that unless especial precautions are observed when experiments involving either one is performed any results reported must be accepted with hesitation.

Kingston (34), medical officer for the 1924 Mount Everest Expedition, reported that at an altitude of 19,000 feet (5,800 meters) two members of the expedition noticed an impairment of the sense of taste. When they descended to 16,500 feet (5,100 meters), taste was restored. Richter (56), during a Himalayan expedition in 1932, reported alterations in taste at an altitude of 16,500 feet. His findings, therefore, corresponded with those of Kingston.

Fleisch and Grandjean (19) in 1944, working with eighteen subjects on the Jungfraujoch, about 11,500 feet (3,450 meters), found a lowering of the threshold to tastes (bitter, sour, sweet, and salty). At higher altitudes—over 17,000 feet (about 5,000 meters) —the threshold was raised.

No reports in the literature could be found dealing with the effect of hypoxia on the sense of smell. It may be that during the observations of the effect of high altitudes on taste just quoted, smell was also affected by the hypoxia. More, well-controlled work is needed on the effect of hypoxia on both taste and smell.

While such studies might appear to be of academic interest only, it is worthwhile recalling that occasionally patients who have suffered a skull injury lose their sense of smell. This distressing condition may be transient in nature but is sometimes permanent. It is possible that in these latter cases the skull injury may have damaged irreparably the blood vessels supplying the olfactory center, so that the loss of smell is due to a local anemic hypoxia.

PAIN

There is little data on the effect of hypoxia on pain. Stokes *et al.* (68) in 1948 studied the effect of anoxic hypoxia and of

hypercapnia on perception of thermal cutaneous pain in man; fourteen males whose ages ranged from twenty to forty-five years were used. It was observed that breathing 10 per cent oxygen did not affect the pain threshold significantly.

Five per cent carbon dioxide and 7.5 per cent carbon dioxide elevated the threshold of pain; the former, by 13 per cent and the latter, by 28 per cent. It was felt that these effects were due to central action and not to any peripheral effects on the pain end-organs.

In 1961 Bullard and Snyder (8) determined the threshold of pain on two mammalian species, the rat (non-hibernating animal) and the ground squirrel (hibernating animal) . The response to thermal pain in the rat was decreased by breathing 7.5 per cent oxygen and abolished by 5 per cent oxygen. The ground squirrel showed no alteration of response until the oxygen percentage was lowered to 2.5 per cent. It is known, of course, that mammalian species which hibernate withstand more severe hypoxia than do non-hibernating animals.

More work is obviously needed on the effect of hypoxia on pain.

RESUME OF THE EFFECT OF HYPOXIA ON THE SPECIAL SENSES

From the practical point of view of the effect of hypoxia on the special senses, the effect on the eye is doubtless the most important. There is evidence that losses of accommodation and visual acuity occur at relatively low altitudes and, further, aftereffects may follow exposure to severe degrees of hypoxia. Since pilots now use oxygen masks or pressurized cabins when flying above 8,000 feet (2,440 meters) , the effect of hypoxia on the eye is no longer as important as it once was.

Nearly all observers agree that the ear is the most resistant of all to hypoxia, and, for practical purposes, it probably functions until psychomotor collapse occurs. Little work has been reported on vestibular sensations. There is some evidence that hypoxia may cause a slight decrease in sensitivity.

The sense of touch is probably somewhat affected at altitudes beyond 18,000 feet (5,500 meters), but this is of no great practical importance.

There is little data on the effect of hypoxia on pain. One study on man has shown that the perception of thermal cutaneous pain is not significantly altered by breathing 10 per cent oxygen.

Nothing authoritatively can be said about taste and smell. While the effect of hypoxia on these two senses is not especially important for practical purposes, nevertheless, as previously mentioned, a careful study of the effects of hypoxia on them might provide a better understanding in certain disorders of both these senses.

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