Chapter 1

BAROMETRIC PRESSURE AND GAS COMPOSITION[1]

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Normal human vital activity and work capacity under spaceflight conditions are insured by the use of regeneration type pressurized cabins, where an artificial gas atmosphere (AGA) is generated before or during flight, then maintained for the duration of the flight. An AGA environment is vital for humans, animals, and plants during space flight, since AGA protects living organisms against the hostile effects of space, especially against the extremely dangerous effects of low barometric pressure. The artificial atmosphere also serves as a source of oxygen required for respiration.

The use of AGA in spacecraft cabins poses questions that specialists (biologists, physiologists, physicians, and engineers) must answer: What should the AGA be? What physiologic, hygienic, and technical requirements must it satisfy in particular? It is a matter of optimum choice of basic AGA parameters, such as total barometric pressure, its chemical composition: the choice of diluent gases, permissible range of variations in partial pressure of oxygen (P_{O_2}) and of carbon dioxide (P_{CO_2}), temperature, and other parameters.

The solutions of these problems, consequently, of the entire problem of the correct composition of the AGA are possible only if the complex interaction among many physiological and technical factors is taken into account. To summarize, production of a correct AGA is essentially a certain compromise between biomedical and technical approaches to this problem. The former determines the efforts to develop hygienic conditions close to comfortable, which requires consideration of design difficulties, i.e., the need to limit weight and size of the craft, danger of explosion and fire, and probability of various emergency situations arising. Emergencies require that in designing the AGA, it is necessary to examine it and consider possible cabin decompression. Another important design factor is to be sure that (depending on flight mission), astronauts can leave the spacecraft and go into space, or onto the surface of a celestial body around which there is practically no atmosphere (e.g., the Moon), or into extremely rarefied atmosphere (Mars), or very high-density atmosphere (Venus). For such conditions, design of the AGA obviously must take into account structural characteristics (especially pressure level) in space suits, pressurized compartments of transport vehicles, and astronaut's living quarters.

[1] Translation of, Barometricheskoye davleniye, gazovyy sostav, Vol. II, Part 2, Chapter 1, of *Osnovy kosmicheskoy biologii i meditsiny (Foundations of Space Biology and Medicine)*, Academy of Sciences USSR, Moscow, 1973.

Sincere gratitude is expressed with pleasure to Dr. E. M. Roth for his excellent survey of US authors' work: *The Effect on the Organism of an Artificial Gas Environment in Spacecraft and Space Stations*, which was used extensively in preparing this chapter. In effect, Dr. Roth is an ex officio author of this chapter. Considerable indebtedness is also expressed to my colleagues, A. G. Dianov and V. P. Nikolayev, who prepared a survey of papers by Soviet investigators dealing with AGA.

This chapter deals with the biomedical problems in designing an AGA for spacecraft cabins. The main emphasis is on the organism's reactions when barometric pressure falls, and changes in the AGA's chemical composition: decrease and increase in P_{O_2} and P_{CO_2}, total exclusion of nitrogen and inert gases from the AGA, or—use of several inert gases as "diluents" in the AGA instead of nitrogen.

Examination has not been made of such important AGA parameters as temperature, humidity, permissible concentrations of harmful impurities, and the aerosol's composition and electrical charge. These data are presented in other chapters.

BAROMETRIC PRESSURE

Spaceflight experience indicates that the level of barometric pressure in manned spacecraft cabins can vary as a function of their design characteristics within wide limits: from 1–1.2 atm in the Soviet Vostok, Voskhod, and Soyuz spacecraft to 258 mm Hg in US spacecraft Mercury, Gemini, and Apollo.

To estimate barometric pressure, one of the vital parameters characterizing the AGA during normal spacecraft operation and under emergency conditions, it is necessary to bear in mind that this parameter is closely linked to others, especially P_{O_2}. This can be seen in Figure 1, where three zones of P_{O_2} values determine the different levels of O_2 supply to the organism. Zone 1 corresponds to various degrees of hypoxia; Zone 2 is indifferent, where provision of the organism with O_2 remains at a normal or near-normal level; and Zone 3 is the zone of elevated P_{O_2}, which is intolerable due to toxic effects of oxygen, which develop the more rapidly, the higher the P_{O_2}.

The physiologic effects of reduced and elevated partial pressure of oxygen in the AGA will receive special attention in subsequent parts of this chapter. Normal oxygen supply to the organism is possible when the barometric pressure drops only to 190–200 mm Hg. (This is shown in Fig. 1 and Table 7.) Therefore, pressure P of the AGA in the cabin must not fall below these values.

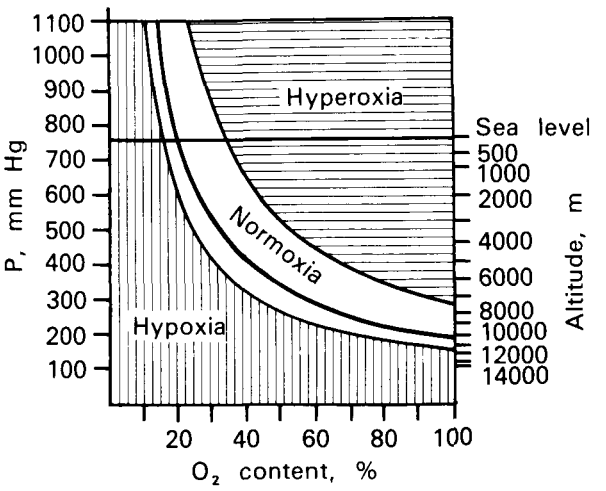

FIGURE 1.—P_{O_2} of the AGA as a function of barometric pressure. Three zones of oxygen supply: hypoxia, normoxia, and hyperoxia.

The oxygen supply is not the sole limiting factor, since when the barometric pressure falls considerably, even when the chemical composition of the AGA ensures normal oxygen supply to the organism, it is necessary to take into account the possibility of onset of dysbarism.

Various phenomena of dysbarism are manifested as functions of physical parameters which characterize the differential in barometric pressure: the absolute value of pressure differential ΔP, determined by the difference between the initial pressure (P_i) and final pressure (P_f)—($\Delta P = P_i - P_f$); the differential factor, which is determined by the ratio between the initial pressure and the final pressure (P_i/P_f), and the time of decompression (t), as well as the decompression rate ($\Delta P/t$).

There are three causes for onset of various dysbarism phenomena:

1. Elevated pressure in body cavities containing gas caused by difficulty in balancing pressures in body cavities with pressure on its surface (various effects of explosive decompression, altitude meteorism, aerootitis, and aerosinusitis).
2. Formation in tissues of gas bubbles formerly in a dissolved state—altitude decompression sickness (ADS).

3. Development in tissues of vaporization phenomena (ebulism, "boiling" of tissues, and altitude tissue emphysema).

There is varying probability of onset of these dysbarism phenomena during space flight. There is little probability of astronauts being exposed to explosive decompression resulting from a sizable defect forming in the cabin wall. However, it will increase as flight time increased. The probability of altitude decompression sickness is much greater.

EXPLOSIVE DECOMPRESSION (ED)

Explosive decompression, which develops from instantaneous depressurization of the cabin, is characterized by rapid and considerable pressure drop in the cabin. There has been no generally accepted definition of the concept of ED so far. Numerous authors [9, 69, 200] have attempted to give quantitative physical criteria for delimiting ED from ordinary dehermetization, which have not been accepted. Accordingly, and considering that onset of overpressure in the lungs is the most significant ED effect, we propose to define as ED all cases of rapid pressure drop in a hermetically sealed cabin during which a substantial overpressure in the lungs can arise of more than 20–30 mm Hg.

There is little probability of onset of ED during flight (it is usually associated with danger from a meteor). However, taking into account that during ED the crew may be subjected to trauma from fragments of the cabin wall, the mechanical action of the stream of gas flowing out from the cabin, and subsequent exposure to extremely low pressure, ED plays a small role in such a tragic situation. Regardless of this, ED must not be ignored when developing and evaluating the AGA, since its harmful effect depends largely on the AGA pressure level, and to a far lesser extent on its gas composition. Cabin volume (V), area of the opening—size of the defect (A), and pressure differential (ΔP) determine time (t_c) and *force* of the ED. Time (t_c) during which the ED occurs in the cabin can be represented at $t_c = V/(A \cdot c)$, where c is the speed of sound (Fig. 2).

The reaction of the organism during ED is a function of its three main parameters:

1. absolute value of the pressure differential ΔP, equal to the difference between the initial pressure P_i and the final pressure P_f in the cabin ($\Delta P = P_i - P_f$);
2. pressure differential—ratio of initial pressure to final pressure: P_i/P_f; and
3. time of decompression — t.

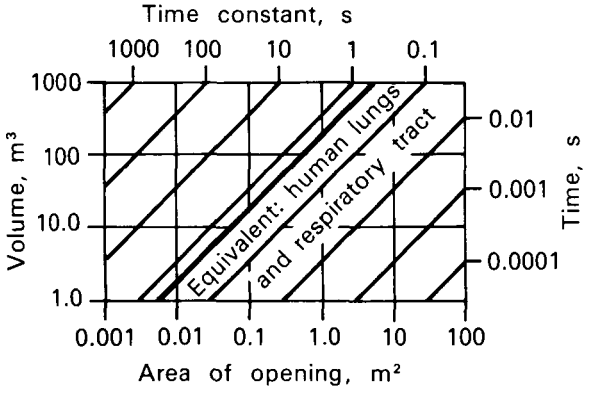

FIGURE 2.—Time characteristics of decompression. (After [126])

During space flight, as a rule, ED will occur under extremely low pressure of the external environment. Thus, evaluation of the harmful effect of ED will place particular emphasis on the P_i of the cabin, also the time of decompression which is a function of cabin volume V and the size of defect A.

A definite role in the reaction of the organism during ED is also played by gas volume in the lungs (V_l), that is, the phase of respiration where the ED action and resistance to airflow along the respiratory tracts coincide. Increases in air volume and in its resistance to flow through the respiratory tracts are factors which aggravate the action of ED.

During explosive decompression, there are rapid increases in the gas volume enclosed in the organs and parts of the body which have cavities filled with gas (lungs, gastrointestinal tract, middle ear, and accessory sinuses of the nose). Since the equilibration of pressure in these cavities, which are connected with the gaseous medium surrounding the organism by passageways of relatively small lumen, is delayed, pressure in them will rise for a certain period.

This leads to distention of tissues which may cause injury–rupture. Animal experiments have indicated that lung damage (development of hemorrhages as a result of distention and rupture of alveoli and vessels) is the most dangerous manifestation of ED [17, 21, 28, 92, 104, 107, 162, 175, 193]. When lungs are subjected to significant trauma, shock and gas embolism of the vessels have been noted, which can lead to death of the experimental animals [104, 107, 128, 162, 192, 193, 196].

To evaluate the harmful effect of ED, it is important to know the overpressure in the lungs (ΔP_l) which can lead to rupture of the alveoli. Since this factor is not known for the lungs of a healthy human, it was decided to use data from animal experiments, but these data are scanty and quite contradictory. Most authors [116, 174, 193, 200], based on the work of Adams and Polak [1], and Benzinger [27], state that at $\Delta P_l = 80$ mm Hg, when there is no protective stress on the stomach and chest muscles (limiting the distention of the lungs), lung injury is quite possible. Several authors give a lower value of 50 mm Hg [67, 170].

Determining the overpressure in the lungs ΔP_l in cases of ED is apparently of exceptional value in evaluating its possible damaging effect on the body. Accordingly, efforts were made to calculate ΔP_l as a function of conditions characterizing ED. In evaluating these studies, it must be kept in mind that when calculating ΔP_l, all authors assumed that the lungs expand uniformly.

To find ΔP_l is relatively simple when ED is acting on an individual with a closed rima glottidis. During passive expansion of the thoracic cavity walls, it can be determined, according to Luft [125], from the following relation:

$$\Delta P_l = \left[\frac{V_i}{V_{max}}(P_i - 47)\right] + 47 - P_f \qquad (1)$$

where V_i is the volume of lungs before ED
V_{max} is the maximum volume of undamaged lungs
P_i is cabin pressure before ED
P_f is final pressure in the environment.

Since the volume of the lungs V_i affects the value of ΔP_l during ED, it was decided to determine ΔP_l for three different V_i: under conditions of total inspiration, when $V_i/V_{max} = 1.0$; at the end of a normal expiration, when $V_i/V_{max} = 0.55$ and with complete expiration, when $V_i/V_{max} = 0.25$ [42]. This expression derived from the Boyle-Mariotte law includes a correction for P_{H_2O} at body temperature.

By using the above equality, it is possible to calculate the overpressure in the lungs during ED for various values of initial pressure (P_i) in the cabin and different volumes of the lungs.

The data in Table 1 show that the level of ΔP_l for astronauts with the rima glottidis closed will exceed the value which is critical for the lungs (80 mm Hg) at all possible levels of initial cabin pressure. Under conditions of ED, when gas escapes from the lungs, the levels of overpressure in the lungs will be less than shown in Table 1. Then the probability of harm to the lungs should be minor while maintaining the cabin pressure at a level of the order of 268–191 mm Hg.

The dynamics of ΔP_l during ED are illustrated in Figure 3 by graphs obtained experimentally by Luft [125]. Violette, in a fundamental monograph [200] dealing with the effect of ED on the living organism, had presented another expression for the calculation of ΔP_l; in contrast with Luft, he attempted to take into account the escape of gas from the lungs. He proposed an equation for the determination of ΔP_l:

$$\Delta P_l = P_c - P_f \cdot ch\ K_c \frac{S}{V}\sqrt{\frac{P_f}{\rho_f}}(t_0 - t) \qquad (2)$$

where P_c is cabin pressure
P_f is final pressure of environment
K_c is experimental equivalent of coefficient of flow compression
S/V is the coefficient of gas escape from the cabin
ρ_f is the final gas density
t is elapsing time.
t_o is time of decompression

This expression, derived in the mathematical treatment of experimental results, does not take into account changes in the lungs during decompression and considers air escape from the lungs as occurring from a rigid vessel with constant cross-sectional opening.

TABLE 1.—*Dependence of* ΔP_l *during ED on Pressure of AGA in Cabin (with closed rima glottidis)*

$\frac{V_i}{V_{max}}$	ΔP_l when $P_i=760$ mm Hg	ΔP_l when $P_i=362$ mm Hg	ΔP_l when $P_i=268$ mm Hg	ΔP_l when $P_i=191$ mm Hg
1.0	760 mm Hg	362 mm Hg	268 mm Hg	191 mm Hg
0.55	439 mm Hg	220 mm Hg	169 mm Hg	121 mm Hg
0.25	225 mm Hg	126 mm Hg	102 mm Hg	83 mm Hg

Thus, the expressions presented in the works of Violette, Luft, and others for calculating ΔP_l reflect one-sided processes occurring in the lungs during ED. This situation comes about from these expressions either not taking note of lung expansion during decompression (Violette), or not taking into account air escape from the lungs (Luft).

In a study by Burger [41], an effort was made to take into account—when calculating ΔP_l—both factors (lung expansion and simultaneous escape of air from the lungs). Based on a series of model experiments and investigations using animals, Burger was able to calculate ΔP_l under certain conditions. The theoretical basis of this work was the general theory of ED developed by Haber and Clement.

Burger elaborated on Haber and Clement's theoretical concepts and proposed a fairly simple expression for calculating maximum overpressure in the lungs during ED:

$$\Delta P_l = \left\{(P_i - 47)\frac{V_i}{V_{\max}} + 47 - P_f\right\}\left[1 - \frac{t_{cc}}{l_c}\right] \quad (3)$$

The structure of this expression denotes that its first term is the expression used by Luft to calculate ΔP_l where ED is with closed rima glottidis without gas escape from the lungs. The second term $(1 - t_{cc}/l_c)$ is the original expression obtained by Burger which determines gas escape from the lungs during ED. The ratio t_{cc}/l_c is a dimensionless factor that takes into account the difference in rates of decompression of the cabin t_{cc} and of the lungs l_c.

The expression proposed by Burger for calculating the maximum value of ΔP_l was derived with the author's assumption that ΔP_l, maximum value, arises at the instant when the cabin pressure is equalized with the ambient pressure. The latter assumption is not always valid, since for small values of P_f, the maximum overpressure in the lungs can arise before the cabin pressure is equalized with the ambient pressure. Further, the formula proposed by Burger has a limited range of application since when $t_{cc}=l_c$, it approaches zero, while actually under these conditions, ΔP_l can reach substantial values, which was indicated by Burger. Comparison of experimental data with calculated data obtained by the authors using the formula presented yielded fairly good agreement.

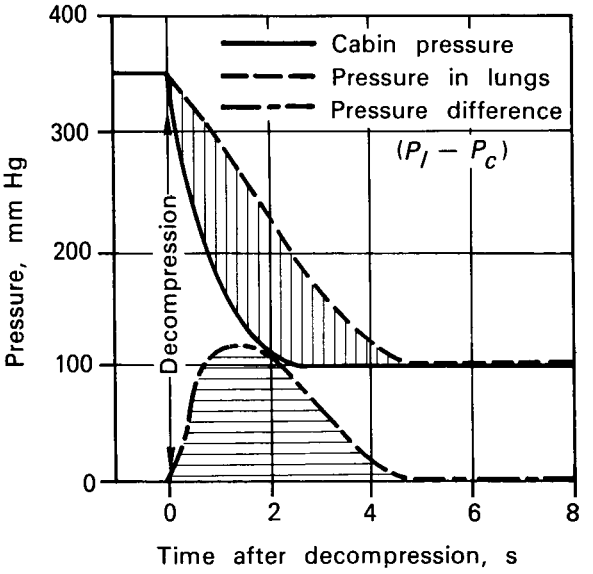

FIGURE 3.—Dynamics of overpressure in lungs during ED. (After [125])

Animal Experiments

The results of experimental investigations on animals permit evaluation, although approximated, of the hazard of ED as a function of its physical parameters.

In experiments with rats, Kolder [108] established that death of 10% of the animals when exposed to ED with ΔP_l of 662 mm Hg and a multiple P_i/P_f of the order of 10, was noted only when the ratio V/A reached 3.3 m^3/m^2. When $V/A = 1.2$ m^3/m^2, 50% of the animals died; when $V/A = 0.12$ m^3/m^2, 100% died. Protecting the lungs from distention by bandaging the trunk significantly protected the animals from the damaging effects of ED [193]. According to data [193, 200], hemorrhages in the lungs were noted only when their volume with regard to the volume in normal inspiration increased by 2.3 to 2.5 times; when the volume of the lungs was increased three times or more, a great number of pulmonary lesions were observed. Studies [128, 162], showed the possibility of reducing damaging action of ED by administering pharmacologic preparations to the animals: atropine and anesthetics. These data indicate the role of reflexive mechanisms in the genesis of grave pathologic states during ED.

Thus, considerable distention of the lungs—which also is probably nonuniform because of the features of regional ventilation—leading to their trauma, determines mainly the damaging action of ED on the organism. The damaging effect of ED when embolism arises can also depend on the gas composition of the AGA. Thus, O_2 embolism (for an AGA composition that includes mainly O_2) must occur, due to the high biological activity of O_2, more readily than embolism with He and N_2 bubbles. According to Gramenitskiy [81], He embolism—because of the more rapid desaturation of this gas—occurs more readily than N_2 embolism.

The composition of the AGA during ED must also affect the curve of the pressure differential in the cabin and the rate of gases escaping from the lungs and, therefore, the overpressure in the lungs ΔP_l. However, this effect evidently is not significant, especially if the pressure in the cabin is held at a level of the order of 0.5 atm or below. Thus, according to Waterspoon, Wibers, and Stand [170], no difference was noted in the damaging action of ED on rats with an AGA where the N_2 in air was replaced with He.

A generalization of results of experiments with animals subjected to ED action at different levels and durations enabled Violette [200] to postulate on dangerous and safe zones of ED action. He established, with a certain degree of approximation, the dangerous and safe zones of actions of ED as a function of the differential factor ($F_p = P_i/P_f$) and the coefficient of leakage $F = A/V$; that is, the ratio between the area of the opening through which gas escapes from the cabin to the volume of the cabin [200] (Fig. 4).

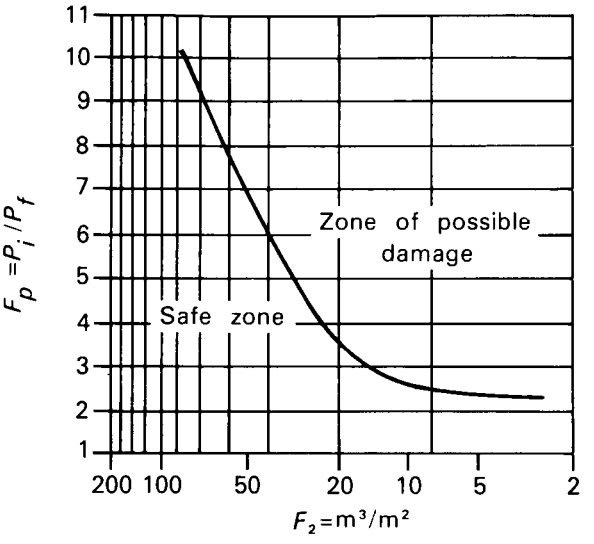

FIGURE 4.—Characteristics of dangerous action of ED. (After [200])

The opinion of Fryer [66] invites agreement—that the curve in Figure 4 divides two zones: the first, which must be considered absolutely safe, and the second, which has been insufficiently studied and a part of which unquestionably poses definite danger. In evaluating the curve in Figure 4, it can be concluded that whenever the ratio is $P_i/P_f < 2.3$, that is, when the volume of the lungs increases by less than 2.3 times, ED will not cause damage to the lungs. The same situation arises at some rate of decompression when the coefficient of leakage A/V does not exceed 1/100 m^2/m^3. The pressure in the lungs will be capable in part of striking a balance with the ambient pressure and will not exceed the critical level. Accordingly, it is extremely important to establish the "law" of gas escape from human lungs during ED.

Stresses During ED

In a significant study by Luft and Bancroft [126], the authors used an esophageal probe with a rheostatic sensor to record the intrapleural pressure in subjects during ED. They showed that the intrapleural pressure in man increases with an increase in both the differential factor P_i/P_f and in the absolute decompression value ΔP. It was established that the time characteristics of the lungs and respiratory tracts in subjects who had been subjected to ED at the end of expiration are equivalent to decompression of the cabin with an A/V ratio equal to 1/200 m^2/m^3. These data are in full agreement with the results of the Hitchcock studies; he found no injury in persons subjected to high-value ED for 1 s. In the studies of Kuznetsov, Zharov et al, no harm was found for ED times of 0.5 s and ΔP values of 300 to 400 mm Hg [92, 116, 214].

Studies with human subjects thus far have shown only isolated cases of lung damage [27, 42], which occurred only when the subjects' rima glottidis was closed at the time of ED.

ED always exerts a definite influence on the general state and work capacity of man, even when there is no damage to the lungs or other tissues. At the moment of ED, the subject feels a blow in the chest region and forceful expulsion of air from the lungs—there is, so to speak, a powerful and deep expiration. It disturbs the normal structure of respiration, quite substantially, when the ED coincides with the inspiration [42, 116]. Those subjects especially who are subjected to instantaneous exposure to ED for the first time cease carrying out their routine work and do not respond to conditioned signals. This period of "confusion" usually lasts 3–5 s, it is much shorter in individuals who have been subjected repeatedly to ED.

ED leads emotional stress, with increased heart rate and corresponding motor reactions. Subjects do not notice temperature drops, but the appearance of a "fog" in the cabin caused by water vapor condensation may cause them to believe (erroneously) that fire has broken out. Accordingly, it has been suggested that spacecrews be familiarized (by showing movies) with the situation that occurs under ED conditions. In anticipated long-term interplanetary flights, when the flight path will pass through regions with a high density of meteoric matter, the readiness of the crew may be questionable for flight in a cabin that has been depressurized because of an ED. This necessitates working out a mode for crewmembers to remain in their space suits. Conditions must also be provided to enable astronauts to begin effective exploitation of individual means of protection before manifestation of severe hypoxic disturbances of the central nervous system (CNS), that is, only 5–8 s after the ED.

INTESTINAL GAS EXPANSION AND OTHER MANIFESTATIONS OF DYSBARISM

ED may have a harmful effect on the gastrointestinal tract, which also contains gas. Studies with humans have shown that during an ED lasting 0.5–1.0 s with ascents to altitudes of 9000–10 000 m or more, just as in slower ascents to these altitudes (30–60 s) similar complaints from subjects are sometimes noted concerning unpleasant or painful sensations in the stomach region. The onset of these sensations is linked to the development of expansion of trapped gases and (indicated by x-rays) is essentially a function of the quantity of intestinal gas as well as its location and conditions of escape from the intestine. Hence, to prevent trapped gas expansion which, as a result of visceral reflex influences, can lead to disruption of cardiovascular system activity (extrasystole, bradycardia, and collapse), astronauts must be supplied with a diet that excludes foodstuffs that form gas in the gastrointestinal tract.

Grave pathologic states resulting from expansion of trapped gas are relatively infrequent. According to data generalized by Berry (cited in [25]), of 4259 cases when abdominal pain developed during ascents to high altitudes, extremely severe (fourth degree) functional disorders were observed in only 12 people. Development of these severe phenomena requires a differential diagnosis, since they can be caused not only by expansion of trapped gas, but also by the altitude decompression sickness. In either

event, assistance to the victim requires, first of all, transferring him as rapidly as possible to a gaseous medium with normal barometric pressure.

ALTITUDE DECOMPRESSION SICKNESS (ADS)

During space flights or while preparing for them, the transition of astronauts to an AGA with low barometric pressure can be the cause of their developing ADS.

ADS results, as a rule, from emergency situations (depressurizing the cabin and the use of space suits at low pressure). In some instances, it can arise from poorly planned conditions for the transitions of astronauts from one spacecraft into another. Such a situation could occur during transition of cosmonauts from an "air" AGA with gas pressure of 760 mm Hg in the cabin of the Soyuz craft to the hypobaric (pressure of 258 mm Hg) oxygen medium of the Apollo spacecraft cabin.

To prevent ADS in the joint Soviet-American space flight, it is planned to lower the barometric pressure in the cabin of the Soyuz craft to 550 mm Hg with a simultaneous rise in the O_2 content in the AGA.

ADS, like caisson disease, develops from gas bubbles in body tissues [83, 91]. The etiologic similarity of these two disorders also accounts for the considerable clinical similarity. Several authors use the term "decompression disturbances" instead of ADS, since they feel that ADS symptoms most often manifested—pain in the joints and muscles—are not caused by development of the sickness, which they link only to onset of relatively stable morphologic changes [80].

Formation and Growth of Bubbles

When the pressure of the gas medium surrounding the organism drops, blood and tissues become supersaturated with gases. Any supersaturated system is metastable, which determines the possibility of gas bubbles forming in it. According to Harvey [86] and others [62, 70, 153], gas bubbles originate from gas nuclei which are constantly being formed in the organism in the course of its vital activity. Gas nuclei arise in the blood at points where blood vessels branch, where there is pronounced turbulence of the blood [70, 86], or in muscle tissue during muscular contraction as a result of local decrease in hydrostatic pressure [51, 70]. During sudden movements in overexpanded portions of muscle tissue or fluid, the hydrostatic pressure becomes negative. The level of the negative pressure peak can periodically reach 100 atm or more [51, 70, 86]. During these brief intervals, the overexpanded portions of the tissue or fluid become supersaturated with gases. A cavity forms in it, into which vapors of the fluid initially try to penetrate due to "local" boiling, after which gas molecules diffuse. After the original pressure is restored the cavity contracts, but the trace of the space is retained in the fluid. The formation of gas nuclei and bubbles that have already formed are retained for long periods on lyophobic surfaces.

From these data, it can be concluded that the existence of gas nuclei is an essential factor in the formation of free gas bubbles in the tissues of the organism under conditions of reduced barometric pressure. It has, in fact, been demonstrated experimentally that conditions which exist for the formation of gas nuclei in the organism are extremely limited. For example, in ground squirrels that are hibernating, after they have been taken to high altitudes, regardless of considerable supersaturation of tissues with the gases dissolved therein, no gas bubbles are formed [70]. Gas bubbles are not formed in living tissues when gas nuclei have been dissolved prior to ascending to high altitudes, for example, as the result of action of extremely high pressure. This has been demonstrated by experiments on shrimps [62].

In experiments with biologic fluids and tissues, Harvey, the US biophysicist, determined that plasma, whole blood, and intact tissues which contain no gas nuclei remain free from gas bubbles even with great pressure differentials (from 1000 to 1 atm) [86]. This is explained by the fact that the formation of a gas bubble, which is free to grow for quite a time, is possible only when its initial size exceeds critical dimensions, that is,

$$R > \frac{2b}{P_b - H} \quad (4)$$

where R is the radius of the bubble (cm),

P_b is the pressure inside a gas bubble, which is the sum of the partial pressure of the gases and water vapor contained in the bubble (dyn/cm^2),

H is the hydrostatic pressure of the fluid, which in a majority of cases is practically equal to the external pressure in (dyn/cm^2),

b is the coefficient of surface tension at the interface between the bubble and the surrounding medium (dyn/cm).

Likewise, a gas bubble with a tendency toward further growth can form only if P_b at the focus of formation is extremely high, which can occur with sudden local supersaturation of the fluid with gases and vapors (freezing, superheating, and electrolysis), considerable extension of the fluid over a small area, that is, a decrease in the value H to negative values (cavitation and local stress). Formation of a gas nucleus with supercritical dimensions can be facilitated also if its surface is formed at points of contact between lyophobic surfaces and the fluid. Then the radius of curvature of the bubble can be large, while it will have a comparatively small volume. For a certain shape of a lyophobic surface, it is easy to imagine the situation (for example, in the formation of a gas nucleus in a conical depression, or in a crack between two lyophobic surfaces) when the capillary forces will not prevent, but will promote, the formation of a gas bubble [70, 152].

Hence, for gas bubbles to form in the organism, it is not sufficient for the tissues to be supersaturated with gases. Certain additional factors are required capable of disrupting the metastable state of the supersaturated solution. In the course of vital activity, especially during active muscular exertion, these additional conditions apparently arise constantly in the human organism. However, they are manifested to different degrees in different individuals and even in the same individual, as a function of many circumstances. This is largely responsible for homogeneity lacking in individual resistance to ADS and its considerable variation in the same individual.

The formation of gas bubbles in the human body is not always accompanied by onset of altitude decompression sickness. In the human and animal organism, following ascent to altitudes, x-ray and ultrasonic methods have frequently made it possible to detect gas bubbles without any manifestation of altitude decompression sickness. With special "traps" inserted into various parts of the circulatory bed of animals, Gramenitskiy [81] succeeded in detecting gas bubbles at altitudes of the order of 4000 m, when ADS does not yet arise. Unfortunately, the factors which determine transition from the latent forms of decompression disorders to the manifestation of altitude decompression sickness still remain insufficiently studied. An investigation of gas bubbles interacting with tissue structures of the organism should promote better understanding of the pathophysiologic mechanisms governing the manifestation of various symptoms of decompression sickness. This will aid in explaining questions about the immediate reason for development of various forms of ADS.

Characteristics of Evolution of Gas Bubbles in the Organism

Gas bubbles which are formed in the organism following decompression exert pressure on the surrounding tissues, which leads to their displacement and deformation, possibly causing painful sensations. When a bubble is in the blood or tissues of the organism, the interaction of bubbles with the tissue surrounding them may be described by:

$$P_b = H + 2b/R + DR \quad (5)$$

where H is the hydrostatic pressure of the tissue (blood), which is the sum of the external pressure (E) and the tissue turgor pressure (T) or the blood pressure (dynes/cm^2)

DR is the deformation pressure, which is produced by the bubble and is a function of its size as well as the volume and elastic properties of the tissue (dynes/cm^2).

Gas bubbles which are formed in the living

organism may be divided conditionally into two specific types:

1. Autochthonous bubbles, the evolution of which is governed solely by the exchange gases with the surrounding tissues through diffusion.
2. Bubbles capable of growth not only due to diffusion but also as the result of merging with each other. Apparently, most of the extravascular, intratissue slightly mobile bubbles should be included in the first group. They probably are important in development of the most frequently encountered osteoarticular form of ADS—the bends. Intravascular mobile bubbles usually must be listed among the second type; their onset determines development of the most serious forms of ADS. The only exception is intravascular bubbles that are "clogged" in the capillaries which must be listed among type–1 bubbles [152].

Evolution of the autochthonous bubbles (type 1) is essentially a function of the exchange rate of gases between the bubbles and their surrounding medium. Evolution of size of type–2 bubbles is governed by the same factors, that is, the value of ΔP in the medium surrounding the bubbles. However, estimation of the maximum sizes and the true growth rate or resorption of the "wandering" bubbles is practically impossible, since the merging of these bubbles or their breakup into individual parts take place in a purely random manner. Movement of bubbles changes distribution of the inert gas reserves in the organism. In those tissues where bubbles have accumulated, the total level of inert gas content rises above the average value; therefore, its washing out from the bubbles is delayed.

Bubbles which have settled in tissues that are slightly perfused by blood should be resorbed particularly slowly. Hence, migration of bubbles, in conjunction with redistribution of inert gas reserves in various parts of the organism, promotes formation of bubbles that are very slowly resorbed in certain tissues. This phenomenon apparently is sometimes associated with inefficient treatment of ADS following recompression to the original pressure and the effectiveness, in such cases, of hyperbaric therapy, as well as the more frequent onset of ADS during repeated ascents.

In conclusion, it should be repeated that the structural characteristics of the living organism and its physiological and biochemical processes are important factors that govern the rate of increase in size of the bubbles and their dimensions and, consequently, manifestation of ADS.

Clinical Aspects of ADS

Data indicate [67, 116] that as long ago as 1906, Schroetter described pains in his joints in a pressure chamber at an altitude of 9000 m, but did not link this phenomenon to the effect of decompression. In 1908, Holden and Boycott, and later Henderson, in 1917, postulated the probability of caisson disease (aeroembolism) affecting persons following ascents in a pressure chamber to high altitudes.

In 1929, Jongbloed [99], in a self-experiment, described the development of ADS in a pressure chamber at altitudes of 10 000–12 000 m, manifested as pains in the region of the talocrural and genual joints. This observation was supported later in 1931 by Barcroft et al, in 1932 by Strel'tsov, and later in many studies [5, 15, 93, 189] with various forms of ADS described. For quite a time, gas bubbles were not detected in tissues during development of ADS, but as the x-ray method became more widespread, and later the ultrasonic method, many investigators observed gas bubbles [9, 67, 174]. Gas bubbles after decompression were also observed in persons who did not suffer from ADS [8, 97].

The impression created among aviation physicians and physiologists at present is that the clinical course of ADS and its severity are governed to a significant extent by the amount and size of gas bubbles in the organism, location, and rate of their growth and resorption [42, 67, 154].

The location of gas bubbles in the vascular bed and in tissues varies considerably, which governs the diversity of clinical symptoms of ADS. Many years' experience of ascents with healthy persons in pressure chambers at altitudes of 6000–12 000 m, as well as onset of ADS on flights at various altitudes (5500–11 000 m), indicate that

the osteoarticular (bends) form of decompression sickness is substantially more frequent (in more than 90% of the cases) than its other forms [93, 94]. More rarely, decompression sickness is manifested as skin damage, the symptoms of which include pruritus, sometimes a urticaria-type rash, edema, and change of color in the affected skin area [5, 67]. The cutaneous form, noted in approximately 10% of the cases, precedes the development of serious forms of ADS that lead to collapse [42].

Serious forms of ADS are rarely found, fortunately. The reason is that during ascent in a pressure chamber, as a rule, prolonged desaturation of the organism to remove N_2 has been carried out in advance; should the first signs of ADS appear, usually pains in the joints, the subjects are brought down from the altitude to prevent development of serious forms of ADS. In flights where prophylactic treatment measures are more difficult to carry out, serious forms of ADS develop more often than during tests in a pressure chamber.

Serious forms of this disease manifest attacks of asthma which frequently precede coughing and chest pain, disorders in cardiovascular system activity including vasomotor collapse, and serious disturbances of the CNS. Such symptoms may lead to loss of consciousness, clonic spasms, hemiparesis, and other symptoms of local damage to various brain centers.

Mirolyubov and Apollonov [5], in 1938, in attempting to classify the various forms of ADS, isolated three forms of the disease in varying stages of seriousness. The first form, mild, included pain of varying intensity in muscles and joints, which disappeared without a trace during ascent to altitudes of 7000–8000 m. The second, more serious form, was characterized by pains in the region of the joints which intensified rapidly and spread to the surrounding tissues. In such cases, 2–3 h following the descent from altitude, palpation of the joint revealed painfulness and retention of a slight edema of the soft tissues surrounding the damaged joint. The third, serious form of ADS, includes severe pains in the joints, chest pains, and other symptoms of ADS accompanied by sharp deterioration of the general state.

This classification of ADS can be refined at present with greater detail. Thus, the osteoarticular form of ADS, which is most often encountered according to Gray [82] and others, may be divided into three stages: mild, moderate, and serious. The mild stage is characterized by low-intensity pains which arise primarily during movement and frequently disappear spontaneously during a stay at altitude, also when the tissues around the affected joint are pressed; the second stage is characterized by pains which are completely tolerable, intensify gradually and always disappear without a trace during descent. The third stage is distinguished by intense pains, sometimes intolerable, that lead to sharp deterioration of the general state.

The mild forms of ADS can include pruritus and paresthesias as the only manifestations; these symptoms sometimes precede serious forms of ADS.

The pulmonary form of ADS is very dangerous because it is frequently accompanied by a precollaptoid or collaptoid state. Researchers have proposed that a cough and attacks of asthma are caused by multiple formations of gas bubbles in vessels of the lesser circulation and possibly in lung tissues. In gradual development of asthma, according to Fryer et al [67], pains start in the chest in an attempt to draw a deep breath, followed by a dry cough in a short time, and the asthma attack begins. In serious cases, coughing attacks and asthma are culminated by loss of consciousness or collapse. After descent from altitude, some asthma attacks last for several hours. In examinations of such cases, lung x-rays and ECGs showed no deviations from the norm. Examination by a physician revealed only hyperemia of the larynx and pharynx mucous membranes.

Injury to the cardiovascular system is symptomatic of neurocirculatory ADS, one of the most dangerous forms. Serious manifestations culminate in loss of consciousness as a result of vasomotor collapse. Multiple gas embolism of the vessels in the greater and lesser circulation apparently account for collapse, as well as frequent and considerable loss of blood plasma from the circulatory system.

In a milder form of neurocirculatory ADS,

hypotonia develops as well as disturbances to cardiac activity rhythm. Some cases are accompanied by pronounced hyperventilation with its usual symptoms: dizziness, pounding, and sometimes tetanic spasms [42, 170].

The neurologic form of ADS is characterized by headache, general dysphoria, clonic spasms, and multiple symptoms of local damage to the brain: hemiparesis, monoparesis, scotoma, various aphasias, and hyperthermia [26, 31, 42, 67, 164, 170].

Manifestations of ADS are varied and often indicate mixed forms of ADS. For example, symptoms of simultaneous injury to skin and asthma attacks, or slight pains in the joints are followed by vasomotor collapse [42, 67, 157, 158].

The Course of ADS

A correct understanding of the course of ADS is important. If victims remain at altitude after the first mild symptoms of ADS appear (descent being impossible or undesirable), there is danger of serious forms of ADS developing. It should be noted that ADS can proceed with clear periods; that is, following descent from altitude, ADS symptoms disappear rapidly and the subjects feel well. However, there is sharp deterioration after a short time and, in serious cases, coma develops with loss of consciousness. Such late syncopes were noted when ADS culminated in the victim's death as a result of acute edema of the brain. These disorders are caused by multiple embolism from gas bubbles in the small vessels of the brain. These damages may be due largely to fat and bone-marrow emboli [42, 88], a question which has not been adequately studied.

Etiologic and pathogenetic studies of ADS, indicating that it results from gas bubbles in tissues and the vascular bed, may be considered proven. However, fat embolism as the leading factor is questionable; apparently, only rarely is fat embolism important in the pathogenesis of ADS, aggravating its course considerably. An indirect proof that fat embolism does not play an essential role, as a rule, in serious forms of ADS, was established by numerous authors: serious forms of ADS can be treated with considerable efficacy by staying at an elevated pressure.

Treatment of ADS

Descent from altitude (recompression) is highly effective in treating ADS. Pains in the joints and muscles at altitudes of 12 000–10 000 m disappear without a trace when the pressure is raised to 250–300 mm Hg during recompression. An important condition in effective ADS treatment by recompression to normal barometric pressure is the time between the first symptoms of ADS and the moment of descent from altitude. The earlier the descent is made, the more rapidly the ADS symptoms disappear. In rare cases, after total disappearance of ADS symptoms, they can reappear after a short time (usually 1–3 h). The course of ADS is then usually serious, making medical observation necessary, for several hours after the ADS symptoms have disappeared.

In all serious forms of ADS, it is advisable, while conducting symptomatic treatment, to place the victims in recompression chambers under increased pressure [42, 67]. The oxygen pressure in the chamber usually is raised to 3 atm, and the time the victim spends in the chamber is limited by the period it takes for toxic effects of oxygen to appear. In the symptomatic treatment of victims with serious forms of ADS, especially with deep brain activity disturbances such as loss of consciousness or comatose state, caution must be exercised to prevent brain edema. Injections of purified urea and similar compounds are recommended to stabilize osomotic pressure in the brain cells [42, 94].

Factors that Influence Probability of ADS

Essential factors that predicate the probability of ADS include: physical parameters characterizing magnitude, frequency, and rate of pressure differential; time spent by the individual at altitude; temperature and chemical composition of the AGA; and certain indices of the individual such as his physiologic state, age, and constitution.

The formation of gas bubbles in the organism following decompression is a function of the degree of supersaturation of the tissues by gases dissolved in them, thus, it would be expected that investigators would try [80, 171, 189] to determine

the significance of this factor for onset of ADS. Biophysically, simple supersaturation of the tissues by some gas is, although necessary, not sufficient for the formation of free gas bubbles in organic tissues. For this reason, the question cannot be answered on the degree of tissue supersaturation at which free bubbles of gas could cause ADS. Theoretically, free gas bubbles in tissues are possible when the barometric pressure drops to a value slightly exceeding the undersaturation degree of venous blood and tissues; for example, when pressure falls from 760 to 700 mm Hg, but, fortunately for man, ADS occurs at much higher pressure differentials [64, 67, 93, 152].

ADS regularly begins only after ascents from the ground to altitudes of 7000 m or more, according to experimental studies. Onset of ADS following elevations to lower altitudes is extremely rare, therefore need no special attention from the practical standpoint [67, 93, 171].

The probability of ADS increases with increase in ascent altitude and pressure differential factor following ascent to an altitude of 8000 m (256 mm Hg, differential coefficient of about 3.0). Experiments show that ADS is observed not only in persons performing physical work (15–25%) but also in those in a state of rest (in 3–5% of the cases) [67, 172] (Fig. 5).

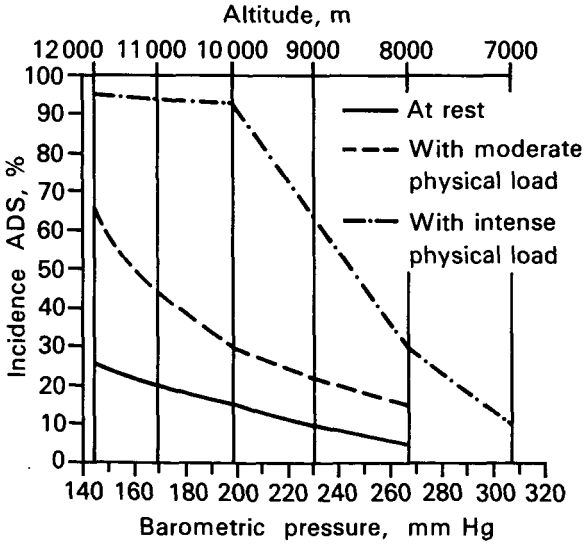

FIGURE 5.—Development of ADS at altitudes of 12 000–7000 m at rest and during various physical loads. (Based on [32, 67, 94, 171, 172, 173])

Following ascent to altitudes of 11 000–12 000 m, the frequency of ADS rises, to 25–48.5%, according to data of various authors, under conditions of relative rest, and to 62–93% when performing physical work [67, 81, 93, 94, 170, 172]. From various studies, the probability of ADS at altitudes of 8000–10 000 and 12 000 m differ, sometimes substantially, which is due to different rates of ascent, inhomogeneity of test subjects according to age, weight, and different activities at altitude.

ADS occurs as a function of the decompression rate. The higher the rate, the greater the probability of ADS during the subsequent stay at altitude. Thus, according to Hitchcock et al, in a normal, slow ascent (at 20–30 m/s) to an altitude of 11 600 m and subsequent stay at this altitude for 90 min, 62% of subjects carrying out standard physical exercises of moderate difficulty had ADS, while after rapid ascents (approximately 1 s), ADS was more frequent (in 88%), all other conditions being equal.

Time Spent at Altitude

A study of the distribution of ADS in time at altitudes of 8000–12 000 m indicates that during the first 3–5 min after ascent, ADS is extremely rare. For gas bubbles to form in tissues requires a certain time. The maximum number of ADS cases was in the interval from 20 to 40 min stay at altitude. After 1 h stay at altitude, the number of ADS cases dropped significantly; after 2 h, ADS was rare [67, 154, 172].

Hence, distribution of ADS cases in time following decompression is similar, to a certain degree, to the Poisson curve of normal distribution with maximum height at 20 to 40 min (Fig. 6).

Temperature of the AGA is a definite factor in the onset of ADS. Strel'tsov and others [24, 80, 189] noted that decreasing the temperature to values which create a sensation of cold promotes development of ADS. This is apparently due to the low temperature leading to spasm of vessels in skin and other parts of the body and thereby, after decompression, retarding desaturation of tissues in these regions with regard to nitrogen or another biologically indifferent gas [80, 171]. However, other data indicate that an

increase in environment temperature promotes acceleration of desaturation of the organism with regard to nitrogen, thereby decreasing probability of ADS [25].

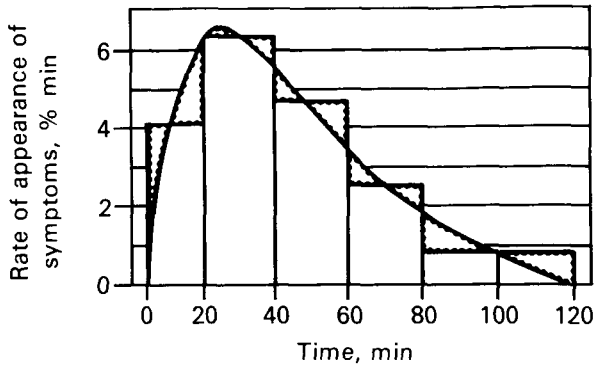

FIGURE 6.—Rate of appearance of ADS symptoms during 2 h at an altitude of 10 500 m. (After Nims [154])

Chemical Composition of the AGA

The role of chemical composition of AGA in forming free gas bubbles in tissues during decompression and, consequently, in the development of ADS has been insufficiently studied. It has been pointed out that increasing the P_{CO_2} in the AGA promotes the development of decompression sickness [24, 70, 80, 96, 209]. Decompression sickness occurred in animals that had been in a gas medium with P_{CO_2} = 22–45 mm Hg; following decompression to 200–145 mm Hg, ADS was significantly more frequent. Their blood gas traps showed a greater number of gas bubbles than in the animals of the control group which had been brought to the same altitude, but which previously had been kept in normal air [81].

Prolonged stay of humans at altitudes of the order of 3000–4000 m for several days [45], regardless of hypoxia developing (which should facilitate manifestation of ADS) to a significant degree, prevents their developing ADS during ascents to an altitude of 11 500 m. This is explained simply by partial desaturation of nitrogen from the organism during ascents to altitudes.

In the formation of AGA, roles played in the development of ADS following decompression by the various biologically indifferent gases comprising it are significant. Theoretical considerations of the basic physical and biophysical properties of inert gases and nitrogen (see Tables 2 and 3) permit a comparative estimate of the properties where one is used as a diluent gas in the AGA.

The group of inert gases includes: helium, neon, argon, krypton, xenon, and radon. Radon, because of its radioactivity, must be excluded from gases that can be used in the AGA.

Two parameters are of basic significance for the formation of free gas bubbles in the organism following decompression: solubility of the gas in various tissues (fat, muscle, and blood), and the coefficient of diffusion of the gas through cell membranes.

The Bunsen coefficient of gas solubility increases as the molecular weight increases, but the ability to diffuse (diffusion constant) decreases (Table 3). Hence, it might be concluded that gases with relatively high molecular weight (xenon, krypton, and probably argon) are scarcely advantageous as components of the AGA. Their use, aside from increasing the weight of the AGA, requires a greater expenditure of energy for cabin ventilation, leading to greater probability of ADS following decompression. Desaturation of the organism to remove these gases, due to their low diffusivity, requires a great deal of time which in certain situations (for example, when the crew is transferred to AGA conditions with low pressure), can be extremely disadvantageous. Consequently, the choice of biologically indifferent gases for the AGA at present can be limited to nitrogen, helium, and neon.[2]

There are no sufficiently convincing experimental data so far to give preference to one of the gases listed. Studies with human beings are needed in which, following total gas equilibrium of the organism with regard to AGA containing He or Ne, decompression would be carried out to 200–160 mm Hg, after which the rate of ADS would be determined. The probability of ADS—its osteoarticular form (bends)—after a pressure drop in the cabin, according to Beard et al [19], is somewhat higher when He rather than N_2 is included in the AGA.

[2]The possibility of using hydrogen (H_2) was not considered because of great danger of explosion in an oxygen-hydrogen gas medium.

TABLE 2.—*Physical Properties of Inert Gases*

Property	Gas					
	He	Ne	A	Kr	Xe	N
Atomic no.	2	10	18	36	54	7
Molecular wt.	4.00	20.18	39.94	83.80	131.30	28.00
Color	Colorless					
Density, g/l, at 0°C and 1 atm	0.1784	0.9004	1.784	3.708	5.851	1.251
Heat capacity (C_p) at 25° C and 1 atm, cal/°C-g mol	4.97	4.97	4.97	4.97	4.97	6.96
Specific heat ratio at 0 to 20° C, C_p/C_g	1.63	1.64	1.67	1.69	1.67	1.404
Sound velocity at 0°C and 1 atm, m/s	970	435	319	213	168	337
Acoustic impedance at 0°C and 1 atm, dyn-s/cm³	17.3	38.5	56.9	— —	— —	42.1
Thermal conductivity at 0°C and 1 atm, cal/° C-cm-s	34.0×10^{-3}	11.04×10^{-5}	3.92×10^{-5}	2.09×10^{-5}	1.21×10^{-5}	5.66×10^{-5}
Viscosity at 20° C and 1 atm, μP	194.1	311.1	221.7	249.6	226.4	175.0
Critical properties:						
Density, g/cm³	0.069	0.484	0.531	0.908	1.105	0.3110
Pressure, atm	2.26	26.9	48.0	54.3	58.0	33.54
Temperature, °C	− 267.9	− 228.7	− 122.44	− 63.8	16.59	− 146.9

TABLE 3.—*Solubility and Diffusion Constants of Inert Gases*

Property	Gas					
	He	Ne	A	Kr	Xe	N
Bunsen solubility coefficient in water at 38° C	0.0086	0.0097	0.026	0.045	0.085	0.013
Bunsen solubility coefficient in olive oil at 38° C	0.015	0.019	0.14	0.43	1.7	0.061
Bunsen solubility coefficient in human fat at 37° C		0.020	— —	0.41	1.6	0.062
Oil-water solubility ratio	1.7	2.1	5.3	9.6	20.0	5.1
Relative diffusion through gelatin at 23° C	1.0	(0.42)	0.30	0.21	0.13	0.35
Diffusion constants through liquids at 37° C $cm^2/s\times10^{-6}$:						
Olive oil	(18.6)	(8.34)	(5.92)	(4.10)	(3.27)	7.04
Lard	(9.28)	(4.15)	(2.94)	(2.03)	(1.62)	3.50
Serum	(57.6)	(25.7)	(18.2)	(12.6)	(10.1)	21.7
Agar gel	(71.3)	(32.0)	(22.7)	(15.8)	(12.6)	27.0
Water	(79.2) 63.2	(34.8)	(25.2)	(17.5)	(13.9)	30.1

Animals administered equal volume amounts of He and N_2 showed that vascular embolism produced by He proceeded more easily than embolism following administration of nitrogen [81]. This is evidently due to the higher diffusivity of He, since its desaturation from gas bubbles is more rapid, and they disappear sooner than N_2 bubbles.

In rat experiments, replacing air nitrogen with helium or neon leads to (following decompression) approximately the same rate of ADS; however, these data can scarcely be extrapolated to man because of the exceptionally high metabolic rate in rats [84].

Theoretically, it has been indicated by several authors [19, 25, 170, 208] that Ne (use of this gas in AGA has been studied little) should have certain advantages over He and N_2. The use of Ne in a helium atmosphere (HEA) must lead to the lowest probability of altitude pains during muscular loads, also severe forms of ADS accompanied by dyspnea and neurocirculatory collapse [25, 170]. It must be added that the difference between He, Ne, and N_2 when used in an AGA will be smaller, the lower the barometric pressure in spacecraft cabins. At a pressure half the atmosphere value (380 mm Hg) and corresponding content in the AGA of 50% diluent-gas and 50% O_2, the probability of ADS will be so negligible that any difference between Ne, He, and N_2 need not be considered for their inclusion in an AGA.

Body Weight

Increased predisposition of overweight persons to ADS has been indicated. Cutaneous and serious forms of ADS are observed more often in those overweight.

Frequent ADS accompanied by dyspnea and collapse is usually related to the high solubility of nitrogen in fat tissues and the low level of their blood supply. These circumstances determine a high probability of free gas bubbles forming in gas in fat tissues. In fat tissue lesions caused by gas bubbles, fat particles can enter the vascular lumen, and with gas bubbles clog vessels. Data in Figure 7 indicate the higher rate of ADS in overweight persons [25].

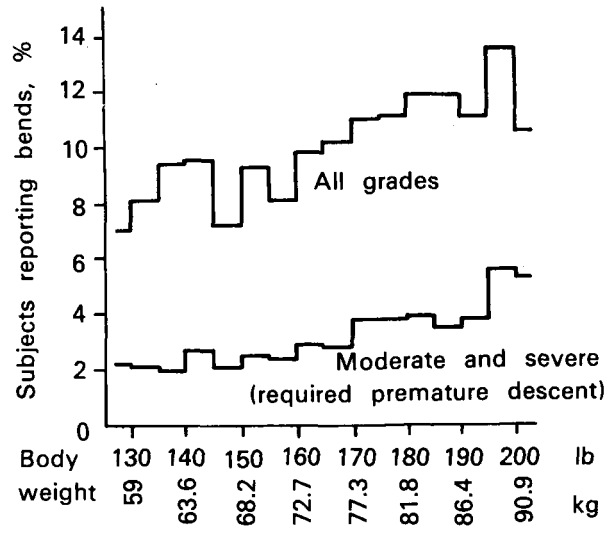

FIGURE 7. — Manifestation of ADS as a function of body weight. (Cited in [25])

Age

The incidence of ADS increases with age of subjects [42, 67]. In ascents of 2633 servicemen aged 17 to 36 (breathing pure oxygen), to 8500 m followed by 2-h exposure at this altitude, the smallest number (0.78%) of ADS cases in a rest condition was noted for persons aged 17 to 20. Among persons aged 21–23 years, the number experiencing ADS rose to 1.67%; among persons 24–26 years of age—4.98%; among those 27–29 years of age, 7.43%; and in the group aged 30–35 years, 5.99% [66].

One of the factors possibly affecting the distribution of ADS cases in relation to age is the change in weight (the increase of weight with age), as well as circulatory characteristics determining the higher rate of nitrogen desaturation from the organism among adolescents and young men.

Physical Exercise

Muscle exercises promote development of ADS. A direct relationship was established between onset of ADS and intensity of muscle activity [56, 67, 98], made clear from the data in Figure 8, which show the results of subjects who performed different numbers of deep knee bends at high altitude [64]. Localization of attack

of joints and muscles during ADS also depends on the kind of muscle activity. Pains are first felt in the same joints and muscles that participate directly in the exercises [93, 171]. For example, when the subjects' legs were flexed at the knee, the altitude pains usually developed in the knee area; similarly when the subjects' arms were raised periodically, the pains tended to appear most often in the shoulder joints.

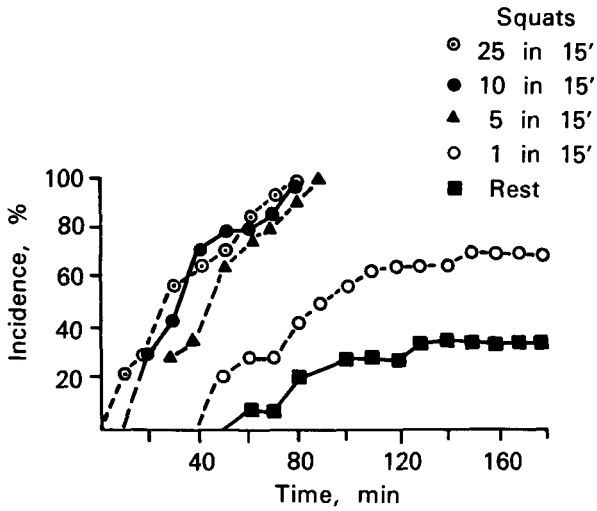

FIGURE 8.—Dependence of ADS incidence on physical load intensity [170].

Intense muscle activity, it has been held, leads to a decrease in the altitude threshold of ADS by 1000–1500 m. This is caused by local foci of low negative hydrostatic pressure in motor activity arising in the working joints, muscles, and ligaments, which promotes formation of gas nuclei and bubbles [51, 70, 86, 152]. During muscle activity the formation of CO_2 increases, which is a major factor in the formation of gas bubbles after decompression, and also promotes ADS during muscle activity [24, 96].

In addition to muscle work and other influences promoting the formation of increased gas nuclei in the organism, onset of gas ADS can be provoked and facilitated. Repeated ascents (after several hours) to altitude, as well as underwater immersion even to relatively shallow depth, preceding an ascent to altitude, promote the development of ADS [42, 80].

Prevention of ADS

Hermetically sealed cabins with a pressure of 1–1.2 atm in Soviet spacecraft and an HEA with a total pressure of 258 mm Hg in US spacecraft cabins increase the urgency of protecting crewmembers against ADS. Astronauts can develop ADS after transition from normal atmospheric pressure to reduced pressure in the cabin or space suit.

Hermetic cabins and space suits with sufficiently high pressure, of the order of 350–400 mm Hg, are effective means of preventing ADS in flights. This approach to solving the problem encounters serious technical difficulties: when the pressure in space suits is raised to the values indicated, the work capacity of cosmonauts wearing space suits falls off sharply due to restrictions on movement. With the use of high pressure in cabins and space suits, the probability of ADS cannot be entirely avoided, since in emergency situations pressure can drop to values where ADS becomes probable. Accordingly, different methods of preventing ADS based on desaturation of nitrogen from the organism, or any other inert gas that is part of the AGA, take on major importance.

The organism can be desaturated either by slow reduction in pressure—by ascent to altitude, or by breathing pure oxygen under normal or reduced barometric pressure. At even relatively rapid ascents to altitude at a rate of 10–20 m/s, there is partial washing out of nitrogen, which determines some decrease in the incidence of ADS.

Aviation medicine experience permits the assumption that desaturation of nitrogen from the organism by breathing oxygen is the most convenient and effective method of preventing ADS [6, 7, 23, 83, 98].

The curve of nitrogen removal from the organism reflects its dissimilar rate of removal from different tissues [83, 98, 207, 211]. The rate of desaturation for different tissues depends on their coefficient of nitrogen solubility and on the level of their blood supply. Individual differences in chemical composition of the body and in the level of blood supply of different tissues determine corresponding individual characteristics of the

desaturation curve of nitrogen from the organism or in any other gas while oxygen is being breathed.

The rate of nitrogen removal is the highest during the first minutes of breathing oxygen, due mainly to the removal of nitrogen from respiratory tract, lungs, and blood. Further, the rate of nitrogen removal slows markedly in 10 to 20 min and its desaturation is predominantly from muscle tissue and internal organs. In the first hour of breathing oxygen, the organism loses approximately 50% of the nitrogen dissolved in its tissues (Figs. 9 and 10).

Desaturation proceeds slowly in the second to third hour of breathing oxygen; about 48 h are required for practically complete washing out of nitrogen [211]. Such slow removal of nitrogen from the organism is because some tissues, such as tendons, joint sacs, and fat tissue, have very low levels of blood supply; the solubility of nitrogen in fat is more than five times higher than in other tissues, where its content is low.

In aviation and astronautics, methods of nitrogen desaturation from the organism should be developed so that a fairly high preventive effect would be achieved in minimum time. Various means of increasing the desaturation rate have been proposed: arbitrary hyperventilation, physical exercise, and intake of caffeine [7, 23, 57]. Ardashnikova [7] noted an increase in the rate of nitrogen removal by arbitrary hyperventilation with oxygen, which was followed by an investigation with 3–5% CO_2 oxygen added. The same effect was anticipated as a result of the nonarbitrary hyperventilation caused by the stimulating action of CO_2 on the respiratory center. The experiments showed that adding CO_2 to O_2, in spite of increased pulmonary ventilation, does not lead to an increase in the rate of nitrogen desaturation for the organism, but slows it by 10–15%. The reason for the slowdown, evidently, is redistribution of the blood flow resulting from vasoconstrictive action of CO_2 on the vessels in many regions of the body. Physical exercise during oxygen breathing time appreciably accelerates desaturation of nitrogen and helium from the organism, which is clear in Figures 9 and 10.

Pure oxygen breathed under normal barometric pressure leads to constriction of vessels

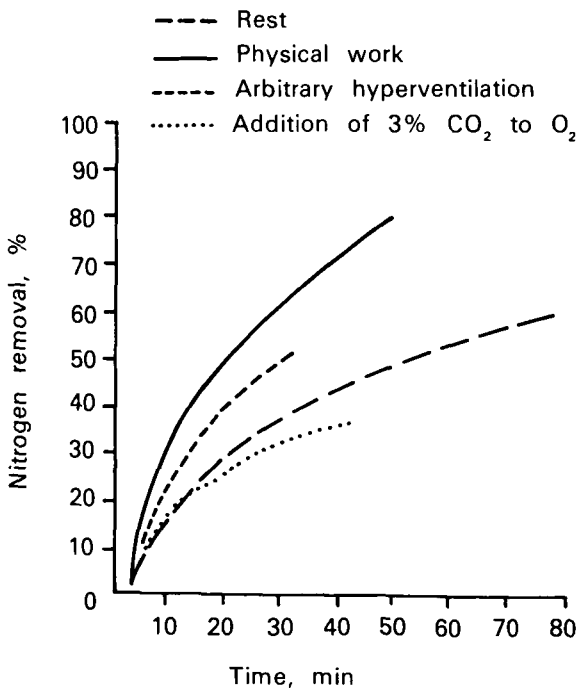

FIGURE 9.—Rate of nitrogen removal from humans while breathing oxygen under different conditions. (Based on [6, 7, 23])

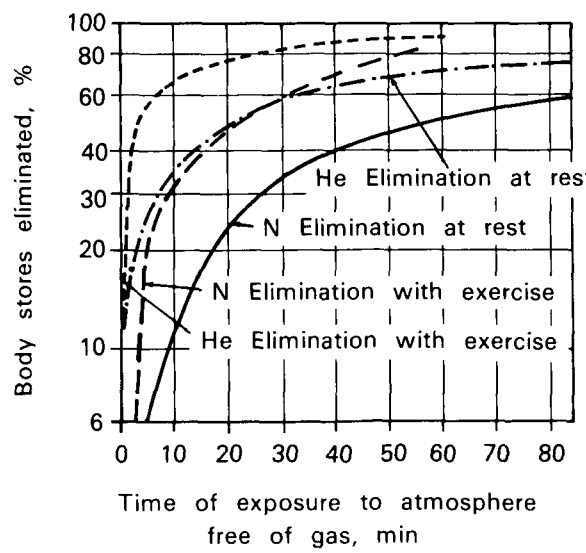

FIGURE 10.—Rate of nitrogen and helium removal when O_2 is breathed at rest and when physical exercises are performed. (Based on [25])

and reduced blood supply in many tissues. This effect was noted as having an unfavorable effect on desaturation; for its elimination, desaturation by breathing pure oxygen at different altitudes was investigated.

Nitrogen removal. The total amount of nitrogen removed in 1 h of breathing oxygen at normal pressure and at an altitude of 8000 m is approximately the same [6]. However, at an altitude of 8000 m during the first 10–15 min, more nitrogen is removed than at normal barometric pressure. In 20 min oxygen breathing, nitrogen removal is slowed at an 8000-m altitude to a greater extent than during desaturation under normal barometric pressure. This is of definite interest in understanding causes determining the reduced protective effect of desaturation when oxygen breathing is under reduced barometric pressure.

According to the data of Marbarger et al [137], the protective effect from 2 h of oxygen breathing before ascent to an 11 600-m altitude decreases with increase in altitude (beginning at 3600 m), when there is desaturation [137]. Thus, when oxygen was breathed under normal conditions after an ascent to 11 600 m, ADS developed in 6.1% of the cases; when desaturation was in the pressure chamber at 3600-m altitude, ADS was noted in 15% of the cases. ADS arose in 21% of the cases when desaturation was at 6700-m altitude; but when ascent was made to an altitude of 11 500 m without preliminary desaturation, ADS was noted in 48.5%. An explanation of the results of this investigation is that during saturation at altitudes of 3600–6700 m, nitrogen, washed from the tissues slowly losing nitrogen, proves to be impeded by the formation of bubbles in the tissues in which N_2 accumulates, even at these altitudes.

When individuals are in the mountains at an altitude of 3000–4000 m for several days, the result is that all tissues uniformly lose approximately 35% of their nitrogen content. This has a more pronounced preventive effect against ADS for subsequent ascents to altitudes of 10 000–11 500 m than preliminary 1-h oxygen breathing under normal barometric pressure, where the organism is freed of 50% of the nitrogen. These data indicate that the preventive effects of desaturation are determined not only by the amount of nitrogen or other biologically indifferent gas removed from the organism, but also by tissues from which the gas is removed. Thus, it is vital that there is desaturation from tissues that are slowly freed of the indifferent gas.

To determine the effectiveness of preventing ADS, after different periods of breathing oxygen at normal pressures, is also important. Since protection against ADS after nitrogen desaturation from the organism depends on many factors, the extent of the anticipated preventive effect can be expressed by three values: minimum, mean, and maximum.

Roth calculated from data of Jones [98], the protective effect for ADS prevention in relation to the time of oxygen breathing for cases subsequently being under reduced (down to 179 mm Hg) pressure when performing moderate physical work.

When the age and weight of the subjects, and the associated curve of nitrogen desaturation from the organism are not known, calculating the preventive effect must be based on "minimum" protection. The extent of the protective effect can be calculated by the percentage of probable reduction in the number of ADS cases. This is compared with the proposed percent of ADS cases in ascents to an altitude of 10 500 m (179 mm Hg) without preliminary oxygen breathing at a rate of no more than 1000 m/min (Table 4).

Determination of probable loss of the protective effect is important when desaturation is disrupted; when the oxygen breathing is interrupted, and the individual again breathes air for some time. Such situations can arise in different periods of flights or flight preparation. Table 5 shows calculated losses of the protective effect under different conditions when nitrogen desaturation from the organism was disrupted. The data provide for only an approximate estimate of the protective effect against ADS after different periods of oxygen breathing before ascents to altitudes of 10 000–11 000 m.

Experimental data indicate that breathing pure oxygen, in addition to reducing the probability of ADS, lowers the incidence of severe forms of ADS and shifts in time the manifestation of different ADS symptoms. For example, breathing oxygen for 1 h before ascent to an altitude of

12 000 m, when light work is performed in this altitude for 1 h, reduces the incidence of ADS nearly twice and leads to ADS being noted 10–20 min later than after ascents without desaturation [94]. Determining the time of breathing sufficient oxygen for the greatest possible protective effects is vital in preventing ADS.

TABLE 4.—*Preventive Effect of ADS in Ascents to Altitude after Preliminary Breathing of Oxygen for Different Periods*

Time of breathing O_2, h	Minimum protection %	Probable protection %
0.5	16	26
1.0	29	45
1.5	41	59
2.0	50	70
2.5	58	77
3.0	61	83
3.5	70	87
4.0	75	91
4.5	79	
5.0	82	
5.5	85	
6.0	86	
6.5	89	
7.0	91	

Oxygen and altitude. Breathing oxygen for 2 h at 4500 m (430 mm Hg) is sufficient to prevent ADS at 7000 m for 5 h while performing work of moderate intensity (300–400 kcal/min) [32, 73]. Without desaturation, ascents to, and work in, this altitude cause ADS in more than 10% of the cases. Breathing oxygen for 5 h at 4500 m is sufficient to prevent ADS at an altitude of 10 000 m for 5 h with work of moderate intensity. This can be achieved by a preliminary 10-h stay at an altitude of 4500 m in an AGA of 45% O_2 and 55% N_2. Subjects remaining for 4–6 h at altitudes of 4000–5000 m in a gas atmosphere with 45% O_2 and 55% N_2 were not provided adequate protection against ADS; in a subsequent ascent to 11 000 m when intense work was performed, ADS symptoms were noted in nine of 30 persons [73]. Preliminary oxygen breathing for 4 h can prevent ADS symptoms at 8000 m. To achieve "maximum" protection against ADS at altitudes of 10 000–12 000 m, preliminary oxygen breathing for 8–10 h is evidently required [73, 170]. The conditions under which there is nitrogen desaturation from the organism must be considered; it must be remembered that when oxygen is breathed under normal pressure, the danger of fire is considerable, since the probability of inflammation is nearly five times greater than in normal air [33, 73].

It has been suggested that, to prevent ADS, individual selection should be made for the crew in order to eliminate those highly sensitive to ADS. Individual differences in resistance to ADS have been shown [67]. After 2 h at an altitude of 8500 m, ADS developed in 71 of 2273 persons (3.12%); in an ascent repeated to the same altitude, of 2202 persons in whom no ADS had been noted in the first descent, ADS appeared in 47 (2.13%). But when 60 of the 70 persons that had been affected earlier by ADS made an ascent, it developed in 13 (21.7%) [67].

TABLE 5.—*Assumed Losses of Protective Effect After Disruption of Desaturation*

	Oxygen	Air	Oxygen	Air	Oxygen	Air	Oxygen	Air
Time, h	1	½ 1	2	½ 1	3	½ 1	4	½ 5
Mean protection	29	26 20	20	40 33	64	54 46	75	62 53
Probable protection	45	33 25	70	52 39	83	62 46	91	67 50

	Oxygen	Air	Oxygen	Air	Oxygen	Air
Time, h	5	½ 1	6	½ 1	7	½ 1
Mean protection	82	68 60	86	74 62	91	74 62
Probable protection	95	70 52	97	72 54	97	73 54

Jones, in 1942, noted positive correlation ($K = 0.56$) between the rate at which radioactive krypton was excreted by the tissues and individual sensitivity to ADS; however, this method can scarcely be used advisedly for selection. Selection for ADS prevention can scarcely be significant, it is assumed, since it is impossible to cancel out entirely the probability of ADS in persons who successfully pass this selection [5, 67, 190].

In conclusion, in selecting the gas composition of cabin AGA, it is vital to obtain information about the rate of desaturation from the organism not only of nitrogen, but also of inert gases that can be part of the AGA.

Experimental data on this problem are limited and apply mainly only to He. The rate of desaturation of He from the organism after sufficiently long stays in a helium-oxygen medium considerably exceeds the desaturation rate of nitrogen. This is evident from data in Figure 10.

Data have not been obtained on neon desaturation from the organism after establishment of gas equilibrium in an oxygen-neon atmosphere; for argon (A), it can be concluded that it is similar to N_2 [80, 170].

Vaporization Phenomena in the Organism

At barometric pressure below 47 mm Hg, the pressure of the gas medium surrounding a person becomes less than the vapor pressure of water at 37° C. Vaporization phenomena develop in organic tissues which determine the distinctive trend of decompression disorders.

The development of vaporization in different body tissues and cavities depends on barometric pressures—ascent altitude, hydrostatic pressure, temperature, elastic properties of tissue, and presence of gas nuclei.

This question has been dealt with in many studies [9, 116, 119, 201]. Vaporization phenomena were first observed by Boyle [36] in 1670, in animal organisms under extremely low barometric pressure. They were then described by Hoppe-Zayler in 1857, whose evaluations were not precise enough, since acute hypoxia at high altitudes eliminated the physiologic effects associated with vaporization in tissues.

Experiments where vaporization phenomena were observed in animals were described by Armstrong (US) and Strel'tsov and Parfenova (USSR), in 1938 [9, 159]. In Strel'tsov's experiments, newly born rats were highly resistant to acute hypoxia. This made it possible to detect, in a pressure chamber, in animals still alive at altitudes of 20 000 m and higher, a sudden, abrupt increase in metabolism, which the investigators considered tissue "boiling." Armstrong also noted in experimental rabbits, when pressure in the pressure chamber was lowered to 47 mm Hg, development of "boiling" of tissues, judging from depressions under the skin and gas bubbles in saliva and blood. Vaporization phenomena in different tissues in animals were later investigated in detail [12, 104, 113, 119, 201].

The roentgenogram method was used extensively by Kuznetsov [116] in animal ascents to high altitudes in a pressure chamber, which enabled him to observe successive vaporization phenomena in different tissues. After rapid pressure drop in the pressure chamber to 40 mm Hg and less, he noted some increase in the body volume of the animals (white rats and dogs) due to expansion of intestinal gases. In 12–15 s, areas of swelling under the skin appeared suddenly in white rats, that is, subcutaneous altitude emphysema developed, subsequently spreading over the entire body surface. It was confirmed that emphysema occurred due to "boiling" by its rapid, explosive development, and only occurred when barometric pressure was lowered to 47 mm Hg or less, also that it was possible to prevent emphysema by cooling the animal body.

The roentgenograms established that in 2–3 s after the pressure was lowered to 47–48 mm Hg, small foci of gas accumulated under the skin. In 7–10 s, the gas was detected in the abdominal region—between the diaphragm and the liver; in 10 to 20 s, gas was observed in the pleural cavity, right ventricle of the heart, and veins. Gas in the veins is due to the pleural cavity and right side of heart being body regions with low pressure. Gas was noted later in the left side of the heart and arteries, which is associated with relatively high blood pressure in these cardiovascular regions. The same phenomenon—vaporization in pleural cavity, heart,

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and vessels of dogs after pressure in the pressure chamber had been lowered to 25–30 mm Hg—was observed by Burch, Kemph, et al [40], not only roentgenologically, but also visually through small "windows" mounted in thoracic cavities.

Experiments on dogs and monkeys [22, 106, 112] indicate that when animals stay in the pressure chamber no longer than 2 min, subsequent rapid recompression—descent from altitudes—leads, as a rule, to the preservation of life. The death of animals in more rapid exposures at high altitude when vaporization arises, is evidently associated mainly with acute hypoxia. This conclusion can be based on the lifespan of animals at altitudes of 15 000–17 000 m when "boiling" of tissues does not yet develop, being approximately the same as at altitudes of 20 000–40 000 m, where it does occur [112, 116].

Thus, acute pathologic state in animals exposed to extremely low pressures is caused chiefly by hypoxia, and decompression phenomena (vaporization and formation of intravascular bubbles) are only factors that aggravate the effect of hypoxia and complicate its course. It must be noted that when first aid is given to individuals severely affected at high altitudes, administration of drugs into the blood and arterial compression of blood can prove ineffective due to gas bubbles in the vasomuscular lumen and heart.

In studies of the mechanism of subcutaneous decompression emphysema, the chemical composition and pressure of the gases forming it have been determined [12, 104, 113]. Kemph, Beman and Hitchcock [104] measured the pressure in subcutaneous emphysema bubbles in animals, developing after pressure in the pressure chamber had been lowered to 25–30 mm Hg. The pressure was determined with a capacitive strain gauge, an ordinary mercury manometer, and an indirect fluoroscopic method, which records external pressure where bubbles disappear in the x-ray. These experiments established that differential pressure fluctuates from 25–40 mm Hg, and absolute pressure from 55–70 mm Hg. The composition of gases in subcutaneous emphysematose bubbles varies widely [12]. In gas samples collected from rat emphysematose bubbles at altitudes of 20 000–22 000 m in different experiments, N_2 content was in the range 25.4 to 78%; CO_2—1.2 to 68%; and O_2—6.3 to 20.8%. In vaporization phenomena, the primary role is attributed to water vapor and carbon dioxide gas, which act as a "second liquid." Accordingly, vaporization in tissues can begin at barometric pressure somewhat exceeding 47 mm Hg, that is, the pressure at which water vapor pressure at 37° C is equal to the ambient pressure.

According to the data of Kovalenko, chemical composition of emphysematose bubbles undergoes a change simultaneously with gradual rise in their pressure: the content of O_2 and N_2 becomes smaller, and CO_2 content rises. In the first 4–5 s after decompression, pressure in emphysematose bubbles is 15–20 mm Hg, subsequently rises to 30–60 mm Hg and remains constant, since at these pressures the skin is already peeling [113, 114].

Investigations on vaporization phenomena in the human organism are few, so that this problem has not been adequately studied.

Subcutaneous decompression emphysema. Decompression emphysema has developed locally in wrists and feet in the course of astronautics. Subcutaneous emphysema was noted in wrists of individuals in pressure chambers who wore altitude suits without gloves when ascending to an altitude of 20 000–40 000 m [97, 170].

In the data relative to subcutaneous emphysema, certain characteristics are striking:

absence of emphysema in the first 1–3 min after ascent to altitude even when pressure in the pressure chamber was reduced to 8 mm Hg;

appearance of emphysema in only one hand;

individual instances of absence of emphysema for relatively long stays (15 min and longer) at altitudes of 20 000–30 000 m.

These results can be explained by the tissue turgor acting as a determinant of the ability to withstand stretching and lesion which are important in the development of emphysema.

Absence of subcutaneous altitude emphysema during the first minutes and its individualized manifestation are associated with tissue turgor which differs in degree among individuals [97].

It may be added that gas nuclei, the sources of decompression bubbles, also probably contribute to individualized manifestations of emphysema, since vaporization of water vapor in the cavity of this kind of gas bubble can determine the initial period of emphysema development.

For altitude emphysema to be manifested, the total of the values of intratissue pressure (*Pt*-turgor) and barometric pressure (*Pb*) must be smaller than 47 mm Hg ($Pt+Pb<47$ mm Hg). It is immediately apparent that various indifferent gases (N_2, He, A, and Ne) that can be part of AGA will not appreciably affect the development of subcutaneous decompression emphysema, since H_2O and CO_2 are its main constituents. Different gases can have effect only on the latent period of emphysema, which is due to decompression gas emphysema apparently having two phases. During the first phase, gases diffuse and bubbles are formed; in the second, fluid in the cavities of these bubbles evaporates.

Emphysema does not cause deterioration in self-awareness and the total state of subjects during several minutes; this makes it possible to observe the dynamics of its development for some time. Emphysema occurs, as a rule, only in one hand—at first in the rear surface of the wrist in the skin between the first and second fingers, and gradually spreads to the entire wrist. The first unpleasant sensations—tightening of skin, prickling, and pain—are noted by subjects only 3–5 min after onset of emphysema. Pain sensations were sometimes absent even in pronounced emphysema when the wrist took on a spherical shape [97].

Roentgenograms of all subjects at altitudes of 12 000 m and higher showed a small amount of gas in the radiocarpal joint. Subcutaneous emphysema at altitudes of 20 000–30 000 m was manifested first by a small accumulation (in the form of a narrow strip) of gas beneath the skin. Later, the amount of gas beneath the skin increased steadily (Fig. 11). After rapid descent from altitude, signs of gas in the radiocarpal joint disappeared. However, in some roentgenograms there were still considerable "lightening" bands in soft tissues of the wrist, which had earlier been affected by emphysema. The ability for delicate differentiated motions was rapidly restored [97].

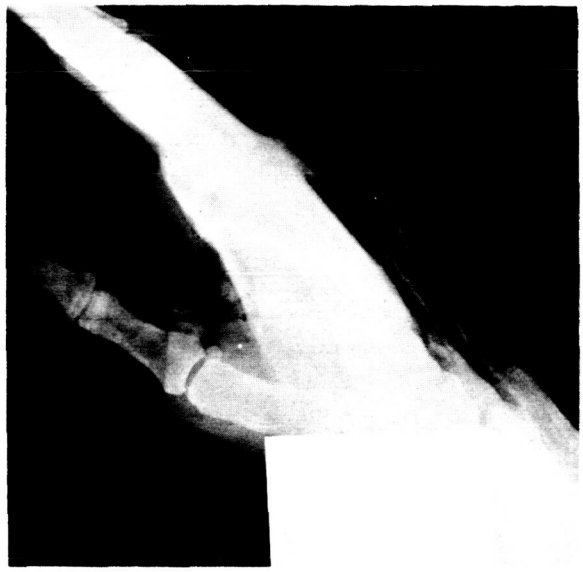

FIGURE 11.—Evidence of subcutaneous altitude emphysema at 20 000–30 000 m. The first manifestation was a small accumulation of gas in a narrow strip beneath the skin. (Based on [97])

HYPOXIA

The biological equivalence of AGA complying with the normal terrestrial atmosphere in terms of P_{O_2} is one of the main principles in AGA design. Maintaining a P_{O_2} in a cabin AGA that is close to the normal P_{O_2} of the atmospheric air is most important for determining flight safety. During flights, unfortunately, instances of cabin depressurization cannot be entirely eliminated, as well as improper operation of the regeneration unit, inevitably leading to decreases in P_{O_2} in the AGA and of high toxic states in crewmembers. Information on the effects of different degrees of hypoxia on the human physiologic state and work capacity is of great importance. Hypoxia has drawn the attention of space medicine specialists as means of selecting and conditioning astronauts. To prevent the unfavorable effects of weightlessness and hypodynamia on the organism, this conditioning should be carried out during actual space flight by periodically decreasing P_{O_2} in the AGA [76, 134].

Acute Effects of Hypoxia

Metabolic processes underlie life. In man and animal, these processes include oxidation of

proteins, fats, and carbohydrates by oxygen intake from atmospheric air. In contrast to the relatively high reserves of fats, carbohydrates, and proteins in the organism, its reserve of O_2 is extremely low. This dictates the necessity for virtually continuous intake of O_2 from the ambient medium.

P_{O_2} must not fall below a certain level for normal, vital activity of organic cells, which is 3–5 mm Hg for brain cells—the most sensitive to O_2 insufficiency [112]. When P_{O_2} in the intercellular fluid drops below this level (called the critical level), the rate of oxygen consumption by the cells is reduced, that is, to actual oxygen starvation.

Intake of O_2 into the tissues is determined mainly by diffusion; effectiveness of diffusion depends on its gradient in different sections of O_2 transport. Figure 12 shows the main step-cascades characterizing the normal diffusion gradients of P_{O_2} in different stages of O_2 transport.

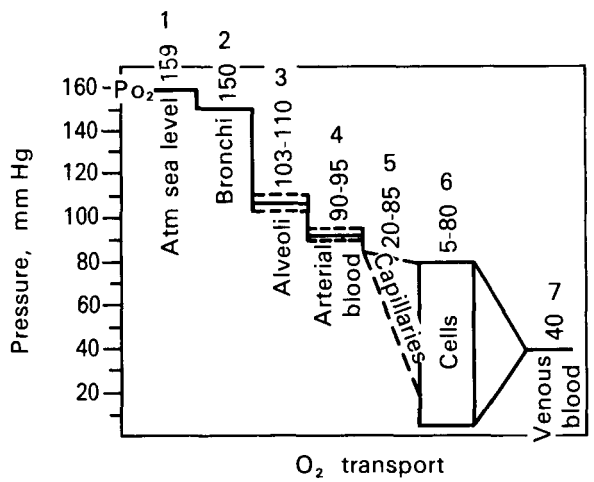

FIGURE 12.—Normal P_{O_2} values in different sections of O_2 transport in the organism.

When O_2 content in the AGA is reduced, just as when barometric pressure in the cabin is lowered, according to Dalton's law, P_{O_2} in the inspired air decreases which inevitably leads to decreased intake of O_2 in the tissues, that is, development of hypoxia. The cells farthest removed from the capillaries are the first to suffer, and diffusion of O_2 to the cells is the most reduced. With increase in hypoxia, the number of these cells undergoing actual oxygen starvation rises steadily, which is significant as a symptom of oxygen starvation.

In evaluating the clinical pattern of oxygen insufficiency, it must be remembered that underlying its pathogenesis—besides effects of hypoxia on cellular metabolic processes—adaptational shifts caused primarily by reflexive increase in pulmonary ventilation also play an essential role. Intensifying pulmonary ventilation promotes, in moderate hypoxia, preservation of P_{O_2}, but at the same time leads to hypocapnia and alkalosis, that is, to new homeostasis disturbances. In acute forms of oxygen insufficiency when severe pathologic states arise rapidly, during 1 to 2 min (after ascents to altitudes of 10 000 m and higher), significant hyperventilation cannot develop, and in the pathogenesis of these states only the oxygen deficit is decisive. In less acute forms of hypoxia, to which the organism can adapt in time (e.g., while remaining in mountains), in the pathogenesis of the functional disorders, including mountain sickness, adaptational shifts contribute to hypoxia, which leads to hypocapnia, disturbance of acid-alkaline equilibrium regulation, acute polycythemia, and so on.

The partial pressure of O_2 in alveolar air (P_{AO_2}) and the partial pressure of O_2, which is close to this value in arterial blood during (P_{aO_2}) indicate the severity of the hypoxic state. Accordingly, it is important to determine these indicators in ascents to various altitudes or when O_2 content changes in the AGA. An approximate calculation of P_{aO_2} relative to barometric pressure was first proposed in 1885 by Sechenov [181] while analyzing the causes of death of two French aeronauts who had reached an altitude of 8600 m in the Zenith balloon. He also considered a drop in P_{aO_2} to 20 mm Hg incompatible with short-term preservation of life. Later, calculation of P_{aO_2} was refined relative to P_{O_2} in ambient gas medium; in particular, the respiratory coefficient was corrected [61]. This quantity is calculated by the formula:

$$P_{aO_2} = (B - P_{H_2O}) \cdot C - P_{ACO_2}\left(1 - C \cdot \frac{1-R}{R}\right) \quad (6)$$

where P_{AO_2} is partial pressure of O_2 in alveolar air, B is barometric pressure, and

P_{H_2O} is partial pressure of water vapor in lungs, which depends only on temperature, and at body temperature of 37° C is 47 mm Hg,

P_{ACO_2} is partial pressure of CO_2 in alveolar air, C is concentration, percent content of O_2 in the AGA, and

R is respiratory coefficient.

The critical value of P_{aO_2} is also revised, based on experimental studies; it varies from 27 to 33 mm Hg [25, 112]. But the critical value of P_{O_2} in mixed venous blood is 19 mm Hg [112].

Significant and rapid decrease in P_{O_2} in the ambient gaseous medium is usually classified as acute hypoxia; as the result of which in healthy persons, but those not previously adapted to hypoxia, pathologic states of varying severity appear in a relatively short time. These effects are apparent after rapid ascents to altitudes of 4000–5000 m and higher or if the O_2 supply is suddenly cut off during altitude flights.

Data on acute hypoxic effects on animal organisms in rarefied atmosphere were first collected by Bert in 1878 [30]. When animals ascended to high altitudes in a pressure chamber they developed pathologic states, the severity of which depended on the decreasing P_{O_2} in inspired air and on the length of time the animals stayed in rarefied atmosphere. Cerebral activity disturbance was symptomatic of severe hypoxic states followed by irreversible disturbances in respiration and blood circulation.

The effects of hypoxia on CNS, shown by electrophysiologic investigations on intact cortices and neuronally isolated cortical flaps, are associated with the direct as well as the reflexive (via chemoreceptors) effects on neurons from O_2 insufficiency in the blood [34, 133]. In the initial period of oxygen starvation when hypoxemia is still relatively limited, stimulation of chemoreceptors with sinocarotid and aortal zones leads, simultaneously with stimulation of respiration, to raised functioning of the reticular formation of the brain stem and its subsequent activating influence on higher brain levels, including the cortex of the cerebral hemispheres [52, 133, 185].

Thus, the first phase of hypoxic influence on CNS is manifested in increased excitability of numerous brain structures. In the EEG, this phase of oxygen starvation is manifested in activation of the β-rhythm [10, 52, 133]. In this same phase of hypoxia, adaptive reactions are also manifested: intensified pulmonary ventilation, increases in heart rate and minute blood volume oriented toward increasing the O_2 transport to the tissues.

With significant degrees of hypoxia and O_2 tension in cerebral tissues dropping off, a second phase commences, characterized by deep disturbances of cerebral activity: complete inhibition of conditional reflexes, loss of active posture, clonus appearance, then tonic spasm [112, 113, 116]. At this time, the δ and θ-waves predominate in the EEG after which—with aggravation of hypoxia—a gradual suppression of bioelectric cerebral activity is noted [10, 112, 133, 156]. The δ-rhythm is accompanied by slowdown or total suppression of neuronal impulse. After restoration of normal oxygen supply, bioelectric activity of several neurons is no longer restored, evidently indicating their death.

Hypoxic reactions. Extensive experimental materials describe the development of acute oxygen starvation in man. Human responses during hypoxia in general are quite similar to those of animals. First, the extremely high sensitivity of CNS to hypoxia was revealed. Disturbances of CNS activity in man are manifested by: reduced intellectual capacity; disturbance in long-term memory; loss of concentration; disturbance of sensory organs, mainly sight; disturbance in coordination of sign movements (handwriting disorder); emotional changes—sluggishness, sleepiness, or in contrast, euphoria, sometimes resulting in loss of adequate response to the immediate environment [8, 57, 61, 132, 139, 163, 190, 191].

Symptoms of an acute, uncompensated hypoxic state can be classified into two symptom complexes [132]. In the first, the collaptoid state develops with bradycardia, drop in arterial pressure, and hyperhydrosis. Simultaneously, there are external changes of paleness or hyperemia, with sluggishness and disinclination to participate. Bioelectric brain activity changes slightly:

initial depression of α-rhythm in EEG followed by low amplitude of θ- and δ-waves, becoming visible against the β-rhythm.

These symptoms characterize relatively mild hypoxia, noted mainly after ascents to altitudes of 5000–6000 m, accompanied in many cases by growing discomfort. Sensations of oxygen, hotness in the head, vertigo, nausea, and appearance of a "gray film" are also noted. Switching to oxygen breathing at times for 5–10 min and longer does not lead to improvement, several functional disturbances are not recovered, and ECG indicators do not improve. Such manifestations suggest that hypocapnia sometimes makes different contributions to the genesis of this pathologic form.

The second symptom complex includes altitude fainting with symptoms of decreased intellectual capacity, loss of adequate evaluation of the immediate environment and physiologic condition, disturbance of motor coordination (handwriting disorder with clonic spasms which begin with hand muscles—writing spasms), and profound consciousness disorders including faints. These CNS disturbances are associated with increased pulmonary ventilation, sinus tachycardia, and some elevation of arterial blood pressure.

Changes in cerebral bioelectric activity are objective indicators of the development of this form of CNS hypoxic disorders [10, 50, 79, 133, 155]. The first visible handwriting disturbances and sluggishness coincide with EEG isolated and short groups of θ-waves of increased amplitude. Spasms and consciousness disturbances coincide in time with the predominant EEG of high-amplitude, slow oscillations of θ- and δ-waves [12, 79, 132].

When θ- and δ-rhythms predominate on the EEG, auditory and light signals or speech commands can temporarily suppress slow waves on the EEG, with partial recovery of work capacity and general improvement. Lack of EEG response to electrical stimuli and persistent θ- and δ-rhythms usually indicate profound consciousness disturbances [10 133].

Profound CNS disturbances develop without the victims' detection. For example, before ascent to a 7000-m altitude, subjects were instructed, in case of oxygen starvation signs, to use oxygen masks and breathe oxygen. Only two of 16 persons carried out the instructions, two other subjects noted that they were in need of oxygen, but did not use the readily available oxygen mask. The remaining 12 felt well during the entire test, despite CNS disorders—loss of consciousness and spasms.

When victims descend from altitude or breathe oxygen, there is rapid restoration of a normal physiologic state and the capacity for intellectual work (in 10–20 s). At this time, retrograde amnesia is noted—events immediately preceding loss of consciousness are not remembered, which can be puzzled out only from indirect data [9, 10, 133]. The insidious course of acute oxygen starvation led investigators to build automatic devices for signaling medical personnel that hypoxia of varying severity was developing [132, 163].

The two classifications of acute hypoxic symptoms formed the basis for an apparatus that automatically signals the development of acute hypoxia [132].

The onset of acute hypoxia in flight is a major danger, since at even relatively low altitudes (5200–6000 m), when oxygen supply is stopped, it can lead to death [9]. When acute hypoxia leads to prolonged or repeated loss of consciousness, the victims' return to normal does not always result in complete recovery. Cerebral edema resulting from hypoxia is evidently the main reason for such serious complications as encephalopathy and persistent disorders of memory and intellectual function [42].

O_2 *Protection.* Data are useful on the time required for retaining consciousness and the ability to work for periods at different altitudes without O_2 breathing, that is, when hypoxic states of different severity develop. This problem was studied pre-World War II mainly in the USSR and Germany. Soviet investigators determined generally the "altitude ceiling," that is, altitude at which disturbances of CNS activity appeared; consciousness disorders; and decreased work capacity during a continuous ascent in a pressure chamber [10, 184, 190]. German investigators introduced the concept of "reserve time," or the time during which a minimum level of work capacity adequate to take rescue measures

is still retained at the altitude after the O_2 supply has been cut off [109, 127, 156]. The term "time of useful consciousness" [8, 61] is referred to in US and British literature.

The reserve time – time of useful consciousness available at different altitudes is shown in Figure 13. Its value depends primarily on the altitude, also on individual resistance to hypoxia. With increase in altitude, individual fluctuations of the reserve time become narrower, which are virtually erased at altitudes above 9000 m [9, 186, 191]. At altitudes of 15 000 m and higher, the reserve time is practically absent (8–10 s). After rapid ascents (1–2 s) to these altitudes, whether air or pure oxygen is breathed, loss of consciousness without previous indications was noted in 15 s [9, 186].

When the time at these altitudes is limited to 8–10 s, followed by rapid descent, there is loss of consciousness in 5–7 s during the first descent – the blood with reduced O_2 content reaches the brain vessels in 5–7 s after start of the descent [127, 186]. The nearly complete absence of reserve time, similar to disappearance of the protective effect of O_2, is due to the fact that when the barometric pressure is reduced to 87 mm Hg (altitude of 15 200 m), P_{O_2} in the lungs equals zero, even if pure O_2 is breathed. The partial pressure of water vapor (P_{H_2O}) in alveolar air at body temperature (37° C) is 47 mm Hg, and P_{ACO_2} under normal conditions is close to 40 mm Hg. Thus, the overall pressure ($P_{ACO_2} + P_{AH_2O}$) is 87 mm Hg. Accordingly, the altitude of 15 200 m at which barometric pressure is

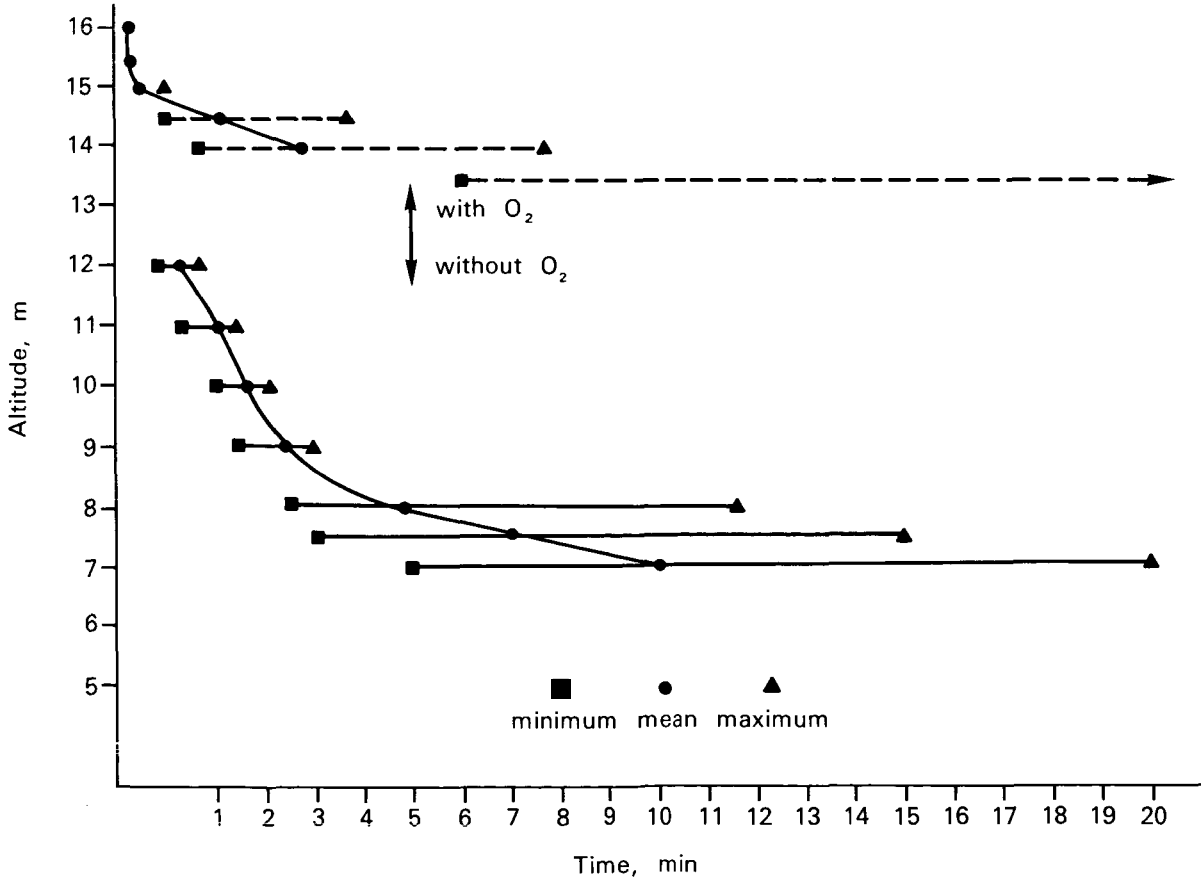

FIGURE 13. – Reserve time at altitudes of 7000–12 000 m (without using oxygen for breathing) and at altitudes from 13 000–16 000 m with O_2 breathing. (Graph plotted from [10, 186])

87 mm Hg, from the oxygen supplied to the organism, is regarded as "equivalent" to outer space.

As pressure is reduced [112, 113], the rate of deoxygenation in tissues must rise steadily, causing the reserve time to decrease also [113]. Animal experiments established that at altitudes exceeding 15 000 m, if the reserve time was shortened, it was negligible.

After cabin depressurization during space flight, an astronaut without protection of a space suit has an extremely short time (5–8 s) to evaluate the situation, reach a decision, and act on it. Severe pathologic states in acute hypoxia arise extremely rapidly—in 20–30 s. Further predictions can be based on animal experiments; animals succumbed in 1–2 min [112, 119].

In anthropoid apes, after 2–3 min in vacuum, subsequent recompression brought about recovery of a normal physiologic state [22, 106]. It is risky to extrapolate these data to predict a human's reactions under these conditions; the data only provide hope that in depressurization during flight, some time will remain for rescue.

Chronic Hypoxia

The establishment of minimum permissible P_{O_2} values in an AGA is essential to space medicine. The chronic effect of hypoxia was studied in detail in high mountain regions as well as in a pressure chamber; during moderate O_2 deficit in the inspired air, adaptive reactions developed. For this reason, after slow ascents, an individual who had previously remained at altitudes of 2000–3000 m for a number of days can remain at altitudes up to 4000–5000 m for quite a time while retaining relatively high work capability [9, 14, 15, 83]. These adaptive reactions can be conditionally divided into two groups.

One group of these reactions is directed toward increasing O_2 transport to tissues. Such reactions show hyperventilation, increased minute blood volume, and increased blood circulation in lungs and tissues, especially those sensitive to O_2 deficiency (brain and heart). There is also a rise in oxygen capacity of blood due to increased erythrocytes and hemoglobin, as well as resulting from adaptive shifts in oxygen-combining properties of hemoglobin due to increased content in erythrocytes of 2,3-diphosphoglyceric acid. Other causative factors are an increased number of functioning capillaries, as well as changes in membrane permeability leading to higher O_2 diffusion [61, 112, 132, 156, 172].

The second group of adaptive reactions is associated with restructuring of tissue metabolism including intensified glycolysis, which arises during hypoxia because the oxidative resynthesis of adenosine triphosphate (ATP) is disrupted and simultaneously ATP expenditure in tissues is increased. The functional activity of ATP rises sharply in heart, marrow, and motor musculature. This process in adaptation to hypoxia is probably limited, due to the low energy effectiveness of glycolysis. When one glucose molecule undergoes glycolytic degradation into two pyruvate molecules, only two ATP molecules are formed. In adaptation to hypoxia, the capacity of mitochondria to remove O_2 from oxygen-deprived intercellular medium intensifies, probably due to increased activity of cytochromes [14] or to their increased content [14, 141]. This type of adaptation is debatable.

The value has been shown of intensified synthesis of nucleic acids and proteins in heart and brain for adaptation to chronic hypoxia [141].

Erythropoesis increases and hemoglobin synthesis intensifies during chronic hypoxia as well as development of hypertrophy of the heart, especially of the right ventricle, indicating that protein synthesis is activated in tissues involved in the hyperfunction. The adaptational character of these reactions is obvious. When evaluating this concept of adaptation to long-acting hypoxia, it must be remembered that the synthesis of the nucleic acids and proteins intensifies in vitally important organs (in brain and heart) due to decreased importance of these processes in other tissues, including sex glands. This is evidently associated with reduced reproduction capacity and weight loss in persons at altitudes of 4000–5000 m and higher for long periods.

Study of the arrangement of villages in mountainous regions suggests that aborigines' adaptation to hypoxia is limited to altitudes of about 4500 m, which evidently is the natural limit of adaptation. Alpinists attempted to stay at an

altitude of 5800 m for many months in the Himalayas, which proved unsuccessful due to a break in adaptation. A chronic form of mountain sickness developed in spite of experienced participants in the expedition that included Hillary, who with Tensing, was the first to climb Mount Everest in 1953.

In the course of adaptation to moderate hypoxia or when it is interrupted, mountain sickness can develop. Its acute forms are manifested by: headache, dizziness, dyspnea, nausea, intestinal disorders, loss of fine coordination of movement, rapid fatigue when performing light physical work, sleepiness; and less often, euphoria, reduced intellectual capacity, and increased irritability. In chronic mountain sickness there is increasing poor health, progressive weight loss with pronounced negative nitrogen balance, sometimes acute erythrocythemia, hypertension of the lesser circulatory system, hypertrophy of heart, arterial hypotension, and sometimes reduced level of pulmonary ventilation.

In both forms of mountain sickness, symptoms of "disease adaptation" are manifested distinctly. In the acute form, there is the unfavorable effect of hypocapnia resulting from hyperventilation; in the chronic form, protein synthesis intensifies greatly in several structures, with simultaneous suppression of protein synthesis in most tissues.

Precaution against mountain sickness must be taken in designing an AGA. It is important to know when symptoms of mountain sickness can appear when there is slow reduction of P_{O_2} in the cabin.

A reduction in P_{O_2} to 120–110 mm Hg in an AGA while maintaining normal barometric pressure in the cabin is the assumed limit; exceeding this limit is not recommended. From investigations in mountains, it was noted that discomfort, especially when performing muscular work, and symptoms of mountain sickness in those in mountains for the first time, are manifested at altitudes of about 2000 m [42, 76, 142, 183].

The effect of various decompression rates simulating gas escaping from the cabin was studied; when pressure chamber pressure is reduced 0.1 m/s and less, symptoms of acute mountain sickness appear at altitudes of 4500–5000 m, that is, 8–13 h after the leakage begins. When O_2 content is reduced 1%/h in a cabin simulator with normal barometric pressure and normal air environment, followed by stabilization of P_{O_2} at 110 mm, subjects continue working satisfactorily for up to 48 h. When the P_{O_2} is stabilized in an AGA at 75–90 mm Hg, in 8–10 h most subjects experienced acute mountain sickness [140].

Individuals who have not previously been adapted to hypoxia can apparently work satisfactorily up to the second or third day only if they are in a gas medium equivalent in P_{O_2} to altitudes up to 3000–3500 m. Crewmembers in flight who perform physical work and simultaneously are in weightlessness, with its undesirable effects on the cardiovascular system and vestibular apparatus, must have an oxygen supply not lower than the level provided for an altitude of 2000 m, especially if the astronauts were not previously adapted to hypoxia.

Two of the devices for expanding human limits of adaptation to prolonged effects of hypoxia should be noted: preliminary conditioning for hypoxia in a pressure chamber or at high altitude [9, 39, 160, 190, 197, 198, 210]; and the addition of carbon dioxide gas instead of nitrogen when there is an O_2 deficit in the HEA.

The effect of adding CO_2 to the inspired gas mixture is favorable when there is acute hypoxia, which is manifested at altitudes up to 7000–8000 m [9, 112, 146, 186]. In a cabin simulator at normal barometric pressure, when the P_{O_2} in the AGA was reduced to 75–90 mm Hg, the addition of 2–3.5% CO_2 prevented acute symptoms of mountain disease, and maintained partial capacity for work up to the second day [134]. Such effects are produced by a rise in pulmonary ventilation resulting in increased oxygen saturation of arterial blood, and by partial elimination of hypocapnia. When there is irreversible reduction of P_{O_2} in a cabin AGA to approximately 1.5–2 times below the normal value, an increased CO_2 level in the AGA should be maintained—P_{CO_2} from 15 to 25 mm Hg [134].

Altitude resistance increases after conditioning in a pressure chamber, especially at high altitudes [39, 125, 160, 183, 197]. The extent of the effect is determined by the time length of con-

ditioning of subjects at certain altitudes versus stay at normal pressure. The question of how useful this conditioning can be is open for discussion.

Changes in individuals' physiologic states and work capacities for different P_{O_2} reductions in the AGA are shown in Figure 14. These data provide a general outline for evaluating the effects of hypoxia relative to the extent of manifestation.

HYPEROXIA—TOXIC EFFECT OF OXYGEN

The toxic effect of oxygen is vital to space medicine and biology since the spacecraft cabin AGA can contain a higher P_{O_2} than in atmospheric air.

Increased P_{O_2} values are used in an effort to utilize a technically most convenient one-gas medium as an AGA with sufficiently high pressure to prevent ADS, and with an O_2 reserve necessary when gas leakage from the cabin increases. This is exemplified by the AGA in Mercury, Gemini, and Apollo spacecraft where P_{O_2} was 258 mm Hg. In certain flight stages, P_{O_2} in the AGA can be much higher; for example, before transition of the crew into an AGA with lower barometric pressure for desaturation of N_2 or another inert gas. Besides planned increase of P_{O_2} in an AGA, heightened P_{O_2} in the AGA can result from improper operation of the regeneration unit.

Studies on the toxic effects of O_2 under normal

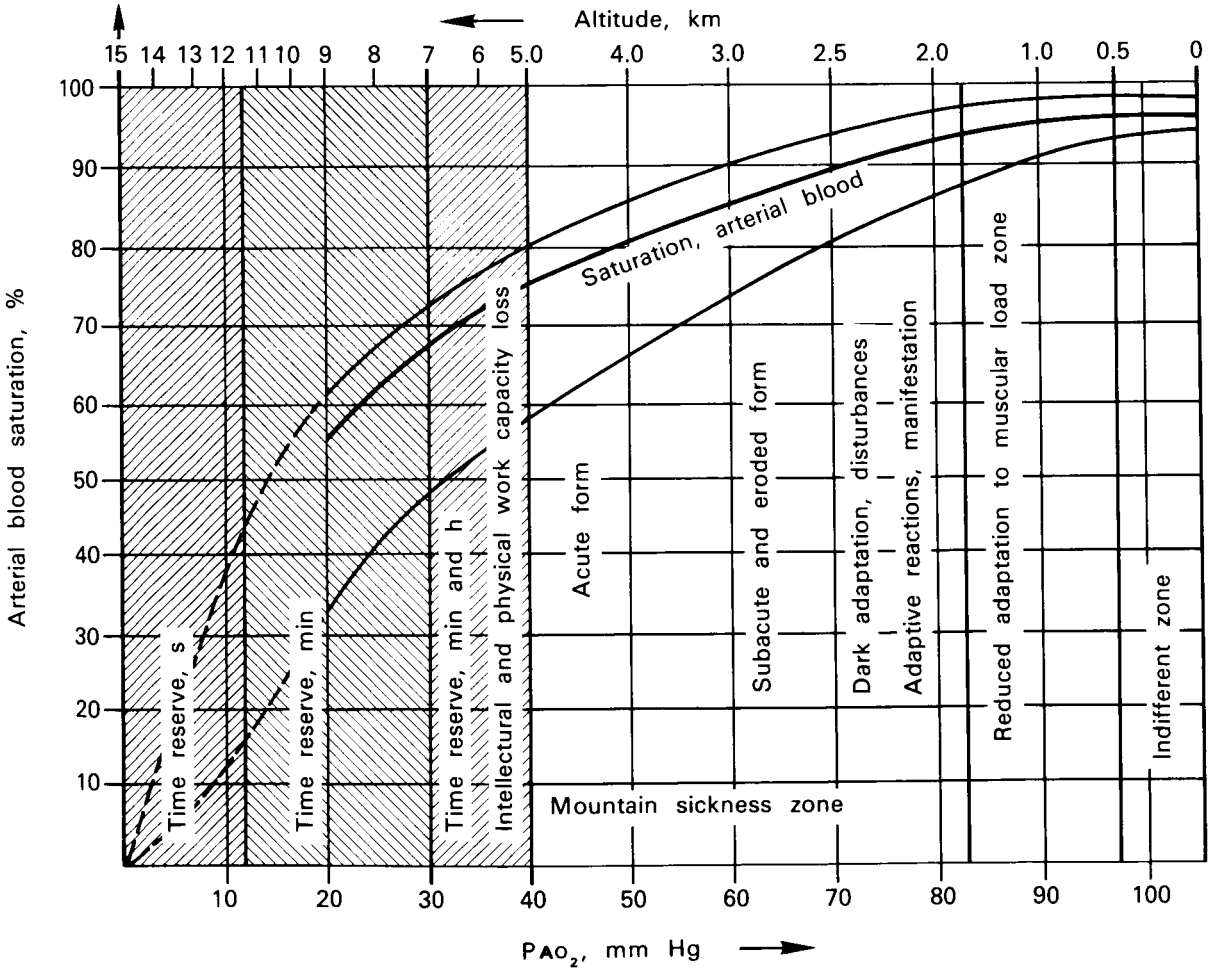

FIGURE 14.—Effects of different altitudes on a person previously unadapted to hypoxia. (After [25, 170])

or reduced barometric pressure are significant in space biology and medicine, since barometric pressure that exceeds normal atmospheric pressure will scarcely be maintained in spacecraft cabins.

An early observation in the study of O_2 toxic effects on living organisms was made by Priestley in 1775, ". . . that although dephlogisticated air can prove highly useful as a medicine, it nonetheless would not be as suitable for us in the ordinary healthy state of the body: like a candle burns faster in dephlogisticated air than in ordinary air, thus also we can live too fast and our vital forces will be too rapidly expanded in this purified air."

Experimental data on the effects of high O_2 concentrations on living organisms were presented by Bert in 1878 [30], who concluded that O_2 in high concentrations is a "general-protoplasmic" poison, exerting a toxic effect on plant and animal cells. This hypothesis was later confirmed [44, 63, 78, 87, 102, 122, 215]. In spite of many years' study of the toxic effect of O_2, information is still inadequate on biochemical changes determining symptoms of oxygen intoxication. Chance et al [44] noted changes in the oxidation-reduction state of reduced nuclear pyridine, and the energetic pathway of pyridine nucleotide reduction in mitochondria of rat liver and guinea pig heart. The oxidation of enzymes or coenzymes containing SH-groups are assumed to be important in the toxic effect mechanism of O_2 at the cellular level, which may be associated with earlier injury when cellular membranes undergo hyperoxia.

Experiments with enzymes containing SH-groups being inactivated in vitro (such as succinic dehydrogenase) are not always confirmed by experiments conducted in vivo. Most enzymes in the organism are evidently protected against the toxic effect of O_2 by their own substrate-coenzymes and other compounds that are permanently in cells [87, 122, 215]. It has remained unclear whether the mechanism of the O_2 toxic effect on a cell includes the influence of O_2 molecules as such, or whether it is associated with the effect of other free radicals produced during hyperoxia.

The mechanism of the O_2 toxic effect is attributed by many to free radicals, which evidently form H_2O_2 and organic peroxides, breaking intramolecular bonds of enzymes containing sulfhydryl groups [78, 87, 102, 215]. This hypothesis is based on increased formation of free radicals in the animal tissue and hyperoxia, and on the possibility of reducing the O_2 toxic effect, in particular, injury to erythrocyte membranes, by administering antioxidants (mexamine, tocopherol—vitamin E, and so on) to inhibit the action of free radicals [100, 101, 102, 215].

Symptoms of the O_2 toxic action, to be understood, require knowledge of the action mechanism of hyperoxia in various organic functional systems. Figure 15 of the Lambertsen scheme, modified according to studies [78, 102, 215], illustrates the mechanisms of O_2 toxic action on animals and humans.

Investigations with humans and animals established that O_2 toxic action depends on the P_{O_2}, length of time in the hyperoxic medium, and sensitivity of animal and man. The latent period of manifesting the O_2 toxic effect differs for various tissues and also depends on P_{O_2}.

Relative to P_{O_2} in the AGA, there are three zones with different manifestation of O_2 toxic action.

1. When O_2 is 1500–2000 mm Hg and higher, symptoms of poisoning are manifested, typical of attack on the CNS: nausea, dizziness, visual disturbances, and local and generalized clonic spasms. There are pathologic changes in blood circulation and respiration. Thus, Wood et al [205] discovered a sharp rise in arterial pressure in animals subjected to hyperbaric pressure, evidently of neurogenic origin; cardiac insufficiency with pressure rise in lesser circulation vessels, also probably the cause of primary disturbance of the pulmonary capillaries structure and subsequent acute pulmonary edema.
2. When P_{O_2} is 760–400 mm Hg, the O_2 toxic action is primarily an attack on respiratory organs: irritation of the upper respiratory tracts, including bronchitis, then pulmonary inflammation and edema.
3. For P_{O_2} of 400–280 mm Hg, prolonged stay in an AGA can evidently cause

changes in respiratory organs, blood, and lymph tissues.

Considering astronautic activity, it is important to determine the maximum permissible P_{O_2} at which the O_2 toxic effect is not yet manifested, for setting standards of O_2 content in AGA. When animals remain in virtually pure oxygen under normal barometric pressure, they die from pulmonary inflammation.

White rats, which are highly sensitive to the toxic action of O_2, were tested to establish the morphologic change sequence in lungs during different periods in the hyperoxic AGA. When P_{O_2} was 1 atm, the animals showed: atelectasis—in 1 h; disturbances of capillary structure and changes in their permeability—in 3 to 6 h; pulmonary edema, thickening of alveolar membranes, enlarged capillaries, and diapedetic hemorrhages—during the first day; pulmonary hyperemia and foci of inflammation—in 1.5 d; further inflammation, leading to "hepatization" of lungs—in 2–2.5 d [105, 111, 153].

Pulmonary inflammation resulting from hyperoxia is assumed to lead inevitably to hypoxia, culminating in death [13, 122, 153]. Genin et al dispute this view [72]; they detected high O_2 tension in cerebral tissues of animals during development of severe hyperoxic toxicosis along with pulmonary inflammation.

Pathologic changes in lungs of rats depend mainly on P_{O_2} in the AGA. An animal which was exposed to pure oxygen developed inflammation in lungs by the second or third day; when O_2 content in the AGA was reduced to 75% (P_{O_2}= 570 mm Hg), the lung inflammation was noted after 2–3 weeks, and in 50–60% O_2 content in the AGA, no lung damage was detected in spite of 30 days spent in this medium [13, 38, 43, 111, 215].

When P_{O_2} increases slightly in the AGA, the primary toxic effect is pulmonary atelectasis [130, 136]. This was concluded from experiments with rats exposed to an AGA consisting almost entirely of O_2 under reduced barometric pressure. The atelectases led to the death of several animals.

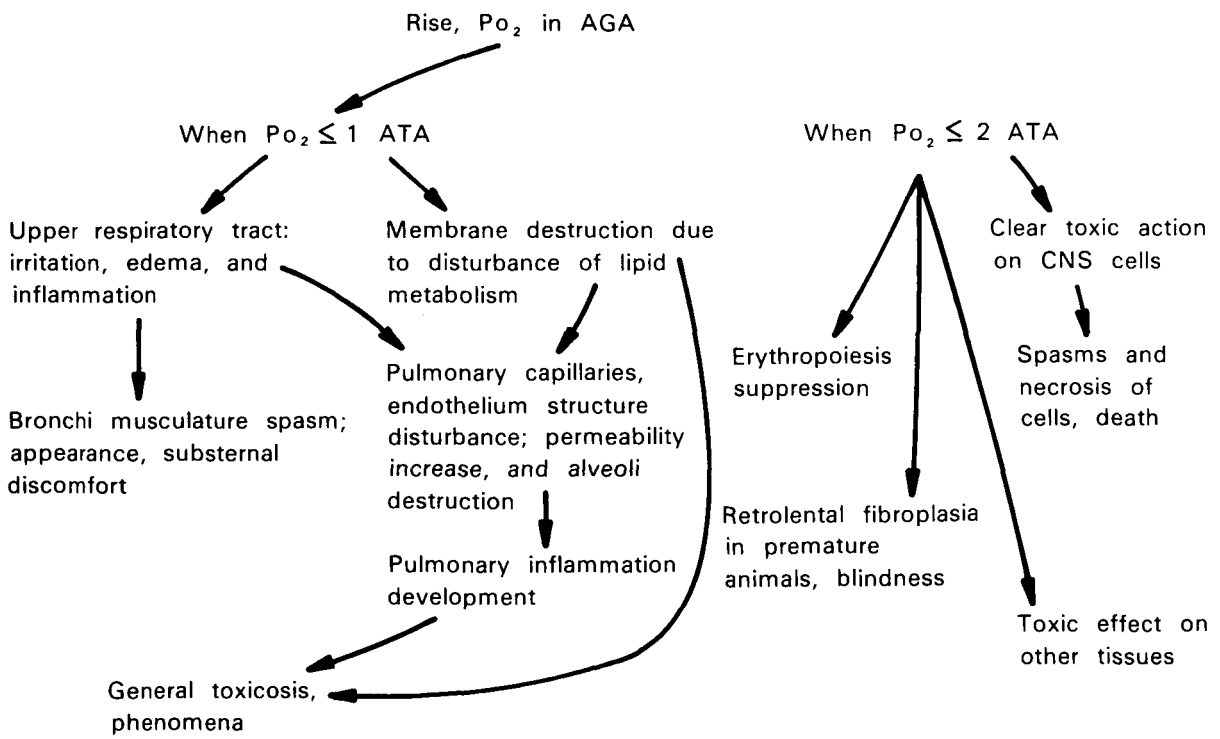

FIGURE 15.—Mechanism of oxygen toxic action on humans and animals. (After [122] modified)

Atelectases developed also in humans breathing pure oxygen [13, 59, 73], caused by mucus congestion in the smaller bronchi. This causes the O_2, from the alveoli associated with the congested bronchus, to diffuse rapidly into the blood. The rate of alveoli collapse depends on the chemical composition of the gases filling them; collapse is slowed when N_2 and other inert gases are present. DuBois et al [59] noted individual differences in predisposition to atelectases, which they attributed to dissimilar patency of air passages.

It is not established that pulmonary atelectases are associated primarily with the toxic effect of O_2; it probably develops from the absence of N_2 gas or another inert gas in alveoli. When elevated P_{O_2} values persist in the AGA, addition of a small amount of a biologically inert gas to the AGA prevents pulmonary atelectases [59, 61, 180, 215]. It was noted in animal experiments that toxic effects of O_2 can develop into "oxidative" and hemolytic anemia, which evidently results from the accelerated breakdown of erythrocytes and simultaneous suppression of hemopoiesis.

In morphologic investigations, changes in red cell growth were noted in animals and man in hyperoxic AGA, indicating suppression of erythropoiesis. Changes were also detected in erythrocyte structure—appearance of sickle-shaped evaginations—acontocytosis, providing grounds to conclude that damage to erythrocyte membranes, like suppression of erythropoiesis, is caused by O_2 toxic action. Administering an antioxidant—vitamin E—prevented damage to erythrocytes [100, 101]. These data apparently were confirmed somewhat in humans; when astronauts completed Gemini 4, 5, and 7 flights, a reduction of hemoglobin and erythrocyte content in peripheral blood was noted [29, 65]. In spite of these results, there are not yet adequate grounds to associate anemia only with the toxic effect of oxygen. Its onset can be caused by the effects of other flight factors as well.

It has also been stated that when there is a slight rise in P_{O_2} (300 mm Hg), the toxic action of O_2 leads to suppression of the immunity system, causing pathologic changes in lymph tissues [103, 161].

The maximum permissible O_2 concentrations, establishing the upper limit of P_{O_2} in AGA where man and animals may remain for long periods, has not been adequately studied. Before hyperoxic AGA was used in spacecraft cabins (P_{O_2}= 258 mm Hg), its effect on animal and human organisms was studied by US investigators [38, 90, 145, 202]. The studies (one lasting 8 months) permit the conclusion that remaining in an AGA with P_{O_2}=258 mm Hg does not cause profound pathologic disturbances, but probably has some unfavorable effects; periodic morphologic changes in internal organs of animals have been noted [101]. The same conclusion was reached in mice experiments conducted with Gramenitskiy. After 23 days in an AGA with P_{O_2}=260–280 mm Hg and a total pressure of 720 mm Hg, experimental animals, not differing visibly from the controls, succumbed much faster than the controls when placed subsequently in a hyperbaric medium of 4 atm with 98% O_2 content. An autopsy revealed acute hyperemia and pulmonary edema.

Functional Changes

To evaluate the significance of changes in various functional systems during hyperoxia, and to set up means of increasing resistance, the mechanism of the O_2 toxic effect must be understood as well as if there is adaptation to this factor, and its manifestations. This problem is still in the initial stage of study.

Adaptational shifts were studied in animals remaining for a long time in an AGA with elevated P_{O_2}. Animals were placed in an AGA with elevated P_{O_2} followed by prolonged exposure to virtually pure O_2 at a pressure of 760 mm Hg. The results were not well-defined: increased lifespan was noted in the conditioned animals, while in others a reliable effect was absent, nor were acute manifestations of the O_2 toxic action noted in the conditioned animals [11, 83, 215].

The functional state of the adrenal glands is important in the mechanism of nonspecific adaptation to various unfavorable factors. On the question of adaptation to hyperoxia resulting from nonspecific adaptational reactions, investigations are significant on the effect of O_2 toxic action in animals with adrenals removed. The

results of these investigations are contradictory. When high O_2 pressures were used (3 atm and higher), increased resistance to hyperoxia was noted in adrenalectomized animals [18, 81]. But in another study [135], there was depressed resistance to hyperoxia in adrenalectomized rats exposed to an AGA with Po_2 of 690–720 mm Hg. Toxicity associated with lung damage was manifest in the operative animals earlier, and progressed to a more severe form than in intact animals.

In normobaric hyperoxia, in contrast to hyperbaric hyperoxia, the mechanism of nonspecific adaptation plays a definite role. Differences in the mechanism of O_2 toxic action at high oxygen pressures and with normal barometric pressure also evidently determine the different effects of adrenalectomy. From a generalization of the literature, animal and human organisms exhibit adaptive reactions to normobaric hyperoxia, but with low effectiveness.

Information on the toxic action of hyperoxia is important in AGA design. Considerations of this matter are difficult because precise criteria for O_2 toxic action are lacking; i.e., symptoms indicating that continuing in a hyperoxic medium will endanger health. The question is further complicated by differences in individual resistance to hyperoxia, and other flight factors that influence resistance to hyperoxia.

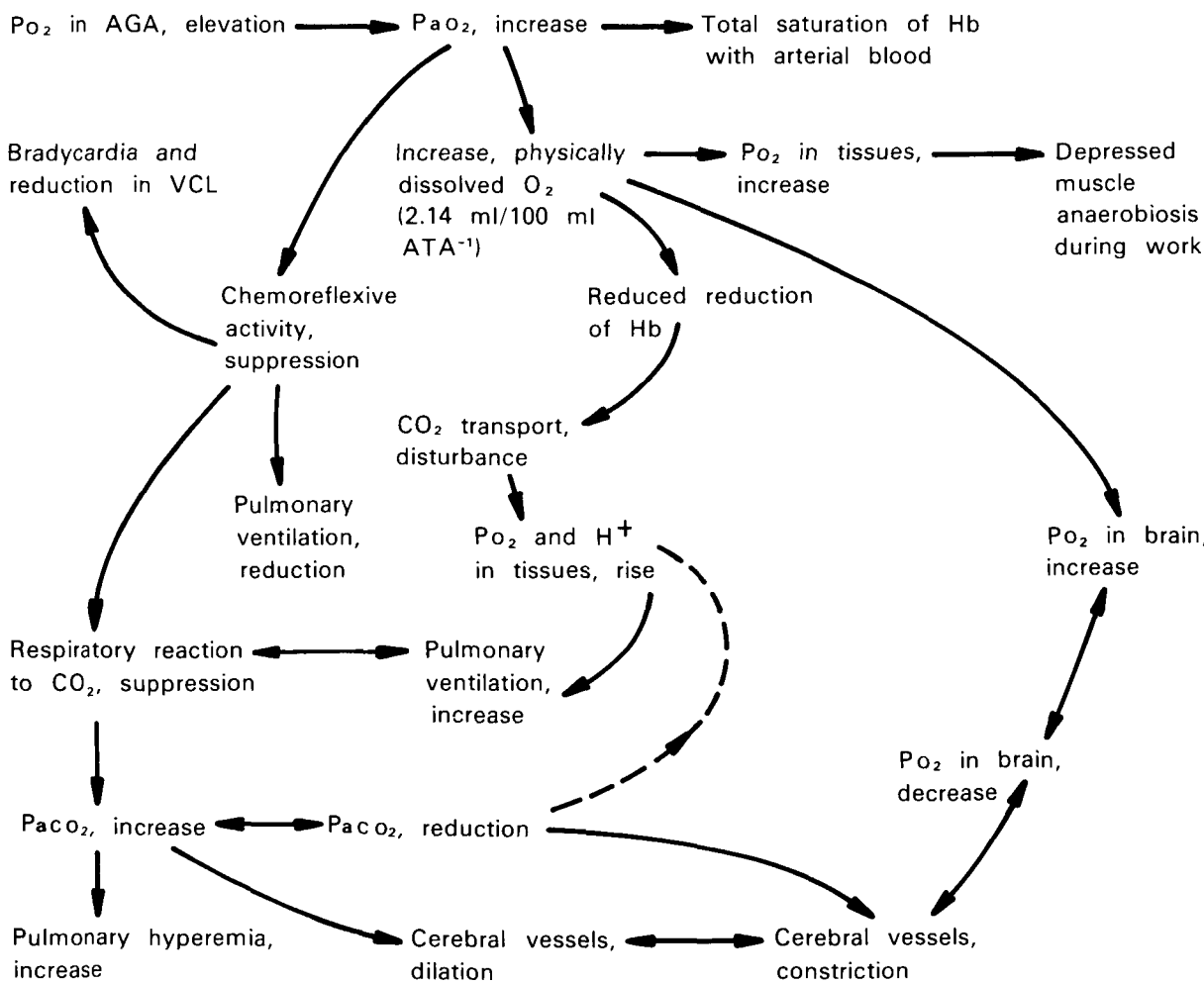

FIGURE 16.–Physiologic shifts on hyperoxia. (After [122])

The physiologic and pathophysiologic mechanisms of the hyperoxic effect on the human organism must be clarified to substantiate earlier criteria on manifestation of O_2 toxic action. Figure 16 shows diverse reactions to hyperoxia, some of which must be considered adaptive since they tend to reduce O_2 transport to tissues. This involves decreased pulmonary ventilation, heart rate, reduced minute blood volume, and narrowing of cerebral vessels. Such reactions start during the first minutes in a hyperoxic medium [47, 75, 215]. Some reactions (decreases in heart rate and minute blood volume) persist for almost the entire time spent in the AGA with elevated P_{O_2}, others gradually disappear. In the initial period of hyperoxia when subjects breathe pure oxygen under normal barometric pressure, pulmonary ventilation is reduced an average 10%, evidently due to inactivation of chemoreceptors in the sinocarotid zone [75, 122, 215]. This effect persists until there is a gradual rise in pulmonary ventilation. This increase is due to retention in tissues of CO_2 produced from reduced transport by blood, which is associated with less content of reduced hemoglobin in blood.

A decrease in vital capacity of the lungs (VCL) during hyperoxia is a significant symptom for early diagnosis of O_2 toxic action. A 20–30% reduction or more in VCL indicates pronounced toxic action of O_2. Such a significant drop usually develops immediately before chest pains or when subjects have chest pain during deep inspiration; that is, during pronounced development of oxygen intoxication.

Since pulmonary pathology is the most important factor limiting man's remaining in AGA with added P_{O_2}, gas exchange parameters and biophysiology of lungs, such as diffusion capacity and extensibility, should help in early diagnosis of O_2 toxic action.

Data are limited and contradictory on changes in the diffusion capacity of lungs (D_L) in hyperoxia. Some authors find no changes in this indicator when several hours are spent in an O_2 medium with pressure of 1 atm; there are also studies establishing decreased D_L while in this kind of AGA. A decrease in an individual's D_L was evident 3 h after he began breathing pure oxygen under normal barometric pressure. A clear reduction in D_m was detected, indicating that this was caused by changes in permeability of lung membrane [25].

Genin [70] also noted progressive reduction in D_L during 24 h O_2 breathing at 1 atm pressure, beginning the 8th hour. In several subjects, in 24 h, D_L reduction was 12%. No reliable correlation was established between this indicator and manifestation of O_2 toxic action. A reduction in extensibility of lungs was also noted, averaging 16%. Extensibility of lungs is an integral indicator, which depends on the elastic properties of the pulmonary parenchyma, condition of hyperemia in lungs, and surface tension of the liquid film underlying the alveoli. Evidently, reductions in extensibility of lungs and in the VCL during hyperoxia are associated with development of atelectases and, possibly, with increased hyperemia of lungs. Thus, changes in D_L and extensibility of lungs can have significance in evaluating O_2 toxic action, but it is difficult to use this indicator in practice.

Clinical Symptoms

Clinical manifestations of O_2 toxic action include coughing, dryness in mouth, and thoracic pain, which indicate pronounced oxygen intoxication. The symptoms, especially the chest pains, usually are signals to end the investigations. This is because chest pains, after starting, usually intensify and are accompanied by pains in intercostal muscles, dyspnea, and worsening of the subject's general condition [47, 75, 202]. Chest pains and substernal discomfort are associated with atelectases, and possibly with bronchial spasm. The bronchial mucosa is probably involved also.

Chest pains are often preceded by irritation of the upper respiratory tracts: dryness in the mouth, tickling in the nasopharynx, and coughing. In 6 to 12 h after the investigation and removal from the hyperoxic medium, these phenomena and chest pains disappear completely. However, irritation of the upper respiratory tracts should be heeded since this manifestation has preceded acute tracheobronchitis and pulmonary inflammation [20, 75].

When P_{O_2} in the AGA is elevated (up to 1 atm),

individual differences are noted in sensitivity to O_2 toxic action [59].

When oxygen was breathed (1 atm) for 24 h [75], O_2 toxic action was not noted in all subjects; the observations were made at different intervals. Figure 17 shows the incidence and time of upper respiratory tract irritation and chest pains [75].

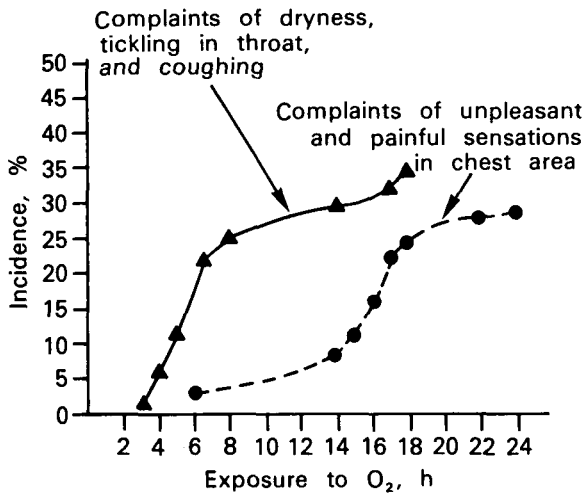

FIGURE 17.—Dynamics of various oxygen toxic action symptoms during 24 h of oxygen breathing. (After [75])

Individual differences in manifestation of O_2 toxic action are probably the reason for discrepancies in the literature on the limit to O_2 toxic manifestation. For example, Genin, Zharov, et al [72] did not detect symptoms of O_2 toxic action after 30 days in an AGA with P_{O_2} equal to 290–280 mm Hg, while Welch [202] found O_2 toxic action during less time in an AGA with lower P_{O_2} (200 mm Hg). Such individual differences in sensitivity to hyperoxia make it difficult to determine the maximum permissible O_2 content in cabin AGA for long flights.

P_{O_2} in AGA

The time when O_2 toxic action appears depends on P_{O_2} in the AGA and it decreases as O_2 increases. Figure 18 shows the time and nature of O_2 toxic action manifestation for different P_{O_2} values in the AGA. Remaining in an AGA with slightly elevated P_{O_2} (200 mm Hg) for 220 h can lead to toxic action of oxygen in some individuals [202]. Since some individuals have high sensitivity to O_2 toxic action, an AGA with P_{O_2} exceeding its value in atmospheric air can scarcely be considered for flights of many months [75, 215]. The causes of different individual sensitivities to hyperoxia have not been adequately studied; there are no reliable criteria for selecting highly sensitive persons, nor are there agents to increase resistance.

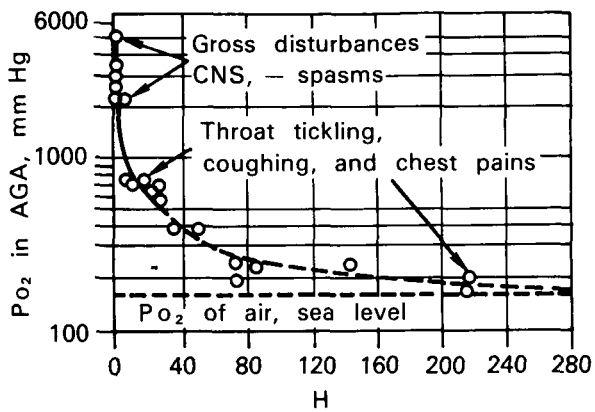

FIGURE 18.—Time of oxygen symptoms toxic action as a function of P_{O_2} in AGA [170].

Thus, the upper limit of P_{O_2} in AGA for flights of many months has not yet been determined. However, studies of O_2 toxic action suggest that the limit to the toxic action decreases steadily, and at present it can only be determined hypothetically in the range of P_{O_2} values in AGA, at which P_{AO_2} increases approximately 150 to 200 mm Hg.

Additional information must be obtained to establish precisely the upper limit of the P_{O_2} in an AGA. There are no data on the influence of physical labor on resistance to hyperoxia, the effects of increase and decrease in ambient temperature, and other flight factors.

When flights in high-radiation zones are necessary and whenever crewmembers may be exposed to ionizing radiation, an elevated P_{O_2} in the AGA probably would prove undesirable. This is based on animal experiments where increased sensitivity to ionizing radiation was established during a hyperbolic AGA [170, 215].

To explain this effect, there is a certain similarity between the mechanism of O_2 toxic action on tissues and the mechanism of ionizing radiation toxic action on tissues.

Thus far we have not discussed the question of whether the sensitivity of an organism to increased O_2 content in an AGA can be affected by such an important flight factor as weightlessness. There are reasons to assume that weightlessness, just like physical labor, or temperature influences, can lead to some elevation in an organism's sensitivity to hyperoxia. One of the adaptive reactions in hyperoxia is constriction of brain, heart, and lung muscles to reduce oxygen transport to tissues of these organs. In weightlessness, there is a blood flow redistribution, and an increase in hyperemia of areas above the heart, hence the above-noted adaptive vascular reactions probably cannot be fully manifested.

In prolonged flights, besides man, plants and various species of animals will be present that may prove highly sensitive to hyperoxia. Accordingly, information is needed on O_2 toxic effects on plant and animal species for use in flights.

HYPERCAPNIA–CO_2 TOXIC EFFECT

During space flights, emergency situations reducing the effectiveness of the AGA regeneration system cannot be entirely avoided. Carbon dioxide in the AGA can increase at different rates to different levels, hence study of its toxicity on the human organism is essential for space biology and medicine.

Man is the source of CO_2 in the gas medium of a hermetic cabin since CO_2 is one of the main end products of metabolism in animal and human organisms. At rest, man gives out about 400 l CO_2/d; during physical labor, CO_2 and its corresponding excretion from the organism is considerably higher. In addition, CO_2 is continuously formed during rotting and fermentation. Carbon dioxide gas is colorless, has a faint odor, and acidlike taste. When several percent of CO_2 accumulate in the AGA, it cannot be detected by man. Its properties (odor and taste) can be detected only at extremely high concentrations of the gas.

Breslav [37] showed that subjects exposed to a "free choice" of gas medium began to avoid an AGA only when P_{CO_2} in it exceeded 23 mm Hg. Here the CO_2 detection is not associated with odor and taste, but with the effect on the organism, especially a rise in pulmonary ventilation and reduction in physical work.

The terrestrial atmosphere contains a small amount of CO_2 (0.03%) from turnover of matter. A tenfold increase of CO_2 in inspired air (to 0.3% [sic]) does not yet have a marked effect on human vital activity and work capacity [83, 138, 179]. Man can exist in this gas medium for a very long time, maintaining normal health and a high work level. This is due to CO_2 formation in tissues during vital activity. The gas is subjected to significant fluctuations, exceeding by tenfold changes of this compound in inspired air. A substantial increase of P_{CO_2} in an AGA causes predictable changes in physiologic state; these changes are due mainly to functional shifts in the CNS, respiration, blood circulation, acid-alkaline equilibrium, and disturbances in mineral metabolism. The functional shifts during hypercapnia are determined by the level of P_{CO_2} in the inspired gas mixture and its action time on the organism.

Acute Hypercapnia

Bernard showed that severe pathologic states in animals, after being in hermetically closed, unventilated rooms for a long time, are associated with CO_2 increase in inspired air. The physiologic and pathologic action of CO_2 was studied in animal experiments [28].

A physiologic mechanism of the hypercapnia effect is evident in Figure 19.

When remaining in AGA where the P_{CO_2} reaches 60–70 mm Hg and higher, physiologic reactions and CNS reactions change appreciably. With CNS changes (besides the stimulating influence shown in Figure 19), hypercapnia has a sedative action and leads to a narcotic state which develops rapidly when P_{CO_2} reaches 100 mm Hg and higher.

Intensified pulmonary ventilation, when the CO_2 in an AGA rises to 10–15 mm Hg and above, is determined by at least two mechanisms:

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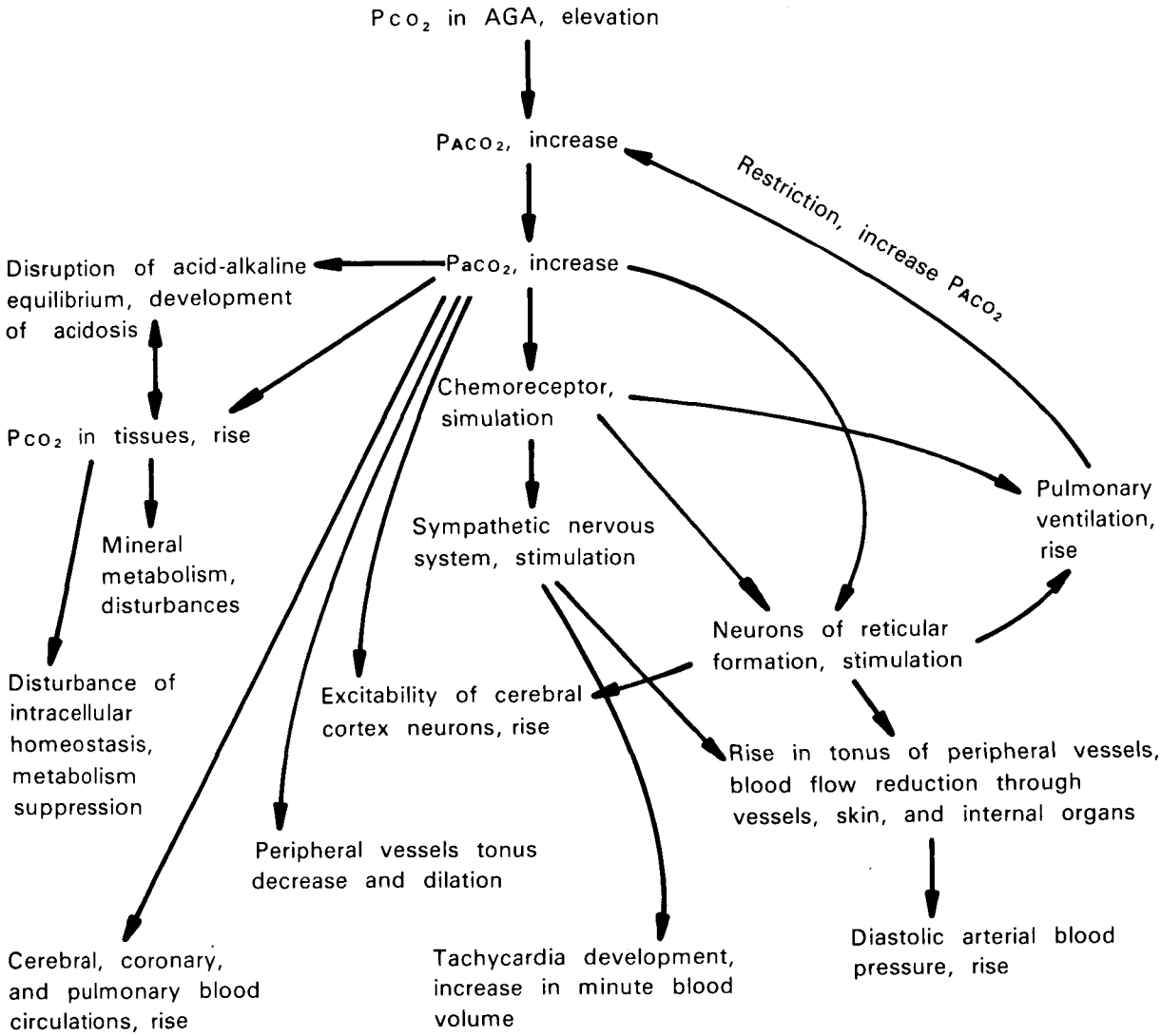

FIGURE 19.—Mechanisms of physiologic and pathophysiologic action of CO_2 on animals and humans.

reflexive stimulation of the respiratory center with vascular zone chemoreceptors (especially those of the sinocarotid zone), and stimulation of the respiratory center with central chemoreceptors. The main adaptive organism reaction maintaining the P_{aCO_2} at a normal level is increased pulmonary ventilation during hypercapnia. Effectiveness of this reaction diminishes as P_{CO_2} is increased in the AGA, since, in spite of the steadily intensifying pulmonary ventilation, P_{aCO_2} also rises steadily.

Increased P_{aCO_2} has an antagonistic effect on central and peripheral mechanisms regulating vascular tonus. The stimulating action of CO_2 on the vasomotor center and the sympathetic nervous system determines the vasoconstrictive action and leads to increased peripheral resistance, quickened heart rate, and increased minute blood volume. Simultaneously, CO_2 has a direct effect on vessel muscle walls, promoting their dilation. Interaction of these antagonistic influences then determines ultimately cardiovascular system reaction during hypercapnia. It can be concluded that upon a sudden drop in

the central vasoconstrictive action, hypercapnia can lead to collaptoidal reactions, which have been observed in animal experiments at a considerable CO_2 elevation in AGA [138].

When there is a great P_{CO_2} increase in tissues, which inevitably develops at a considerable P_{CO_2} elevation in AGA, a narcotic state accompanies a drop in metabolism. This reaction can be considered adaptive, because it sharply reduces CO_2 formation in tissues during the period when the transport systems, including the blood buffer systems, are no longer able to sustain Pa_{CO_2}—the most important constant of the internal environment at a near-normal level.

The threshold of the reactions of various functional systems differ in the development of acute hypercapnia. Thus, hyperventilation becomes evident when P_{CO_2} in the AGA is raised 10–15 mm Hg, and at 23 mm Hg, this reaction is pronounced—ventilation increases nearly twofold. Tachycardia and elevated arterial blood pressure are manifested when P_{CO_2} in the AGA reaches 35–40 mm Hg. Narcotic action was at still higher values of P_{CO_2}, 100–150 mm Hg, in the AGA while CO_2 stimulation on cerebral cortex neurons was noted when P_{CO_2} was 10–25 mm Hg. Effects of various P_{CO_2} levels in the AGA on the organism of a healthy individual can be examined.

When practically healthy persons were in AGA with excess P_{CO_2} levels, the investigations were highly significant in evaluating resistance of an individual's hypercapnia and in setting CO_2 standards. The nature and dynamics of reactions of CNS, respiration, and blood circulation were established, as well as changes in work capacity at different P_{CO_2} levels in the AGA.

No appreciable shifts in physiologic state were found, despite slight respiratory acidosis, when an individual was in AGA with P_{CO_2} to levels of 15 mm Hg for relatively short intervals. Persons retain normal intellectual work capacity and do not complain of deteriorating condition when in such an environment for several days. Some subjects showed reduced physical work capacity, especially when performing heavy work, when the P_{CO_2} was 15 mm Hg.

Increased P_{CO_2} in the AGA to 20–30 mm Hg caused respiratory acidosis and increased pulmonary ventilation. After a relatively short rise in the rate at which psychologic tests were performed, reduced intellectual work capacity was observed. The ability to perform heavy physical work was markedly diminished and there was disturbance in night sleep. Subjects complained of headaches, dizziness, dyspnea, and lack of air sensation on performing physical work [131, 180].

When P_{CO_2} in the AGA was raised to 35–40 mm Hg, pulmonary ventilation of subjects increased three times and higher. Functional shifts appeared in the circulatory system: the heart rate and arterial pressure increased. Subjects complained of headache, dizziness, vision disturbance, and loss of spatial orientation after brief periods in this AGA. Performing even light physical work involved considerable difficulties and led to acute dyspnea. Psychologic tests proved difficult, and intellectual work capacity diminished. When P_{CO_2} in the AGA was raised above 45–50 mm Hg, acute hypercapnic disorders arose rapidly—in 10 to 15 min [42, 46, 131].

Generalization of data is difficult on man's resistance to CO_2 toxic action and the maximum permissible time in an AGA with increased CO_2 content. An individual's resistance to hypercapnia depends largely on his physiologic state and the level of physical work. Investigations were mostly with subjects at rest and psychologic tests were performed only periodically.

Zones of Hypercapnia Toxic Action

Based on studies, four zones of hypercapnia toxic action in relation to P_{CO_2} level in the AGA (Fig. 20) have been suggested.

The P_{O_2} rate of increase in the inspired gas mixture is vital to physiologic reactions and resistance to hypercapnia. When placed in an AGA with a high P_{CO_2} level, just as when the individual is switched to breathing a gas mixture enriched in CO_2, Pa_{CO_2} rises rapidly accompanied by more acute hypercapnic disorders than when P_{CO_2} in the AGA is slowly elevated. Fortunately, the latter is more characteristic of a CO_2 toxic effect under spaceflight conditions, since the increasing volume of spacecraft cabins permits a relatively slow rise of P_{CO_2} in the AGA whenever the air regeneration system breaks down. More acute hypercapnia can occur

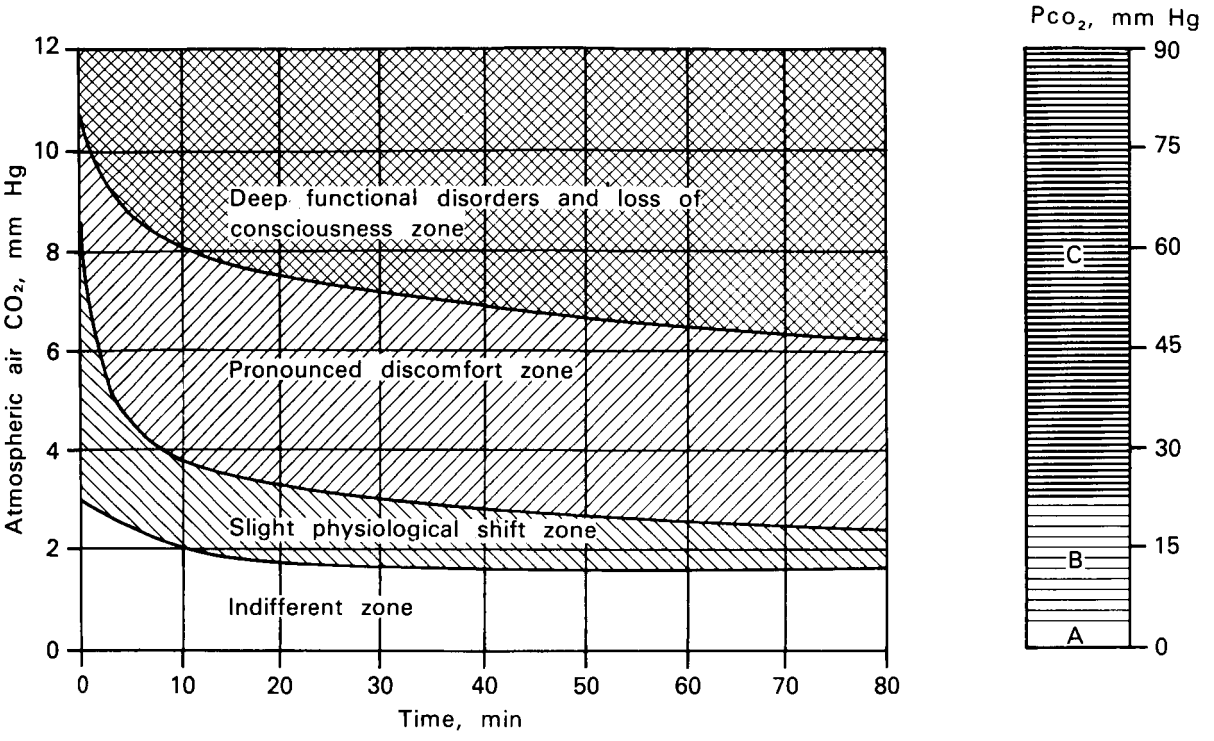

FIGURE 20.—Classification of CO_2 toxic action effects in relation to P_{CO_2} value in AGA. (Graph plotted from [25])

when the space suit regeneration system malfunctions. In acute hypercapnia, the difficulty of precisely delimiting the zones determining the qualitatively different manifestations of CO_2 toxic action, relative to P_{CO_2}, is associated with "primary adaptation" phase, the duration of which is the longer, the higher the CO_2 concentration [131]. After an individual's rapid entry in an AGA with a high CO_2 content, pronounced shifts develop in the organism, which are usually accompanied by complaints of headache, dizziness, spatial orientation loss, vision disturbance, nausea, lack of air, and chest pains. Hence, investigation is often discontinued 5 to 10 min after the subject has entered the hypercapnic AGA.

When P_{CO_2} in the AGA is raised to 76 mm Hg, this unstable state gradually passes and a seemingly partial adaptation to the altered gas medium develops [131]. Some normalization of intellectual work function is noted in subjects who complain less of headaches, dizziness, visual disturbances, and so forth. Duration of the unstable state is determined by the time during which P_{aCO_2} increases and continuous rise in pulmonary ventilation is noted. Soon after stabilization at the new level of P_{aCO_2} and pulmonary ventilation, a true adaptation begins, accompanied by improved well-being in the general state of subjects. Considerable deviations in evaluation by different investigators of possible time limit of man under high P_{CO_2} in the AGA is caused by the dynamics of acute hypercapnia.

Unfortunately, in evaluation of various P_{CO_2} level effects (Fig. 20), "primary adaptation," although recorded in time, still does not show that the physiologic state of an individual differs in different periods in an HEA with high CO_2. The results shown in Figure 20 were obtained while subjects were resting. Accordingly, these data, without appropriate correlation, cannot be used to predict physiologic changes of astronauts when CO_2 accumulates in the AGA, because it may be necessary in flight to work physically at different intensity levels.

It was established that an individual's resist-

ance to CO_2 toxic action decreases with increase in physical work. Accordingly, studies of CO_2 toxic action on practically healthy persons working physically at different intensity take on vital importance. There are few reports in the literature, so this problem needs further study. Nonetheless, based on available data [42, 80, 131, 138, 142, 180, 210] it is possible to approximate the length of time and varied physical work in an AGA relative to its P_{CO_2}.

When the P_{CO_2} is raised to 15 mm Hg, prolonged heavy physical work proves difficult, according to Table 6. When the P_{CO_2} is raised to 25 mm Hg, even moderate work is limited and heavy work is difficult; when the P_{CO_2} is raised to 35–40 mm Hg, light work is restricted. When the P_{CO_2} is raised to 60 mm Hg and higher, the individual at rest could remain in this AGA for some time, although he is incapable of work. The best way of removing the adverse effect of acute hypercapnia is to place victims in "normal" atmosphere.

The rapid transition from long periods in AGA with elevated P_{CO_2}, to breathing pure oxygen or air often causes deterioration of their well-being and general state. This phenomenon, expressed in acute form, was first detected in animals by Albitskiy [4], who termed it the reverse CO_2 effect. When hypercapnic syndrome develops, individuals must be gradually removed from CO_2-enriched AGA by reducing its P_{CO_2} [42, 138, 168]. Attempts to weaken the hypercapnic syndrome by administering alkalis, such as tris-buffered soda, did not give stable, positive results, in spite of partial normalization of blood pH [42].

The study of an individual's physiologic state and work function is significant when breakdown of the regeneration unit in an AGA will reduce P_{O_2} simultaneously with a rise in P_{CO_2}.

When breathing in a closed, small volume, there is a considerable CO_2 increase and a corresponding O_2 decrease [83]; this leads to abrupt deterioration of physiologic state and well-being when CO_2 in the inspired gas mixture is raised to 5–6% (P_{CO_2} = 38–45 mm Hg), even though O_2 reduction during this time is relatively small. A slow development of hypercapnia and hypoxia causes appreciable disturbances of work function and deterioration of the physiologic state when P_{CO_2} is raised to 25–30 mm Hg with a corresponding drop in P_{O_2} to 110–120 mm Hg. According to Karlin et al [170], in the third day of exposure to an AGA containing 3% CO_2 (22.8 mm Hg) and 17% O_2, the work function is markedly reduced. These data contradict results showing relatively small changes in work function even for considerable (up to 12%) O_2 decrease and a CO_2 increase to 3% in the AGA [134].

In simultaneous development of hypercapnia and hypoxia, dyspnea is the main symptom of toxic action. Pulmonary ventilation proves more significant than in equivalent hypercapnia. Such a significant rise in pulmonary ventilation is determined by hypoxia-elevated CO_2 sensitivity of the respiratory center, as a result of which the combined action of excess CO_2 and O_2 deficiencies in the AGA does not lead to an additive effect, but to synergism. Hence pulmonary ventilation is higher than the ventilation level that would have occurred with simple addition of the effects from reduced P_{AO_2} and increased P_{ACO_2}.

It can be concluded from these data and disturbances in the physiologic state that hypercapnia is dominant in the development of pathologic states when the regeneration system breaks down fully.

Chronic Effects of Hypercapnia

Study of the prolonged effect on humans and animals of elevated levels of P_{CO_2} in AGA established that clinical symptoms of chronic CO_2 toxic action is preceded by regular changes in the acid-alkaline equilibrium—development of respiratory acidosis leading to metabolic disturbance. Shifts occur in the mineral metabolism and evidently are adaptive, since the acid-alkaline equilibrium is preserved. These changes can be judged from the periodic rise of blood calcium and from changes in the marrow calcium and phosphorus. Calcium combines with CO_2; hence, the amount of CO_2 combined with calcium, in the bones, rises with increase in P_{aCO_2}. As a result of shifts in mineral metabolism, calcium salts form in the excretory system, a

TABLE 6. – *Toxic Effects of Elevated* CO_2 *Content in AGA*

No.	P_{CO_2} in AGA, mm Hg	Nature of manifestation of toxic action of CO_2 on human organism	Time at rest	Performance of physical load	Performance of mental work
1.	To 7.5	No unpleasant sensations; no functional changes detected	Up to 3–4 months	Possible (all kinds)	Possible
2.	To 15.0	No subjective symptomatics; some rise in minute respiration volume noted; development of limited acidosis	Up to 30 d	Of light and moderate intensity Heavy work is difficult	Possible
3.	To 25.0–30.0	State of discomfort; dyspnea especially during work; increase in minute volume of respiration 2–2.5 times the rest value; for exposure longer than 3 d, readily reversible changes in metabolic processes, followed by acidosis	Up to 7 d	Light work is possible Moderate work is restricted Heavy work is extremely difficult	Possible for formulated stereotype
4.	To 35.0–40.0	Dyspnea even at rest, "heaviness" in head, dizziness, increase in minute volume of respiration 3–4 times with relative stability of indicators of the functioning of the cardiovascular system; respiratory acidosis; disturbances of activity of cerebral cortex; disturbance of sleep	Up to 15 h	Light work is restricted Moderate work is extremely difficult Heavy work is impossible	Restricted even for routine mental work
5.	To 50.0	Dyspnea; headache, dizziness; disturbance of vision, disturbance of sleep, increase in minute volume of respiration of 4–5 times, respiratory acidosis, pronounced shifts of the functioning of the cardiovascular system; tachycardia, rise in arterial pressure; disorders of the activity of the central nervous system	Up to 3–4 h	Light work is difficult Moderate and heavy work are impossible	Difficult
6.	To 60.0	Intense rise in subjective and objective symptomatics	Up to 1 h	All kinds of work are impossible	Impossible
7.	Above 60.0, but not more than 75.0	Acute intensification of subjective and objective symptomatics	Up to 15 min	Excluded	Excluded

consequence of which can be kidney stone disease. Stones were detected in rat kidneys after a prolonged stay in an AGA with $P_{CO_2}=21$ mm Hg and higher, which validates this conclusion [178].

Metabolic changes caused by moderate gas acidosis were noted in humans who remained for long periods in AGA with P_{CO_2} exceeding 7.5–10 mm Hg, in spite of visible preservation of normal physiologic state and work capacity.

During Operation Hideout, subjects stayed 42 d in a submarine AGA containing 1.5% CO_2 ($P_{CO_2}=11.4$ mm Hg). The main physiologic parameters—weight, body temperature, blood pressure, and pulse rate—were essentially unchanged. However, in a study of respiration, acid-alkaline equilibrium, and calcium-phosphorus metabolism, adaptive shifts were detected. It was established that approximately from the 24th d in the AGA containing 1.5% CO_2, uncompensated gas acidosis occurred [179]. According to Zharov et al [213], no changes in blood pH were detected in a healthy young man after a month in an AGA with 1% CO_2, in spite of a small increase in P_{ACO_2} and an 8–12% rise in pulmonary ventilation, indicating a slight compensating gas acidosis. A decrease in blood pH, a rise in P_{ACO_2}, and a 20–25% increase in pulmonary ventilation were observed in subjects after prolonged periods (30 d) in an AGA with CO_2 elevated to 2%. Subjects felt normal when at rest; however, when performing intense physical work, some complained of headaches and rapid fatigue [213].

Subjects did not note a deterioration of well-being in an AGA with 3% CO_2 ($P_{CO_2}=22.8$ mm Hg). Blood pH changes indicated rapid development of uncompensated gas acidosis. A stay in this medium, although possible for many days, is always associated with increasing discomfort and a progressive reduction of work capacity.

From these studies it was concluded that remaining for many months in an AGA with P_{CO_2} above 7.5 mm Hg is undesirable because of chronic CO_2 toxic action [180, 213]. When an individual is in an AGA for 3 to 4 months, the P_{CO_2} must not exceed 3–6 mm Hg [123].

Shaefer [180] believes it desirable, when totally evaluating the effect of the chronic influence of hypercapnia, to single out three main levels of increased P_{CO_2} in an AGA which determine different individual tolerances to hypercapnia. The first level corresponds to raising P_{CO_2} in the AGA to 4–6 mm Hg, from which there is no significant effect on the organism. The second level corresponds to raising P_{CO_2} in the AGA to 11 mm Hg, when main physiologic functions and work capacity do not change appreciably. However, there is a slow development of shifts in respiration, acid-alkaline equilibrium regulation, and electrolyte metabolism, resulting in possible pathologic changes. The third level—elevating P_{CO_2} to 22 mm Hg and higher—leads to reduced work capacity, pronounced shifts in physiologic functions, and pathologic states after different time periods.

ARTIFICIAL GAS ATMOSPHERE (AGA)

History of AGA Development

The idea of producing an artificial atmosphere to protect man in high-altitude flights and during underwater immersions and swimming was first expressed by the famous French science fiction writer, Jules Verne. This idea received scientific commentary by the French physiologist Paul Bert [30], and the famous Russian chemist, D. I. Mendeleyev, who was the first to propose, in high-altitude flights, using sealed cabins with air pressure exceeding its pressure in the ambient environment [140]. Later, Tsiolkovskiy [194] pointed out the need for an AGA in spacecraft cabins.

This idea was applied to flight in the early 1930s. First in Switzerland (August Piccard in 1931), and then in the USSR and the US in 1933–1934, flights were made to altitudes of 15 500–22 000 m in stratosphere balloons equipped with sealed cabins. Flights in open cabins are not possible at such altitudes because the O_2 supply for the crew, at a pressure corresponding to ambient pressure, no longer prevents acute oxygen starvation. During preparation for these flights, variants of the AGA were examined and studies made with humans in sealed cabin simulators [8, 183]. Important information was obtained, not only on different

technical means of regenerating the AGA, but also on such physiologic parameters as O_2 requirement and CO_2 expiration of crewmembers.

Soviet and US investigators reached similar conclusions: to have stratosphere balloons in cabins in order to lighten their structure; maintain pressure below atmospheric (550–450 mm Hg); and increase O_2 in the AGA so that oxygen supplied to the crew would be wholly preserved. US and Soviet investigators rejected use of a one-gas oxygen medium, just as they rejected use of liquid nitrogen as the O_2 source, because of fire danger in such an AGA [8, 124, 183].

The short, hours-long duration of stratosphere balloon flights greatly simplified the AGA designing problem. The same problem as related to space flights, especially those of long duration, became considerably more complicated. It would not be advisable to forget the above studies, since for the first time, definite useful experience was obtained.

Thus, in working on the spacecraft AGA, Soviet and US scientists relied not only on sanitary investigations to set standards and design of a gas medium for living and production quarters, but also on investigation data in designing a submarine AGA, and experience in designing stratosphere balloon cabins AGA. Historically, Soviet and US investigators were guided extensively by common principles; however, in practice, designing the spacecraft AGA was solved quite unexpectedly.

Soviet investigators selected the AGA similar in parameters, pressure, and gas composition to standard terrestrial atmosphere (STA), thus developing suitable living conditions in normal flight regimes. US investigators, because of several technical advantages, use a one-gas AGA of oxygen at a total pressure of 258 mm Hg, suitable for astronauts. It is evidently convenient to use it when astronauts, in space suits, leave the cabin to enter very low total pressure [148, 149, 150].

These AGA, successfully used in flights, generally met the main physiologic principles of AGA design. During flight under normal gas exchange there was no appreciable stress of the adaptive mechanisms, therefore the adaptive reserve of the organism was not reduced.

Soviet and US specialists are continuing research on designing spacecraft AGA, indicating that the AGA currently used can scarcely be optimal for long-term flights. During work on this problem, variants of the AGA were discussed. Thorough examination and evaluation of AGA variants are best made according to some systematization of the possible AGA formulations. The basis of the AGA classification comprises chemical composition, physical properties, and main physiologic characteristics.

Physiologic evaluation of AGA in terms of gas exchange and P_{O_2} and P_{CO_2} levels in the internal environment (blood and alveolar air) can be classified into those equivalent to standard terrestrial atmosphere, and those not entirely equivalent, containing some excess O_2 and CO_2, or O_2 deficit. Chemically, AGA can consist of only one gas (O_2); two gases—O_2 and some biologically indifferent gas—or, finally, it can include, besides O_2, several indifferent gases (N_2, He, Ne, and Ar). Physical properties of an AGA depend not only on its chemical composition, but also on barometric pressure, which fluctuates widely.

Numerous AGA variants are theoretically possible for practical use in space flights. Only those which have attracted the greatest attention at present are considered, therefore are being studied in laboratory experiments, or have already been used in flights.

AGA Equivalent in Gas Exchange to STA and Composed of Two Gases (N_2 and O_2)

AGA can be considered as simulating the Earth's standard gaseous atmosphere which consists basically also of two gases, O_2 and N_2, and 1% of other gases. Simulating standard terrestrial atmosphere in spacecraft cabins means providing comfort according to standards set by hygienists for living quarters in geographic regions at sea level. Thus, reproduction of closely studied artificial conditions will be arbitrarily denoted STA.

In Soviet spacecraft cabins, the use of an AGA close to STA is entirely justified, it has been widely assumed [76, 118, 214]; biologically, it is entirely adequate for man who has been histori-

cally adapted to it. An AGA close to STA can be used in extended space flight as one of the most reliable AGA variants [76, 118]. Although STA was assumed applicable as an AGA in spacecraft cabins [68, 76], its use was not optimal in most cases. Thus, Gazenko and Genin argued: ". . . copying the terrestrial atmosphere unjustifiably limits the possibility of AGA variations that could prove desirable from the standpoint of engineering and human protection in an emergency situation" [68].

Selection of an AGA entails parameters: the higher the AGA pressure, the thicker the cabin walls and the greater the cabin weight. The adverse features of STA during emergencies have been pointed out [46, 76, 118]. A disturbance in cabin hermeticity causes significant barometric pressure drop which leads to detrimental action in explosive decompression. Low-pressure transition from STA to AGA, as when passing from one ship to another or when using space suits with low pressure, is fraught with development of altitude decompression sickness. Space suits with low pressure complicate not only the time spent by astronauts during emergencies, but can also adversely affect their egress into "free" space and on the surface of celestial bodies that are practically devoid of atmosphere or have an extremely rarefied one. Using STA in cabins only in limited cases has been recommended, besides possible emergency need. Long flights can cause functional organic shifts (asthenia—loss of conditioning) when the comfortable, quite stable parameters of STA prove far from optimal [71, 74, 76].

Soviet and US investigators [33, 46, 76] used a two-component AGA in spacecraft cabins, equivalent in gas exchange to STA, but with a barometric pressure lower than STA. Data in Table 7 and Figure 1 show maximum permissible reduction in AGA pressure to 190 mm Hg. To retain normal O_2 supply to the organism at low pressures, AGA gas composition must consist of O_2 only, i.e., no two-component gas. Accordingly, in examining AGA consisting of O_2 and N_2, four ranges of reduced pressure were used: 526, 405, 308, and 267 mm Hg, corresponding to 3000, 5000, 7000, and 8000 m of altitude.

Three of the above-listed AGA at 526, 405, and 308 mm Hg were successfully tested under laboratory conditions by Ivanov et al [95]. Studies at lower pressures were not carried out to prevent AGA which begins at altitudes of 7500–8000 m and to avoid fire due to increase of O_2 in the AGA.

Results showed that a month in AGA equivalent in O_2 to STA, at pressures corresponding to altitudes of 3000–7000 m, has no unfavorable effect. All three AGA variants tested proved equivalent from the physiologic standpoint. Changes in certain physiologic parameters were: 10–15% reduction in O_2 requirement, rise in heart rate especially in the orthostatic test, changes in diurnal periodicity of the EEG-frequency spectrum, and increase in the number of slow waves during the day. These changes did not depend on gas composition and AGA pressure, but were caused by hypodynamia and changes in work, rest, and sleep routines.

In continuing investigations by Kunetsov et al [117], subjects were kept for 2 months in an AGA with a total gas pressure of 308 mm Hg. Functional shifts were detected in subjects, caused mainly by hypodynamia. Considerable attention was given to developing an AGA with a total gas pressure of 300 mm Hg, but was not successful [33, 95, 117]. A pressure of 300 mm Hg is considered optimal, because it is still high and protects against decompression, therefore does not require desaturation of N_2 from the organism when N_2 is used in the AGA. It is also convenient to use space suits with low pressure, which preclude ADS. ADS develops only rarely in emergency depressurization during the first flight hours. The use of a two-component AGA with a pressure of 300 mm Hg is a probability, since it reduces cabin and AGA weight as such; but fire in this AGA is not more likely than when the STA is used (Tables 8 and 9).

On purely theoretical considerations, it is remarkable that as early as 1940, Spasskiy [187] considered an AGA with a total pressure of 260 mm Hg as promising for high-altitude aircraft cabins. The flight difference between this AGA and the above-considered AGA with a total pressure of 308 mm Hg eliminates detailed comparison. Small, mainly technical advantages of its use compared to the preceding AGA (308 mm Hg)

TABLE 7. – *Change of Barometric Pressure and* P_{O_2} *at Different Altitudes and Oxygen Conditions*

H altitude		Atmospheric pressure based on int'l st. atmosphere				Millibars	Partial pressure O_2 in dry air P_{O_2} (dry), mm Hg	Partial pressure O_2 in moist air P_{O_2} (moist), mm Hg	O_2 % providing respiratory conditions analogous to:			
m	ft	P mm Hg	Technical atmosphere kg/cm²	Physical atmosphere atm	(P_1S_1) lbs/in²				Terrestrial	2000 m	4000 m	5000 m
0	0	760.0	1.033	1.000	14.7	1014	159	150	21.0	16.2	12.25	10.5
500	1640	716.0	0.975	0.943	13.84	955	150.3	140.5	22.4	17.3	13	11.2
1000	3230	674.1	0.917	0.887	13.04	900	141.5	132	23.9	18.4	13.9	12.0
1500	4920	634.2	0.863	0.834	12.3	846	133	123.3	25.5	19.7	14.9	12.8
2000	6560	596.3	0.812	0.785	11.5	795	125	115.3	27.2	21.0	15.9	13.7
2500	8200	560.2	0.761	0.736	10.8	748	117.5	107.7	29.2	22.5	17.0	14.7
3000	9840	526.0	0.717	0.693	10.2	702	110.4	100.6	31.2	24.1	18.2	15.7
4000	13 100	462.5	0.63	0.609	8.94	617	97	87.2	34.3	27.3	21	18.1
5000	16 400	405.4	0.552	0.534	7.84	540.5	85	75.2	41.8	32.2	24.3	21.0
6000	18 700	354.1	0.482	0.466	6.85	472	74.4	64.5	48.8	37.6	28.4	24.5
7000	23 000	308.3	0.419	0.405	5.96	411	64.7	54.9	57.3	44.2	33.4	28.8
8000	26 200	267.4	0.364	0.352	5.17	356.5	56.1	46.3	68.0	52.4	39.6	34.2
9000	29 500	231.0	0.315	0.305	4.47	308	48.5	38.6	81.3	62.7	47.5	40.8
10 000	32 800	198.7	0.271	0.262	3.84	265	41.7	31.9	98.7	76.1	57.5	49.6
11 000	36 100	170.2	0.232	0.224	3.29	227	35.7	25.9	–	93.7	71	61.0
12 000	39 400	145.3	0.198	0.191	2.81	194	30.5	20.6	–	–	88.8	76.5
13 000	42 600	124.4	0.17	0.164	2.41	166	26.1	16.2	–	–	–	97.7
14 000	46 000	106.3	0.145	0.140	2.06	142	22.3	12.45	–	–	–	–
15 000	49 200	90.8	0.124	0.12	1.76	121	19.05	9.2	–	–	–	–
17 000	55 800	66.4	0.09	0.087	1.28	88.6	18.9	4.07	–	–	–	–
18 000	59 000	56.6	0.077	0.074	1.09	75.5	11.9	2.02	–	–	–	–
20 000	65 600	41.5	0.057	0.055	0.803	55.4	8.7	–	–	–	–	–
25 000	82 000	18.9	0.026	0.025	0.366	25.2	3.97	–	–	–	–	–
30 000	98 400	8.9	0.012	0.012	0.172	11.9	1.87	–	–	–	–	–
40 000	131 000	2.2	0.003	0.003	0.0426	2.94	0.46	–	–	–	–	–
60 000	164 000	0.6	0.001	0.001	0.0116	0.8	0.126	–	–	–	–	–
Working formulas	$\frac{M}{0.305}$	—	$\frac{P}{785}$	$\frac{P}{760}$	$\frac{P}{51.713}$	1.335 P	0.21 P	0.21 (P – 47)	$21\frac{760-47}{P-47}$	$21\frac{596-47}{P-47}$	$21\frac{462-47}{P-47}$	$\frac{21(405-47)}{P-47}$

Compiled by V. S. Yakovlenko.

TABLE 8.—*Flame Spread Rates for Materials in Various Atmospheres* [1]

Atmosphere	Air[2]		Air[3]		20% O_2 80% He		46% O_2 54% N_2		46% O_2 54% He		70% O_2 30% N_2		70% O_2 30% He		100% O_2 [3]		100% O_2 [2]	
Pressure	760 mm		760 mm		760 mm		380 mm		380 mm		258 mm		258 mm		258 mm		258 mm	
	cm/s	in/s	cm/s	in/s	cm/s	in/s	cm/s	in/s	cm/s	in/s	cm/s	in/s	cm/s	in/s	cm/s	in/s	cm/s	in/s
Wood	–	–	0.064	0.025	0.10	0.04	0.305	0.12	0.46	0.18	0.46	0.18	0.69	0.27	0.89	0.35	–	–
	–	–	±0.064	±0.025	±0.013	±0.005	±0.051	±0.02	±0.076	±0.03	±0.076	±0.03	±0.076	±0.03	±0.076	±0.03	–	–
Paper	–	–	0.076	0.03	0.76	0.30	1.07	0.42	1.60	0.63	1.4	0.55	1.9	0.74	2.28	0.90	–	–
	–	–	±0.025	±0.01	±0.15	±0.06	±0.051	±0.02	±0.13	±0.05	±0.13	±0.05	±0.15	±0.06	±0.18	±0.07	–	–
Cellulose acetate	0.0305	0.012	0.0076	0.003	–	–	0.28	0.11	0.38	0.15	0.51	0.20	0.46	0.18	0.76	0.30	0.71	0.28
			±0.0051	±0.002	–	–	±0.025	±0.01	±0.051	±0.02	±0.076	±0.03	±0.051	±0.02	±0.025	±0.01	±0.305	±0.12
Cotton fabric	0	0	0.25	0.10	0.43	0.17	2.28	0.9	2.8	1.1	4.6	1.8	3.05	1.2	8.1	3.2	3.8	1.5
			±0.025	±0.01	±0.025	±0.01	±0.76	±0.3	±0.025	±0.1	±0.76	±0.2	±0.051	±0.2	±0.51	±0.2	±0.13	±0.05
Foam cushion	0.48	0.19	0.36	0.14	0	0	6.9	2.7	5.3	2.1	0.25	0.1	15.2	6.0	33	13	31.5	12.4
			±0.051	±0.02	0	0	±2.0	±0.8	±0.76	±0.3	±1.3	±0.5	±1.3	±0.6	±2.5	±1	±1.3	±0.5
Plastic wire	0	0	0	0	0	0	0.64	0.25	0.89	0.35	1.1	0.48	1.52	0.60	2.13	0.84	0.84	0.33
	0	0	0	0	0	0	±0.025	±0.01	±0.051	±0.02	±0.025	±0.01	±0.051	±0.02	±0.076	±0.03	–	–
Painted surface	0	0	0	0	0	0	0.53	0.21	0.69	0.27	0.81	0.32	1.1	0.42	1.14	0.45	0.97	0.38
	0	0	0	0	0	0	±0.025	±0.01	±0.025	±0.01	±0.051	±0.02	±0.13	±0.06	±0.13	±0.05	±0.10	±0.04

[1] ± indicates average deviation.

[2] Previously reported SAM–TR–65–7S.

[3] This investigation.

TABLE 9.—*Energy Required for Ignition of Materials in Various Atmospheres*

(cal/cm²)

Atmosphere	Air	20% O_2 80% He	46% O_2 54% N_2	46% O_2 54% He	70% O_2 30% N_2	70% O_2 30% He	100% O_2
Pressure	760 mm	760 mm	380 mm	380 mm	258 mm	253 mm	258 mm
Wood	25±1	108±11	25±2	24±0.5	25±1	22±1	23±1
Paper	32±1	39±0.5	25±2	26±0.5	26±0.5	25±0.5	25±1
Cotton fabric	13±0.5	Nl	12±0.5	17±0.5	15±0.5	16±0.5	15±0.5
Plastic wire	20±1	Nl	16±1	Nl	17±1	46±1	16±1
Painted surface	30±1	Nl	56±5	70±4	81±3	57±5	36±1

cannot justify certain of its adverse qualities. At a pressure of 260 mm Hg, there is probability of ADS, and with reduction in reserve time, inevitable at lower AGA pressure, there is increased leakage of gases from the cabin.

AGA Composed of O_2 and He

Replacing nitrogen in an AGA with helium poses an important question. Is presence of N_2 in an AGA important and does it have the same biologic role in the STA to which man and animals have been adapted during their long evolutional development?

Man and animals can live normally in an AGA devoid of N_2, according to Soviet and US investigators [54, 76, 118, 130, 169]. Vertebrates and invertebrates develop normally in an AGA where N_2 is totally absent [35, 130, 206]. In man, the biologic role of N_2 is to fill body cavities, primarily the lungs—to sustain specific volume and prevent atelectases. Other inert gases, including He (to be discussed), can fulfill this role [2, 54, 85, 147, 151, 166, 167, 169, 177, 182]. Use of He as one of the main components of an AGA demands that it have no unfavorable effects.

Studies on animals and humans with nitrogen mixed with helium in AGA, at normal and reduced pressures, showed that helium had no toxic effect and like N_2, is a biologically inert gas [2, 16, 49, 54, 60, 165, 169]. Functional shifts caused by the heat-physical properties of He are: increase in oxygen requirements, reduction in erythrocyte count and hemoglobin level, and associated increase in diurnal iron requirements. Hamilton et al [84] detected such changes in rats in a helium-oxygen medium and Dianov [55] found changes in an animal's resistance to hypoxia.

After it was shown that He can replace N_2 in AGA, its replacement advisability was questioned. According to data of Yakobson, Dianov, and Kuznetsov [53, 207], when He is used, the onset of ADS and especially of its severe forms in astronauts after transition to conditions of low barometric pressure is somewhat reduced. This is based on the Bunsen coefficient of N_2 solubility in fat which is approximately four times higher than for He. In contrast, studies of US investigators Beard et al [19] established a more frequent appearance of the "bends"—the musculoarticular form of ADS in persons present in an AGA in which He was used. The incidence of severe ADS forms, when a He-containing AGA is used, is not settled.

Dianov et al have shown that when oxygen is breathed, the time of virtually complete desaturation of He from the organism is considerably less than for N_2 desaturation because of the low helium solubility in tissues and its high diffusion coefficient. This is an essential and indisputable advantage of using He in the AGA. Temperature increases in the cabin, due to He high thermal conductivity, will be much better tolerated by astronauts [33, 54, 55, 169]. In this medium, hypercapnia resistance, intense physical loads, and other influences leading to a significant rise in ventilation must also be increased [55, 115]. This effect is due to forced breathing of a helium-oxygen mixture, when resistance of air passages, owing to the low density of He, is less than when air is breathed. In normal,

quiet breathing this effect does not show up, since air passage resistance is now determined partially by inspired gas viscosity. The viscosity of He does not differ appreciably from that of N_2.

Nitrogen Replacement

Nitrogen replacement in an AGA with helium is justified by the high stability of the He atom to different kinds of radiation exposure. This advantageously differentiates He from N_2. The relatively high weight of N_2 determines its weak protective properties with respect to cosmic radiation; primary nucleons absorption and formation of secondary particles. According to data of Dmitriyev [58], excited nitrogen atoms and ions are formed by ionizing radiation in air. They enter into chemical reactions with O_2, resulting in formation of toxic compounds such as nitrogen oxide, nitrous oxide, and nitrogen peroxide. The advisability of replacing nitrogen in an AGA with helium also has an engineering justification. The density of He is approximately one-seventh that of N_2, hence use of a helium-oxygen atmosphere in spacecraft leads to reduction in launch weight, and in gas reserves weight necessary to replenish the craft atmosphere. This advantage of the helium-oxygen AGA cannot be manifested fully owing to high He fluidity. This is the reason for reducing reserve time if gases escape from the cabin when AGA nitrogen is replaced with helium, which must be considered as a disadvantage of this replacement. Replacement of AGA nitrogen with helium must lead to reduction in energy required to ventilate the cabin. In spite of the definite advantages of using He in an AGA, there are few experimental studies on humans. Soviet experiments [53, 187] dealt with an AGA consisting of O_2 and He at normal barometric pressure (1 atm).

Studies show that remaining in a helium-oxygen medium does not cause any essential changes in well-being, behavior, and work function. However, replacing nitrogen in the AGA with helium is still accompanied by some functional shifts which include changes in heat exchange, speech, and respiration [53, 54, 176]. Thus, remaining in a helium-oxygen AGA at temperatures that are comfortable under normal air atmosphere (18–24° C) was accompanied by appreciable cooling. At 21° C, subjects rapidly displayed unpleasant heat sensations when the mean-weighted skin temperature dropped nearly 2° in 2 h. In the helium-oxygen AGA, the zone of heat comfort shifted markedly toward higher temperatures and was 24.5–27.5° C during the day while at night it was 26–29° C. These data show considerable narrowing (by 3° C) of the heat comfort zone in the helium-oxygen medium compared with the similar zone in air [53, 54]. This effect of the helium-oxygen atmosphere is associated with the high thermal conductivity of He.

Replacing nitrogen in air with helium led to speech changes in subjects in the helium-oxygen AGA; the speech spectrum shifted toward high frequency by a value of 0.7 octave. Speech intelligibility deteriorated somewhat but was still retained at an acceptable level of 90–95%. The speech function was restored immediately after breathing ordinary air. The speed of sound in the helium-oxygen medium at a pressure of 1 atm and a temperature of 27° C is 1.85 times higher than in air, which explains speech distortion after nitrogen in air was replaced with helium [48, 120].

Functional changes of respiration in the helium-oxygen medium were manifested in an improvement of maximum possible ventilation of lungs, due to reduced resistance of the air passages. Thus, studies on air nitrogen replaced with helium showed the practical possibility of using this AGA. US investigators studied helium-oxygen AGA with a total pressure of 380 mm Hg [60, 155, 212], 360 mm Hg, and 258 mm Hg [2, 16, 89, 147, 166, 167, 182].

These studies suggest that prolonged (up to 56 d) stay in a helium-oxygen medium has no unfavorable effects on metabolism, respiration, blood circulation, and CNS. Pathologic shifts noted in these experiments were caused by various factors unrelated directly to the replacement of nitrogen in the AGA with helium. For example, in experiments by Zeft et al [212], irritation of eyelid mucosa (conjunctivitis) was due to the low humidity of the AGA (pressure of 380 mm Hg); when the humidity was raised, these disturbances disappeared. A decrease in one subject's orthostatic stability, as well

as in most investigations in cabin simulators, was evidently due to hypodynamia.

Mucosa dryness and development of conjunctivitis, noted in subjects after 56 days in a helium-oxygen AGA with a total pressure of 258 mm Hg (P_{O_2} = 175 mm Hg; P_{He} = 74 mm Hg; and P_{N_2} = 2 mm Hg), were also associated with low humidity. Abdominal pains cannot be related to He in the AGA, but were evidently due to other factors, possibly the unsuccessful diet. Only slight speech distortions and skin temperature changes when physical exercise was performed were related to He in the AGA. However, such changes have no significance, since speech distortions can be eliminated by technical means; also, unfavorable heat sensations in helium-oxygen media are easily remedied by raising the temperature of the artificial gaseous atmosphere.

In a comparative evaluation of helium-oxygen AGA with low pressure, when there is a slow leakage of gases from the cabin, the reserve time (during which the pressure drops to the critical value determining development of acute hypoxia) will be shorter for crewmembers, compared with AGA containing N_2, the higher the percent content of He in the AGA. Therefore, at the lowest total pressure (258 mm Hg), this difference between helium- and nitrogen-oxygen AGA will be relatively small [46, 174].

In conclusion, if in underground immersions the possibility of using He in AGA has been demonstrated, this question is still in the study stage for the AGA of spacecraft cabins.

One-Gas AGA

The advisability of using pure oxygen in cabins of high-altitude aircraft was discussed before World War II by Spasskiy [187], who assumed that O_2 might be used at a pressure of 230 mm Hg in hermetic cabins of high-altitude aircraft. He maintained that the pressure must not be reduced to lower levels since the probability of ADS and altitude meteorism are significant and even a small O_2 reserve during increased gas leakage in the cabin will be virtually absent.

Animals remaining for a long time in a one-gas AGA equivalent in gas exchange to STA and composed virtually of only oxygen ($P_{N_2} < 10$ mm Hg) with a pressure of 190–200 mm Hg was demonstrated [3, 56, 72, 130, 145]. It was established that in a single-gas medium equivalent to STA in terms of O_2, pulmonary atelectasis can develop in experimental animals. Pulmonary atelectasis in mice during the first 48 h in a one-gas atmosphere caused the death of several animals, although most animals spent the entire 59-d experiment without visible behavior disturbances or injury [130]. In later experiments on rats in this AGA [3, 72], atelectases developed in several animals during the first days, soon disappearing, after which the animals retained normal physiologic state for up to 100 d. There was moderate dehydration in the experimental animals caused by increased evaporation of liquid in the reduced (down to 200 mm Hg) AGA pressure.

In a one-gas AGA (P_{O_2} = 196 mm Hg), no atelectasis or other unfavorable effects were found in young growing rats [169]: only reduced urine excretion was noted during 24 d in this AGA. This effect is associated with increased fluid loss caused by evaporation in the rarefied atmosphere of the one-gas AGA.

Biologic Effects

A biological criterion was used to judge the influence of a single-gas medium—the capability of reproduction—in an experiment lasting 11 months. If a rat's lifetime is approximately 2.5 years, this experiment must be regarded as extremely long. According to the data, the one-gas medium has no unfavorable effect on the physiology and biology of the white rat. Pregnancy occurs normally and progeny grows and develops normally in this medium. The only puzzling result was the death of several animals born in the one-gas AGA after they had been transferred to STA 21 d after birth [169]. Death of animals in the STA probably was caused by side factors not directly associated with the one-gas AGA which they were in earlier. It can be concluded that the one-gas medium is biologically suitable, although there is risk of ADS and pulmonary atelectasis.

The effect on the human organism of an AGA mainly of O_2 with total pressure of 190–200 mm

Hg was studied in the US [143, 144, 145, 202], and in the USSR [72]. It was established that it is possible to use this AGA when necessary, but certain unfavorable effects were noted. Chest pains which developed in one subject in a medium with $P_{O_2} = 176$ mm Hg were possibly associated with pulmonary atelectasis. The pains disappeared when the AGA pressure was raised. Aural atelectasis developed in some subjects, and signs of dehydration were noted in all. In another investigation [145], pulmonary influenza was detected in six subjects, pain in joints in one, and a small drop (to 90%) in oxygen saturation of arterial blood was noted in two.

Thirty days in a one-gas atmosphere (N_2 content in the AGA was 5–10%) was tolerated well; subjects maintained physical and intellectual work at high level [72]. No atelectases developed in lungs or middle ear cavities, which, possibly, was due to subjects periodically performing physical exercise. Also, it is significant that N_2 content in the AGA was somewhat higher than in the experiments by Welch et al [202] and by Morgan et al [145]. Some adverse features were in the AGA tested. The necessity of prolonged desaturation of N_2 from the organism before beginning the experiment was noted. When desaturation time was less than 3 h, transition into the one-gas AGA usually led to ADS symptoms. Thus, investigations with humans showed that when preliminary desaturation and pulmonary atelectasis is prevented by physical exercises, one-gas AGA with a total pressure of 200 mm Hg can evidently be used in flights.

The advantages of using a one-gas AGA are that it provides for simplifying and carrying out more reliable regulation of life-support systems, and reducing the weight of the AGA and the cabin. Another advantage of this AGA is that low pressure reduces the probability of organic damage in the event of explosive decompression; using space suits at low pressure is also considerably simplified. At the same time, the one-gas AGA has several serious adverse features, which include increased fire danger (Tables 8, 9, 10). This is caused primarily by absence of diluent gases in the AGA (N_2, He, and Ne) reducing the combustion rate of various materials (Table 8). The great danger of fire breaking out necessitates limiting the use of several materials in the spacecraft cabin and necessarily imposes higher fire safety requirements.

Another serious disadvantage of a one-gas AGA with 200 mm Hg pressure is the near total absence of "reserve time" when there is increased leakage of gases from the cabin. The pressure drop of 70–80 mm Hg is a great danger to crewmembers. Such disadvantages of this AGA require lengthy desaturation of N_2 at launch, anticipating the possibilities of pulmonary and middle ear atelectases and rapid dehydration of the organism in the event of reduced moisture in the AGA.

Hyperoxic AGA was examined partially in the discussion of O_2 toxic effects on the organism. Again, the one-gas AGA with 258 mm Hg total pressure was investigated and successfully tested in US flights of 2 weeks' duration. Its further use in flights of longer duration is an object of discussion. With longer time spent in this medium, the probability of the O_2 toxic effect on respiratory organs and blood system, as well as its high fire danger, will possibly eliminate use of this AGA for lengthy interplanetary flights [33, 46, 76].

Based on a comparative evaluation of AGA variants (shown in a general way in Table 10), it is held that a two-gas AGA consisting of O_2 and N_2 or He (possibly also Ne) with total pressure of 300–400 mm Hg will have definite advantages on certain occasions [76, 118]. These considerations evidently led to the fact that a two-gas atmosphere consisting of 70% O_2 and 30% N_2 at a total pressure of 258 mm Hg was used in Skylab in flights up to 86 days.

Active AGA

In examining AGA variants, most investigators fear preeminently that a particular AGA variant could affect the organism and cause adaptive changes (Table 10). It is assumed that the more inert the AGA from the biological point of view, the more suitable it is. In opposition is the idea that one of the factors preventing signs of asthenization during lengthy flights can be an AGA which actively stimulates adaptive reactions to different unfavorable flight conditions. Such an AGA acquired the term *active AGA*.

TABLE 10. – *Comparative Estimate of AGA Variants*

No.	Evaluation criteria	Artificial gas atmosphere (AGA)							
		P = 760 mm Hg O_2 – 21% N_2 – 79%	P = 760 mm Hg O_2 – 21% He – 79%	P = 405 mm Hg O_2 – 42% N_2 – 58%	P = 405 mm Hg O_2 – 42% He – 43%	P = 308 mm Hg O_2 – 57% N_2 – 43%	P = 308 mm Hg O_2 – 57% He – 53%	P = 258 mm Hg O_2 – 100%	P = 200 mm Hg O_2 – 100%
I.	Possible damaging action:								
	Disturbance of tissue structure, pulmonary atelectases, hemolysis of erythrocytes, and so on	–	–	–	–	–	–	±	±
II.	Danger of ADS developing:								
	a) at launch	–	–	–	–	–	–	+	+++
	b) in flight with use of pressurized space suit (200–170 mm Hg)	++++	+++	±	±	–	–	–	–
III.	Necessity of desaturation	+++	+++	±	±	–	–	+	+++
	a) at launch	–	–	–	–	–	–	+	+++
	b) in flight with egress from cabin	++++	+++	±	±	–	–	–	–
	c) desaturation time	6–8 h	2–3 h	?	?	–	–	4 h	6–8 h
IV.	Danger of damage from ADS	++++	+++	++	++	+	+	+	+
	a) severity of gas embolism	+++	+++	++	++	+	+	–	–
V.	Extent of damage when gases leak from cabin	±	++	++	+++	++	++++	+++	++++
VI.	Resistance to high temperatures	4	1	3	2	3	2–3	3	2
VII.	Resistance to ionizing radiation	2	2	2	2	3	2–3	3	2
VIII.	Danger of fire and explosion	±	±	+	+	++	++	++++	+++
	a) manifestation of toxic products	+	–	+	–	+	–	–	–
	b) rate of combustion of tissues and plastics	±	+	+	+	++	+++	++++	+++
IX.	Weight of AGA	5	3	3	2	3	1–2	2	1
	a) weight and capacity of fan	5	3	3	2	3	1–2	2	1

NOTE: The following symbols were used for a comparative evaluation of the estimate of probable degree of danger of damaging effects: No (–), extremely slight (±), low (+), moderate (++), high (+++), highest (++++). A 5-point scale was used for the comparison of AGA variants: 1. highest, 2. good, 3. moderate, 4. poor, 5. worst.

In nearly all studies in cabin simulators, when remaining for a long time in AGA regardless of its variants, the possibility of asthenization developing was noted, as the result of reduced motor activity [95, 117, 203]. The signs were: reduction in physical work capacity and orthostatic stability, and reduced resistance to influences such as acceleration and hypoxia [110, 198]. In lengthy flights also, weightlessness aggravates the adverse effect of hypodynamia, indicated from investigations where physiologic effects of weightlessness were simulated by immersing subjects in liquid or restricting them to bed rest. Substantial disturbances in blood circulatory regulation were noted, with reduction in orthostatic stability and disturbed regulation of motions, changes in the support motor apparatus, and shifts in protein and mineral metabolism.

In 1964, Genin in the USSR [71, 74], and (independently) Lamb in the US [121] proposed using a purposefully altered AGA to prevent asthenia during lengthy space flights. Lamb noted that biochemical and physiological shifts during adaptation to a moderate degree of hypoxic hypoxia must prevent several adverse effects of weightlessness; therefore, he proposed using a hypoxic AGA. This idea was implemented [129, 188] by investigating a lengthy stay with strict bed rest during two gradually increasing degrees of hypoxia.

Soviet investigators noted that change in AGA gas composition is only one of the possible ways to condition subjects; it is also possible to use changes in other parameters of the medium for the same purpose: fluctuations in AGA temperature, for example. Significance of the actual hypoxic conditioning regimen was also shown. Vasil'yev et al [197] made a comparative evaluation of hypoxia conditioning, establishing that the highest effectiveness of the stepwise "fractional" regimen is in ascents to increasingly higher altitudes, remaining in an O_2 deficit atmosphere for 6 h followed by 18 h in an AGA with normal P_{O_2}. Later, animals secured in special cases to severely restricted motions were exposed to AGA variants. Tests were made of AGA with O_2 content reduced to different levels, with excess CO_2 content, and with simultaneously reduced P_{O_2} down to 70–80 mm Hg and P_{CO_2} elevated to 30–38 mm Hg. Data indicated that the AGA used were stimulating in different intensities on blood, respiration, and the cardiovascular system of experimental animals, and promoted increased resistance to G-loads and acute hypoxia [199].

In pressure-chamber experiments with humans restricted to bed rest, a daily 6-h conditioning session (ascents to gradually increasing "altitudes" from 2500 to 4500 m) brought milder symptoms of hypodynamia. However, initially it caused short-term moderate discomfort in some persons due to the effect of hypoxia. Conditioning prevented reduced resistance to G-loads considerably; it even increased resistance somewhat to acute hypoxia. It was thought that to prevent asthenization, an AGA with nonstationary, cyclically varying gas composition should be used. This idea is based on spending time in this AGA which should not form stable adaptation to the altered gas medium. At the same time, changes in the AGA can be selected in time so that work function is increased. It should be added that use of these AGA can also prove useful to retain normal periodicity in processes of vital activity, which can be substantial in lengthy flights [76].

A deficiency of motions was experienced in nonstationary AGA with significant fluctuations in P_{O_2} (from 110 to 320 mm Hg) on different days of the investigation. This showed a possible marked purpose for influencing various functional systems through the use of these AGA [77]. The rational selection of all parameters for use of these AGA to prevent asthenia in crewmembers on long flights is far from resolved; further intensive experiments are needed.

In conclusion, space flights of many months and many years impose new requirements on criteria for evaluating the AGA. It will be necessary in the future to evaluate the quality of an AGA, based not only on accepted physiologic-hygienic parameters, but also in regard to general biologic indicators that delineate the effect of the AGA on lifespan, aging, reproduction, and other body processes.

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