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RELATIVE DECOMPRESSION RISKS OF SPACECRAFT CABIN ATMOSPHERES

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16. Abstract

The miniature pig has been examined as a possible model for the study of altitude decompression sickness. With suitable qualifications it is acceptable for use as a decompression model. However, it was necessary to separate hypoxic and decompression sickness symptoms by "calibration" of each animal. Rats were used to compare relative decompression risks after saturation with nitrogen, argon, neon, a neon-helium mixture, and helium. Neon and neon-helium were relatively less hazardous than even helim in terms of overall incidence of decompression sickness. Helium and neon-helium were least hazardous in terms of severe symptoms. Incidences of severe symptoms were similar for neon (21%) and argon (26%). With nitrogen-and to a lesser extent, argon, neon and neon-helium-but not helium a dependence of decompression sickness severity on body weight was observed. Weight, therefore, must be controlled as a parameter when using rats to compare gas environments. Neon-helium and helium appear to be possible inert gas diluents to be considered most carefully in further large animal or manned studies of two gas space cabin atmospheres as these relate to decompression hazards.

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I. SUMMARY

The miniature pig has been examined as a possible model for the study of altitude decompression sickness. With suitable qualifications in terms of establishing behavior of individual animals the miniature pig appears to us to be acceptable for use as a decompression model. It was found necessary to separate hypoxic and decompression sickness symptoms by "calibration" of each animal under controlled conditions wherein only hypoxia or decompression but not both existed.

Rats were used in a second task of this study to compare relative altitude decompression risks after saturation with nitrogen, argon, neon, a neon-helium mixture, and helium. Nitrogen and argon both produced a high overall incidence of decompression sickness; argon, however, was considerably better than nitrogen (26% versus 56%) in terms of incidence of severe symptoms (paralysis or death).

Neon and neon-helium were relatively less hazardous than nitrogen or argon or even helium in terms of overall incidence of decompression sickness. Helium (4%) and neon-helium (8%) were least hazardous in terms of incidence of severe symptoms (paralysis or death). Incidences of severe symptoms were similar for neon (21%) and argon (26%). Only a general trend, without predictive capacity, was noted for the relationship between computed supersaturation ratios for any of fifteen theoretical inert gas exchange compartments of the body defined in terms of blood flow rate and lipid:water composition.

With nitrogen—and to a lesser extent argon, neon and neon-helium—but not helium a dependence of decompression sickness severity on body weight was observed. Weight, therefore, must be controlled as a parameter when using rats to compare gas environments.

Neon-helium and helium appear to be possible inert gas diluents to be considered most carefully in further large animal or manned studies of two gas space cabin atmospheres as these relate to decompression hazards.

II. INTRODUCTION

Man's first steps toward the exploration of his extraterrestrial universe are a tribute to his physiological adaptability as well as to his engineering skill. In the earliest stages of Project Mercury it was decided that the atmosphere of United States spacecraft would consist of pure oxygen, and structural constraints caused the use of a system pressure of about one-third atmosphere. It had been established that both man and animals could live in the absence of any inert gas, (1, 2) and there was one physiological argument for this approach in addition to the many engineering and weight advantages. A man saturated with an atmosphere containing no inert gas need not be concerned with the problems of evolved gas when the pressure on his body is reduced, as it necessarily will be in extra-vehicular activity and in the event of an unintentional pressure loss. This one-gas atmosphere turned out to be a wise choice, and the successful completion of the first phases of lunar exploration were no doubt facilitated by the simplicity provided.

But the one-gas approach is not without its problems. At pressures greater than the 5 psi used in flight there is a serious fire hazard, and where the flight duration is longer than a day or two certain adaptive changes take place, some of which may be detrimental. When flights are planned that last weeks or months the unknown factors are too important to be ignored. For these reasons the orbiting laboratory environment and those of future long duration flights will involve a two-gas atmosphere, in which the oxygen is diluted by one or more "inert" gases. For the immediate post-Apollo period the inert component will be nitrogen.

The experiments being reported here are concerned with the problems of selecting the optimal inert-gas diluent for future flights. Although it is well established that nitrogen is safe to breathe and its fire, decompression and engineering characterisitics are well understood, the possibility exists that some other inert gas may offer considerable overall

operational advantages over that gas. A comprehensive literature review and theoretical analysis completed in 1967 by Dr. E. M. Roth of the Lovelace Foundation (3, 4, 5, 6) suggested that neon may be a better choice, but it at the same time pointed out that little is known about the long-term biological effects of any of the appropriate "exotic" inert gases--helium, neon, or argon.

Biologically there are two major considerations involved in the choice of the best inert gas: physiological consequences of living in the synthetic atmosphere, and risks of decompression sickness. Other properties such as weight, storage volume, leak rate, engineering complexities, fire safety, and cost are of course important, but they do not represent areas where vital information is lacking.

Many gases are regarded as "inert" because they do not enter directly into known biochemical processes of higher animals and man. Of these nitrogen, helium, neon, argon, krypton, and xenon have been considered as possible space cabin diluents. Krypton, xenon, and perhaps argon, have generally been considered to be unsuitable because of their high solubility, a factor expected to result in an increased risk of decompression sickness.

Of the remaining gases--nitrogen, helium, and neon--the present state of knowledge does not disqualify any of them with respect to their long-term effects as a diluent for oxygen. Nitrogen of course has been used without known detriment in the space program of the USSR. On the other hand, experiments have failed to show that nitrogen <u>per se</u> is a necessary component in a mammalian breathing atmosphere. Familiarity with the properties of nitrogen rather than any known adverse effects of helium or neon probably accounts for the fact that nitrogen is favored by many as an oxygen diluent in manned spacecraft.

There is a reasonable amount of information in the literature dealing with the effects of breathing or living in a helium-oxygen atmosphere.

Helium no doubt causes a slight increase in oxygen consumption in small fur-bearing mammals (7). This is generally considered to be due to the peculiar thermal properties of helium and the resulting increased cooling of the skins (8, 9). There is also some suggestion that this effect may work via a mechanism that acts at some level below that of the intact animal (10), but the data on this topic are not all in agreement (11, 12, 13, 14).

When humans are kept in helium at a comfortable temperature, there seem to be no physiological derangements (15, 16, 17), even under greatly increased pressures (18, 19). In an extremely thorough study involving the exposure of man to a helium-oxygen atmosphere for 56 days, the USAF School of Aerospace Medicine (20) found nothing to indicate that this atmosphere would not be suitable.

An earlier report (21) of an anomaly in heart muscle protein possibly due to long-term exposure to helium has been resolved. Recent experiments (22) produced a consistent duplication of soluble tissue protein electrophoresis patterns in mice raised in both helium-oxygen and air. These animals were raised for three consecutive generations in environmental chambers which had as their only difference the inert gas diluent.

Much less is known about neon, but because of its similarity to nitrogen in molecular weight and other physical properties, few deleterious results are expected. In several one-week exposures of rats and rabbits at ground level and at simulated altitude performed in this laboratory, (9) no meaningful differences were found between neon-exposed and nitrogen-exposed animals. This study also involved exposure to argon, and again there were no portentous changes. Weiss, et al., (23) kept mice and rats in a predominately neon atmosphere for three weeks without any significant ill effects, although these animals did not do quite as well as "control" animals which were not in an environmental chamber. Aldrete and Virtue (39) exposed rats for six days to atmospheres containing helium, neon, argon

and xenon, with 20% oxygen, and found a significant reduction in leucocytes and red blood cells only in those exposed to xenon. This dose of xenon is mildly anesthetic.

One recent development connected with the Apollo missions has added a new dimension to the one-gas:two-gas controversy, if any controversy remains. There was some evidence early in the Gemini program that in vivo hemolysis was taking place in the astronauts (24, 25), possibly associated with lipid peroxidation in the red blood cell membrane.

In the early Apollo flights this effect was clearly absent, but it reappeared with the resumption of missions involving extra-vehicular activity (26). The significant factor involved is that the Apollo flights were all flown after the fire, and all ground operations were conducted in an atmosphere which contained 40% nitrogen up to the time of launch and in some cases nitrogen remained in the cabin even to the end of the flight. The conclusion is that this small amount of inert gas exerted some protective effect on the erythrocytes. Although the biophysical implications of this are intriguing, the pertinent factor here is that these findings strongly reinforce the reasoning that led to the decision to use a two-gas atmosphere. If indeed there is an inert gas effect at the red cell membrane it might not be the same for different gases. Landaw, et al., (27) however, feel that alterations in erythropoesis under the levels of hyperoxia involved here will be minimal and self-limiting. Clearly more research is needed in this area.

We conclude that no important biological effects have been demonstrated that augur against the use of nitrogen, helium, neon, or argon and none is anticipated, at least for flights of several weeks' duration. Whether or not there will be long-range effects is still an open question: e.g., even a small increase in metabolic rate might impose payload restrictions on a year-long flight.

Another matter is of more immediate concern, because it will involve flights which may not last for more than a few hours yet may extend

to any duration, and because it involves certain physical properties of the gases which have been shown to be important in human environmental biology. This is the matter of decompression. Decompression to the pressure required for extravehicular activity in a space suit is a planned activity on many space flights, and some degree of unscheduled decompression is always a possibility. Whether the choice of gas will have an important effect on the astronaut's chances of avoiding decompression sickness and what the relative advantages of the different gases might be must be determined before an intelligent choice of cabin atmospheres can be made.

Roth (5) presents a detailed analysis of bubble formation based on the physical properties of the gases in question and arrives at the conclusion that neon is the gas most likely to be the best choice. His conclusions are based on diffusion and solubility in several hypothetical models which represent different ways gas may be distributed and transported in the body. Roth recognizes the lack of experimental data that bear on his theoretical analysis. Some pertinent experiments conducted by Van Liew and Passke (22) show that for non-fatty tissue bubbles of nitrogen and neon grow and are absorbed at about the same rate.

One source of experience in decompression of humans breathing various gas mixtures is the field of diving. A wealth of information has been accumulated on the decompression of divers from dives involving nitrogen, and for the last 40 years much has been learned about helium. No information is available about decompressing divers who have been breathing mixtures containing neon.

The evidence from diving is not as clear-cut as it might be, nor is it entirely pertinent, since divers are exposed to breathing gas mixtures for relatively short times. It is clear that helium moves both into and out of the tissues more quickly than does nitrogen (29). Longer decompressions may be required for helium than for nitrogen in the case of short dives

where this increased tissue uptake is predominant, but for longer dives helium offers an advantage. Helium bends occur more promptly than those due to nitrogen, and it is necessary to use slower rates of ascent with the more easily diffusing helium.

Duffner and Snider (30) exposed men for 12 hours in simulated dives to air or helium-oxygen mixtures. Uneventful surfacing was possible from a slightly greater depth when helium was the inert gas. This duration of exposure is great enough to stress some of the tissues involved in decompression from a saturated condition and might therefore be applicable to the altitude situation.

Gersh, et al., (31) compared nitrogen, helium, and argon as to their efficacy in forming bubbles in various guinea pig tissues after decompression from 3 to 11 atmospheres pressure. The order of increasing bubble formation was found to be helium < nitrogen < argon.

A series of earlier experiments from this Laboratory (32) ranked the gases in the order helium = neon > nitrogen > argon when decompressions to 0.7 ata were carried out after two hours of exposure at 6 ata. There was no distinguishing difference between the results with helium and neon.

Comparative studies utilizing different inert gases in decompression to altitude are not common. One series of experiments that attempts to attack the problem head-on is that of Beard and her colleagues at the USAF School of Aerospace Medicine (33). They compared helium and nitrogen in men exposed to a simulated Manned Orbiting Laboratory decompression profile. Their conclusions leaned very slightly in favor of nitrogen over helium, but this seemed to be based more on their analysis than on their data. They also found helium bends had a quicker rate of onset and took a slightly greater pressure to relieve. The profile followed involved only four hours of exposure to the experimental atmosphere. It is important to note that because of the relative short duration of this exposure the subjects were

not saturated with the helium-oxygen atmosphere; on the contrary, their four-hour exposure period may have been of such a duration to favor helium uptake over nitrogen elimination, and very likely does not reflect the results that might follow saturation of the body tissues with helium in the absence of gaseous nitrogen.

Kellet, Coburn, and Hendler (34) have compared effects of decompression to 180 mm Hg of subjects which had been breathing 50 per cent oxygen and either helium or nitrogen for several hours. They found about the same incidence of bends in both groups, and as in the case of divers and the subjects of School of Aerospace Medicine study, they too noticed that the subjects breathing the helium mixture developed symptoms much sooner than those exposed to nitrogen-oxygen. The bends incidence did not seem to be particularly affected by the duration of helium breathing.

In experiments of a preliminary nature performed in this Laboratory (9), rats saturated with mixtures containing nitrogen, neon, helium, or argon were decompressed from one atmosphere to 100 mm Hg and forced to walk on a treadmill. Using a semi-quantitative rating scale, it was possible for us to rank the gases in the following way, in the order of increasing severity of symptoms: helium = neon > nitrogen > argon. These experiments are not conclusive for two reasons. First, there were too few animals involved (the somewhat random nature of decompression sickness demands considerable replication). Also, it is not necessarily safe to extrapolate from an animal as small as the rat to man, especially with regard to whole-body gas transport.

Maio, et al. (35), report that young men are quite likely to get bends if they are exposed to four hours of a 60% oxygen-40% nitrogen atmosphere after three hours of denitrogenation on 100% oxygen at sea level, and if they are then decompressed to 3.5 psia and made to exercise. This shows that a regimen that might be used on an Apollo or similar mission can cause decompression sickness, at least in the early part of

the flight. A report from the Soviet space program (36) revealed that decompression from a two-gas atmosphere at 400 mm Hg to 170 mm Hg could be carried out without bends. The key, of course, to successful altitude decompression without bends is to remove the inert gas by a period of breathing pure oxygen (37). Operationally, this may be easily accomplished or it may under other circumstances be difficult or impossible. The nature of the inert gas plays a role, possibly a significant one, in the optimization of this process.

One additional comparative study of the different gases is that of Bennett and Hayward (38). In simulated depth decompressions of rats these authors found a 50-50 mixture of helium and neon slightly better than other inert gases used, which were: helium, 30-70 helium-neon, nitrogen and argon. These data have been compared with previous work from our laboratory in a review by Schreiner (29). The most salient point in Schreiner's analysis, from the point of view of the current work, is that comparative decompressions with different gases must be made from the saturated condition. This is especially true in decompressions to altitude, where a relatively small amount of inert gas is involved in comparison with depth decompression. Experiments such as those of Beard are appropriate for a specific mission profile, but they may not provide data that is really applicable to the situation where an astronaut may be required to decompress after becoming saturated with the special atmosphere of his spacecraft.

III. THE MINIATURE PIG IN ALTITUDE DECOMPRESSION

A. Background

Because of the discomfort, risk and expense of using human subjects in the study of decompression sickness, and because of the obvious difficulties of extrapolating to man from rats or hamsters, there is a pressing need for a good animal model that simulates man with regard to his susceptibility to decompression sickness. Several criteria are paramount in the proper selection of an animal to be used in studies of altitude decompression sickness.

1. A minimum tissue perfusion rate very close to that of man.
2. Physiological control of regional blood flow (i.e. response to neurological, hormonal, and pharmacologic entities) similar to that of man.
3. Predictable susceptibility to altitude decompression sickness and display of objectively assessable signs thereof.
4. Ease of handling and convenient size.

The medium-sized domestic animals, i.e. dog, goat, sheep, and pig, are probably more physiologically similar to man than many of the species (e.g. rodents) usually found in the research laboratory. Some of the similarities between these animals and man are body weight, respiratory rate, heart rate, systemic blood pressure, etc., with the seeming similarity between two species usually being a function of body size.

The dog has been well studies from a physiological point of view, including diving physiology (40), and comes in a wide variety of shapes and sizes. However, the dog has relatively large lungs and heart, giving it a cardiopulmonary reserve capacity somewhat greater than that of man. This increases tolerance to environmental stress, whereas an ideal

experimental animal would be more sensitive to the stresses under study than man.

The goat has been the traditional animal for diving research since the days of Haldane, and with the sheep, appears to have many desirable properties. However, because of the substantial reductions in pressure involved in the study of altitude decompression, we felt that a ruminant would be susceptible to trapped gas problems that might be more debilitating than the evolved gas effects which are under study.

The pig remains as the animal of choice. Pigs have a gastro-intestinal tract and diet similar to man's (43), and should have a fat/lean ratio at least as great. These and other physiological and pharmacological advantages (41), plus the recent development of miniature pigs whose size and amount of fat can be somewhat controlled, have led us to the choice of the miniature pig as a possible subject for the study of altitude decompression sickness.

The work being reported here is in the nature of a feasibility study. We were concerned with the question of whether or not the miniature pig would furnish an acceptable model for use in comparing effects of various inert gases in altitude decompression. To do so, it must tolerate the degree of hypoxia necessary to elicit decompression symptoms, and must show distinct symptoms of decompression that can be distinguished from those of hypoxia.

B. Experiments

Our purpose was to decompress pigs to simulated altitude, under carefully controlled conditions exercise them on a treadmill, and to observe and record the development of decompression symptoms.

As subjects we used six two-year-old barrows (castrated males) of the miniature strain developed by the Hormel Laboratories, Austin, Minnesota. Their weights ranged from 61 to 73 kg, and they were fully grown. All had previously been subjected to decompression from simulated diving conditions. These pigs have a somewhat lean conformation, with a look something like a "razorback". All were in good health, and they should have been free of internal parasites since they were obtained "pathogen free" and had not been allowed to graze on the ground.

Decompressions were carried out in a retired single-lock Navy-type decompression chamber of about 700 liter capacity (Figure 1). This was connected to a 3 H. P. Stokes model 149-H vacuum pump rated for 80 cubic feet per minute. The lubricant in this pump was replaced with tricresyl phosphate for oxygen safety.

The problem in creating an altitude bends situation with animals is that pressures low enough to show symptoms of decompression sickness are much too low for breathing air. The pilot or astronaut, of course, breathes a mixture enriched in oxygen. It is necessary in decompression of animals to provide supplementary oxygen; this can be accomplished either by use of a mask or by flushing the chamber with pure oxygen. We have tried both of these methods, and have found the latter one to be more dependable.

For the initial attempt we felt that mask breathing would be better for two reasons. First, it enables the decompression to be accomplished more quickly, and it avoids the fire hazard of an oxygen-filled chamber. A mask was constructed from a rubber bucket, and a constant flow of oxygen was supplied to the mask during decompression of a pig. At

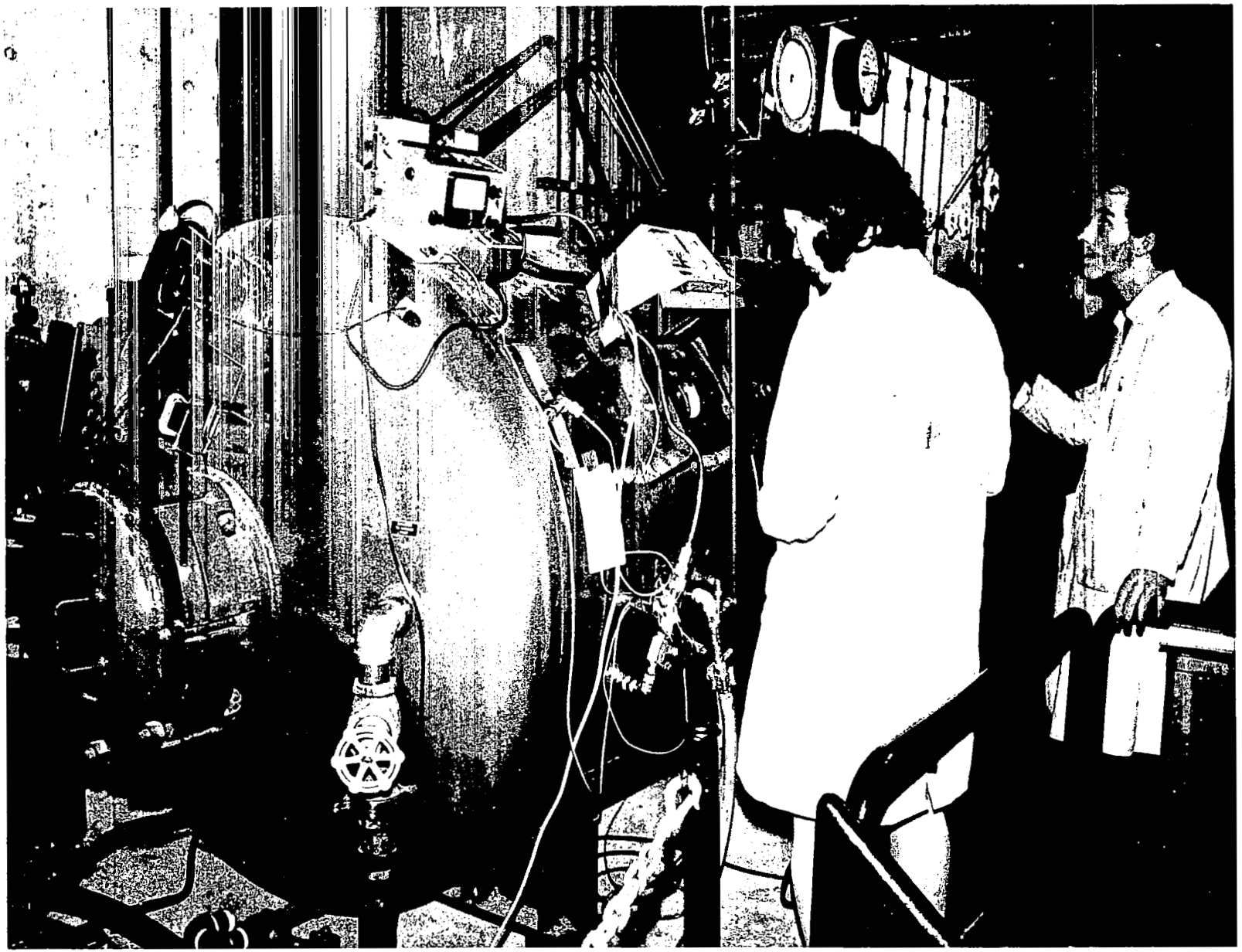


Figure 1. Chamber used for decompression of pigs to simulated altitude.

0. 27 atm, about 200 mm Hg, the animal was in obvious distress within about 7 minutes. At this pressure it is not likely that this distress was due to decompression sickness. Attempts to improve the equipment were not successful. In another experiment after 12 minutes at 200 mm Hg the animal died, and this approach was abandoned.

The project was resumed using the method of purging the chamber with oxygen and having the pig breathe the chamber atmosphere. Large lines were provided to the chamber for oxygen purging, and a Linde LC-3 liquid oxygen container was attached directly to the chamber, in addition to cylinder oxygen. To reduce danger of fire we decided not to operate any electrical equipment inside the chamber after the oxygen purge had begun and until after the minimum pressure had been reached. Also, the treadmill was lubricated with a fluorocarbon lubricant which is less flammable than oil.

The treadmill (Figures 2 and 3) is one which was constructed in our laboratory shop especially for pigs. Initially it was possible for the pigs to stop the belt by stiffening all four legs and resting against the back gate. To prevent this a sheet of teflon 1 mm thick was cemented to the backing plate in order to reduce friction, and an electric fence shocker was attached to electrodes mounted on the gate. The full strength of the shocker was so effective that it caused the animals to break stride and try to jump out of the cage, and generally disturbed the experiment. It was attenuated by placing a resistor in series with the leads to the extent that it produced a mild shock but no jolt. It was surprisingly easy to get the pigs to climb into the treadmill and all subjects learned to walk on it quite readily, though there was some variation in the individual strides. The motor is equipped with a variable-speed drive, but it was set at a speed of 5 m/min for all experiments.

A typical protocol for a decompression experiment:

Time 0 min - Oxygen purge of chamber begins, to 70% O_2.

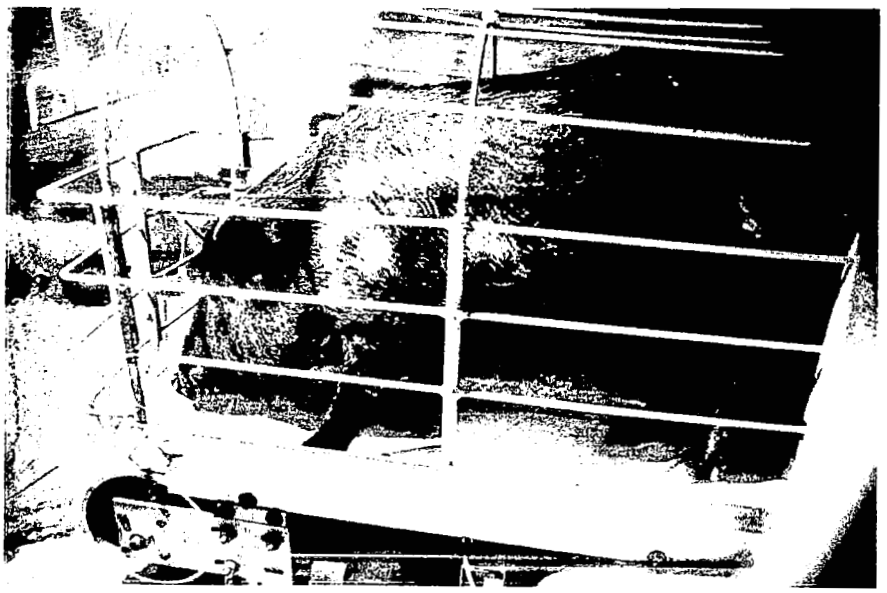


Figure 2. Pig walking normally on treadmill.

Figure 3. Pig showing symptoms of decompression sickness. He is unable or unwilling to extend his front legs and is favoring his hind legs.

2 min - Pig put in chamber, hatch closed, begin pressurizing with 0_2.

4 min - Hold at 22 psia to seal hatch, begin decompression

7 min - Hold at 380 mm Hg, purge with 0_2. PO_2 usually 350-370 mm Hg.

13 min - Reach 180 mm Hg. Hold at 180 for one hour, alternating 10 minutes rest with 10 minutes of treadmill operation. PO_2 170 mm Hg.

Some pigs tolerated this regime without showing many signs that could be objectively attributed to decompression sickness, but in most experiments there was clear evidence that things were not normal, and in time we learned to associate certain behavior with situations which we felt were surely decompression sickness. These impressions were, to be sure, subjective, and no attempt was made to carry out any sort of blind study. A summary of some of these experiments, with salient words selected from the commentary recorded in the logbook, is given in Table I.

In general, pigs suffering from mild bends seemed to paw at the belt or cage walls, scratch, paw at their jowls, favor one or more legs in walking, drag the hind legs or all four legs, walk on their "elbows" (Figure 3), sit and refuse to stand or walk, and in severe cases showed neurological symptoms such as twitching or convulsions. Vomiting was common, but was probably not a specific sign.

The problem of interpreting this type of data is that there are at least two prominent derangements of normal physiology operating at the same time, hypoxia and decompression sickness. To see if signs of hypoxia were confounding our observations, we exposed a pig to a situation frankly hypoxic but without reducing the pressure enough to cause decompression symptoms. The results showed that although some symptoms were similar, it should be possible easily to distinguish between these two situations.

Using the alveolar ventilation equations (42) it can be shown

that an inspired oxygen tension of 75 mm Hg at a total pressure of 380 mm Hg should produce about the same alveolar oxygen tension as breathing pure oxygen at 115 mm Hg total pressure. By the same token, breathing pure oxygen at 180 mm Hg should be equivalent to breathing air at the surface. Neither the respiratory exchange ratio nor the alveolar carbon dioxide tension are avilable and values must be assumed. For more detailed work using these equivalent altitudes it will probably be necessary to make measurements of some of the key parameters.

To separate further the symptoms of hypoxia and decompression, we exposed an animal to increased pressure (approximately 3 atm. abs.) for three hours before decompressing him (Table I). Some confirmation of the typical decompression signs was provided, but this animal had such severe symptoms that the experiment was terminated only seven minutes after reaching 180 mm Hg. Despite immediate recompression for a short (20 minute) treatment this pig died two hours after return to sea level pressure.

(A 16 mm color movie was made of these several situations, showing representative signs of hypoxia and both mild and severe decompression sickness, as well as normal behavior. Commentary prepared to accompany this film is included as Appendix A to this report. The film was included as part of the third quarterly progress report submitted to the Technical Monitor under this contract, and is considered as part of this Final Report.)

Table I reveals to some extent a subjective observation critical to further application of this technique. Though there seems to be a set of observable signs that are characteristic of decompression sickness, these vary somewhat between different individuals. This individual distinction is even more important when the added factor of relative hypoxia is superimposed. It is likely that when using helium as the inert gas a more stressful profile will be needed than the one used here, and this will tend to increase this

TABLE 1

Excerpts from Logbook of Pig Decompression Experiments

Date	Pig	Profile	Symptoms
21 January	Hitler	5 min to 150 mm Hg	Pawing, biting foot
23 January	Mike	5 min to 145 mm Hg, for 20 min.	Sliding hind legs
		To 100 mm Hg, back to 150 mm Hg	Jerking, drooping, crouching
		After 30 min to 175 mm Hg	Convulsion, down, couldn't get up
		0_2 treatment	Animal okay
26 January	Casper	5 min to 180 mm Hg	Turned around, rooting, pawing, favoring hind feet
27 January	Huff & Puff	3 min to 180 mm Hg	Tried to lie down, won't use hind legs (not relieved at one atm)
28 January	Hitler	4 min to 180 mm Hg	Pawing, few other symptoms
28 January	Hitler	~10% 0_2, 75 mm Hg $P0_2$ Total Pressure 380 mm Hg	Different behavior - walking, smelling belt, looking for food, rarely pawing. Curious, nervous, alert
		~10% 60 mm Hg $P0_2$ Total Pressure 380 mm Hg	Biting cage, awkward gait, stands quietly, hyperventilating heavy breathing, pawing, chewing, looks good
29 January	Napoleon	8 min to 130 mm Hg	Turned around, no other symptoms walking backwards
30 January	Hitler	6.5 min to 130 mm Hg	Pawing, chewing, favors hind leg, legs unsteady
		to 105 mm Hg for 4 min	Drags one leg. Penis extended; it looks cyanotic
		to 90 mm Hg	Threw up, began salivating excessively
2 February	Mike	3 hr @ 30 psi then 180 mm Hg in 8 min $P0_2$ 150 mm	Twitching, twisting, struggling, eyes rolling, sat down, could not get up - died 2 hrs after decompression ended.

confounding factor. But the differences in individual response can be used to advantage if each animal is "calibrated" and used as his own control. By learning the individual responses to known stresses the relative effectiveness of unknown ones can be readily determined.

C. Conclusions

From these experiments we draw the following conclusions:

1. It is possible to cause distinct symptoms of decompression sickness in small pigs under simulated altitude conditions, where the animals have been saturated with the sea-level air atmosphere and where they are decompressed in an oxygen-enriched environment.
2. These symptoms, though they may overlap those of hypoxia and resemble them to some extent, are different and can be distinguished with some objectivity.
3. To use this technique for subtle distinctions between different gases should be possible, but will require some refinements. The obvious ones are to "calibrate" each animal by exposures under controlled conditions to decompression sickness and hypoxia separately, and to increase the inert gas loading before decompression.

IV. ALTITUDE DECOMPRESSION OF RATS AFTER SATURATION EXPOSURE TO DIFFERENT INERT GASES

A. Methods

To study the relative altitude decompression hazard of various inert gas-oxygen systems, heavy rats were exposed to saturation in each inert gas mixture and subsequently decompressed to an altitude of 100 mm on a more-or-less stressful profile empirically defined to give a high incidence of bends for air saturation.

For saturation exposure of rats we used a closed environmental system, which we designate CES-2, which was designed, built, and used previously in our laboratory. This is shown in Figure 4 and described more fully in Appendix B and reference 9. The apparatus automatically controls the parameters of total pressure, oxygen partial pressure, relative humidity and temperature, and removes carbon dioxide, ammonia and other contaminants.

Male Sprague-Dawley rats (retired breeders) of weight range 400-650 gms were used in groups of 24 each. Duplicate experiments of 24 each were conducted in nitrogen and helium; single experiments of 24 each were conducted in neon, neon-helium, helium, and argon. Each group of 24 animals was exposed to the gaseous mixture for 48 hours under controlled conditions in CES-2 at a total pressure of 900 mm Hg and with an oxygen partial pressure of 120 mm Hg. This environment was chosen because it resulted in an increased inert gas loading to a value half again as much as it would have been if the animals had been equilibrated with air at sea level. Also, the slight relative hypoxia could be expected to make the animals more tolerant of the hypoxia involved in the decompression phase of the experiment.

Nitrogen levels in CES-2 as checked by gas chromatography were usually 0.3% to 0.5% during the exposures to exotic gases, never more than 1%. The neon-helium mix had a composition of 73% neon, 27% helium, with a trace of nitrogen.

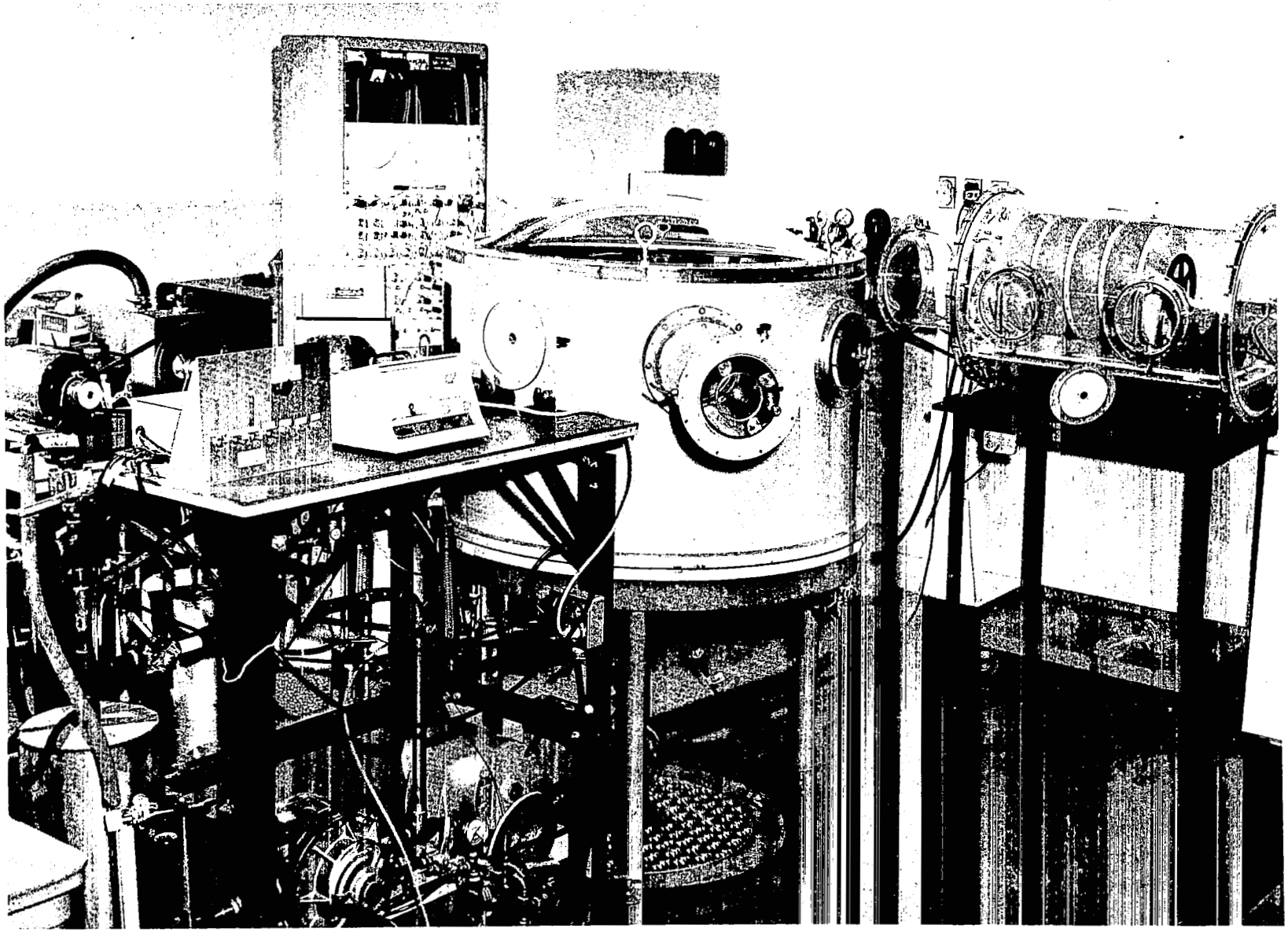


Figure 4. CES-2 chamber in center, with life support machinery at left. Decompression chamber is at right.

From each group, six subgroups of 4 rats each were "locked out" (Fig. 5) and subjected to decompression to a similated altitude pressure of 100-110 mm Hg. The locking out procedure and decompression were accomplished according to a strict schedule so that the rate of decompression of different groups would be as alike as possible. Nine minutes were allowed to reduce CES-2 pressure to sea level, lock out the animals, load them in the decompression chamber and decompress this chamber. (CES-2 pressure was immediately returned to 900 mm Hg.) Three minutes were allowed for oxygen flush and the decompression was timed so that the rats arrived at 110 mm Hg exactly 15 minutes after beginning the procedure. All steps used here were considered in the decompression computations and are discussed further in B below.

Decompressions were carried out in a large cylindrical "dry box" vacuum chamber, shown in Figures 4 and 6. This chamber was partially purged with pure oxygen before the animals were put in, and during the course of the decompression the purge was continued, so that by the time minimum pressure was reached the oxygen concentration was above 90%, with the balance water vapor and nitrogen.

During the 30-minute observation period the rats were forced to walk in a slowly moving treadmill, at a linear speed of 1.8 m/min. The purpose of the walking is not to "exercise" the animals, but rather to elucidate symptoms, since an observer cannot determine if a leg is paralyzed unless the animal attempts to move it (44). Observations were noted on a strip chart recorder which also recorded chamber pressure and oxygen partial pressure. The method of scoring the observed symptoms is given in the first column of Table 2. Figure 7 shows two rats walking in the normal way. At the top of the figure can be seen the pressure gauge and the oxygen analyzer. In Figure 8 it is possible to see the right hind limb of the rat on the right, being dragged in the manner which we rate as "paralysis".

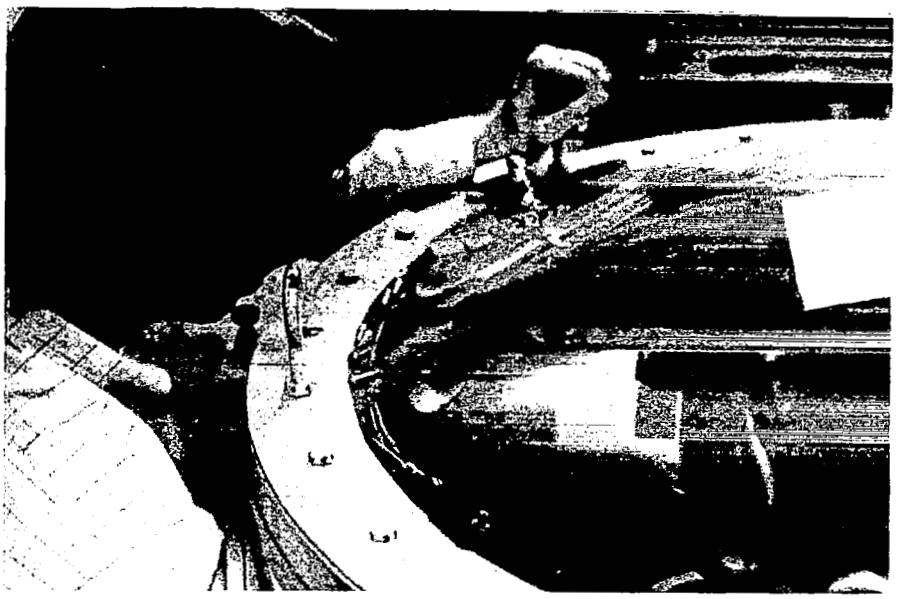


Figure 6. Setup of rat decompression chamber; treadmill can be seen inside.

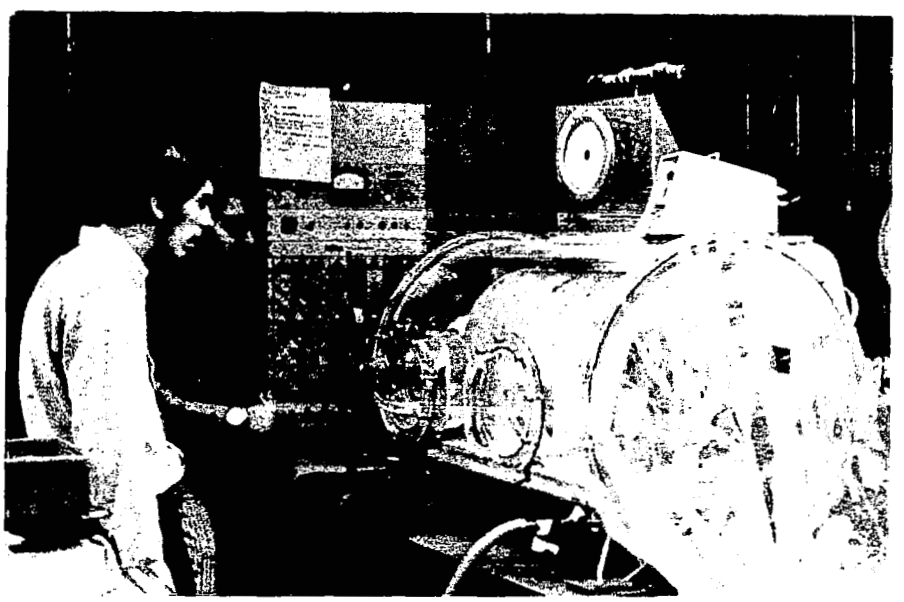


Figure 5. Dome of CES-2 chamber, showing cardboard transfer carton being inserted into lock.

TABLE 2

Criteria for Scoring Rat Decompression Sickness

Observations*	Raw Initial Score	Condensed Score Linear	Geom.	Expon.
No Symptoms	1	1	1	1
Mild Disturbance in Walking	2	2	2	10
Serious Disturbance in Walking (Reluctance to Walk)	3			
Distinct Paralysis of one or more legs	4	3	4	100
Tumbling - severe paralysis	5			
Death	6	4	8	1000

* Observed every minute for 30 minutes on treadmill.

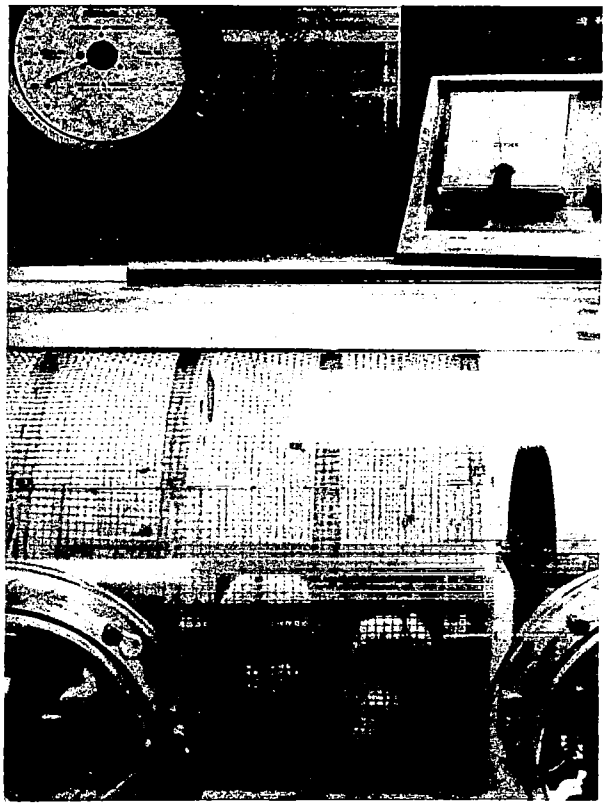


Figure 7. Rats in chamber at 100 mm Hg. This is typical walking behavior.

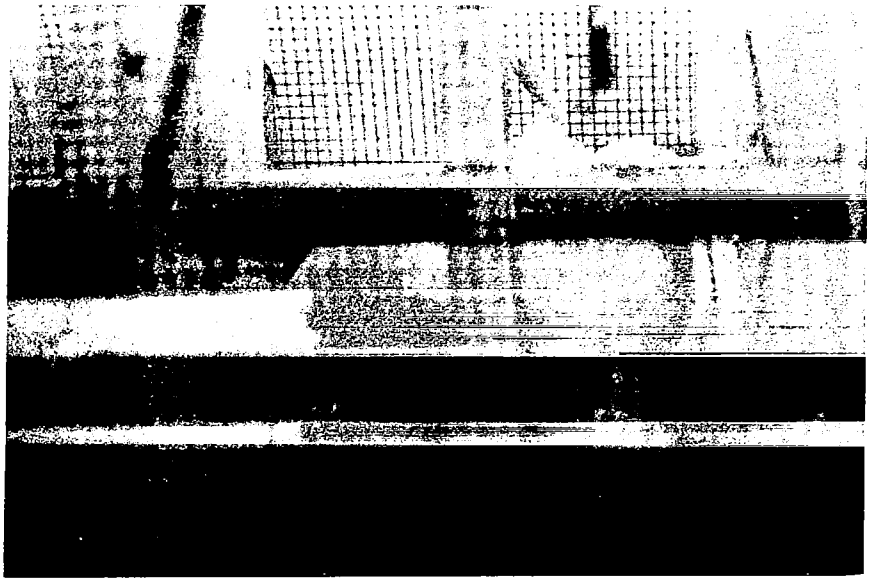


Figure 8. Closeup showing rat (right) with hind leg paralysis.

B. Experimental Results

1. Decompression Results

Results of seven experiments involving altitude decompression of 24 rats each in oxygen at 100 mm after saturation at 900 mm with various inert gas mixtures are summarized in Table 3 and analyzed in the subsequent figures and tables in terms of incidences of decompression sickness, types of symptoms, distribution of symptoms within an experimental population, correlations to body weight, time of appearance of maximum symptoms and relation of decompression sickness to theoretical tissue supersaturation ratios for the different inert gases.

After an initial scoring of animals on a scale of 1 to 6 (see Table 2) it was decided to condense the scale to a more objectively reproducible basis: (1) no symptoms, (2) mild to serious disturbance of gait, (3) definite paralysis, and (4) death. On this basis a percentage distribution of symptoms for the several gas systems tested are given in Table 4. Nitrogen killed 33% of the animals; argon and neon each killed 17%; neon-helium and helium groups exhibited no deaths.

In Table 5, results are expressed for each gas on the basis of total incidence of decompression sickness (all grades of symptoms) and incidence of severe decompression sickness (paralysis or death). Nitrogen and argon were most hazardous, followed by helium and by the least hazardous pair, neon and neon-helium, when compared on the basis of total incidence of decompression sickness. When compared on the basis of severe symptoms neon-helium and helium were least hazardous.

Helium and neon-helium exhibited similar patterns of distribution of symptoms (Figure 9). Neon and argon exhibited similar, slightly bimodal distributions (Figure 9). The distribution of nitrogen symptoms was bimodal and considerably different from that observed with the other gases.

Because the physiological factors underlying the

TABLE 3

Decompression Sickness Symptoms in Rats Exposed to Different Inert Gas Environments and Decompressed to Altitude

Inert Gas	No. Animals	Number of Animals Exhibiting Symptoms of Each Degree					
		1	2	3	4	5	6
Nitrogen	24	1	8	2	1	4	8
Nitrogen	24	0	4	6	2	4	8
Helium	24	2	16	6	1	3	0
Helium	24	3	13	8	0	0	0
Neon	24	5	5	9	0	1	4
Neon-Helium	24	5	8	9	1	1	0
Argon	23	1	9	7	1	1	4

TABLE 4

Percentage Distribution of Decompression Sickness Symptoms in Rats Decompressed to Altitude (100 mm) After Saturation in Various Inert Gas Environments

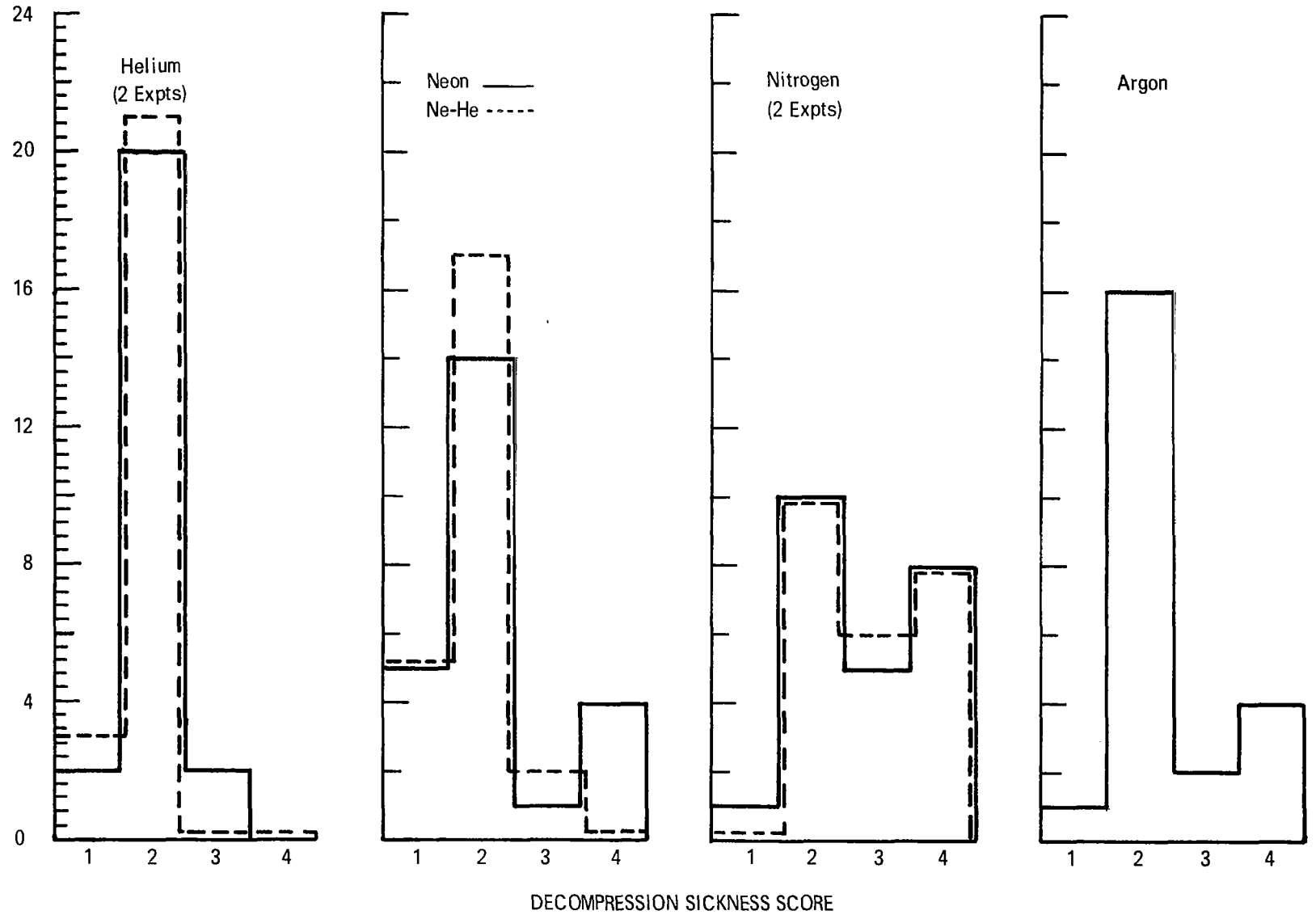
Inert Gas	% of Animals Exhibiting Symptoms			
	None	Walking Difficulty	Paralysis	Death
Nitrogen	2	42	23	33
Argon	4	69	9	17
Neon	21	58	4	17
Neon-Helium	21	71	8	0
Helium	10	85	4	0

TABLE 5

Decompression Sickness Symptoms for Rats Decompressed to Altitude: Summary of Total Incidence and Incidence of Severe Symptoms

Inert Gas	% Total Incidence All Symptoms	% Incidence of Severe Bends or Death
Nitrogen	98	56
Argon	95	26
Neon	79	21
Neon-Helium	79	8
Helium	89	4

Figure 9. Histograms Showing Frequency Distribution for Maximum Symptoms in Different Inert Gases



symptoms observed are not necessarily linearly related, we attempted to analyze our data on the basis of other scoring scales - a geometric scale: 1, 2, 4, 8, and an exponential scale: 1, 10, 100, 1000. The same relative ranking of the several gases was found regardless of the scale employed (Table 6).

Correlation was looked for between body weight and decompression sickness symptoms (using 1-6 scale) for each gas. No correlation exists for helium. Relatively poor correlation exists for argon. Apparent correlation between symptom severity and body weight exists for neon and neon-helium (Figure 10), and similarily for nitrogen (Figure 11).

Figure 12 illustrates the relations between time of appearance of maximum symptoms and the severity of the maximum symptoms observed for each animal in each gaseous system. Correlation appears to exist between these parameters for neon and neon-helium and possibly argon but not nitrogen or helium. Table 7 shows a similar analysis of time of appearance of maximum symptoms without regard, however, to severity. Maximum symptoms appear faster in helium and argon saturated animals than in the others. This might be expected for helium on the basis of its high diffusivity. Diffusivity, however, cannot explain the argon results and perhaps relates to the high relative and absolute solubility of argon. Once nucleation occurs, helium bubbles grow rapidly because of rapid diffusion even though the tissue concentration is low; on the other hand argon bubbles grow rapidly because of the high tissue gas concentration in spite of its poor diffusivity.

TABLE 6

Summary of Decompression Sickness Scores for Rats Exposed to Different Inert Gas Environments and Decompressed to Altitude: Comparison of Different Scoring Procedures

Inert Gas	% of Maximum Possible Score			
	Linear Scale	Geometric Scale	Exponential Scale	Relative Ranking *
Nitrogen	72	56	36	1
Argon	60	40	18.2	2
Neon	54	36	17.7	3
Helium	49	25	1.3	4
Neon-Helium	47	24	0.8	5

* Most Hazardous = 1

Least Hazardous = 5

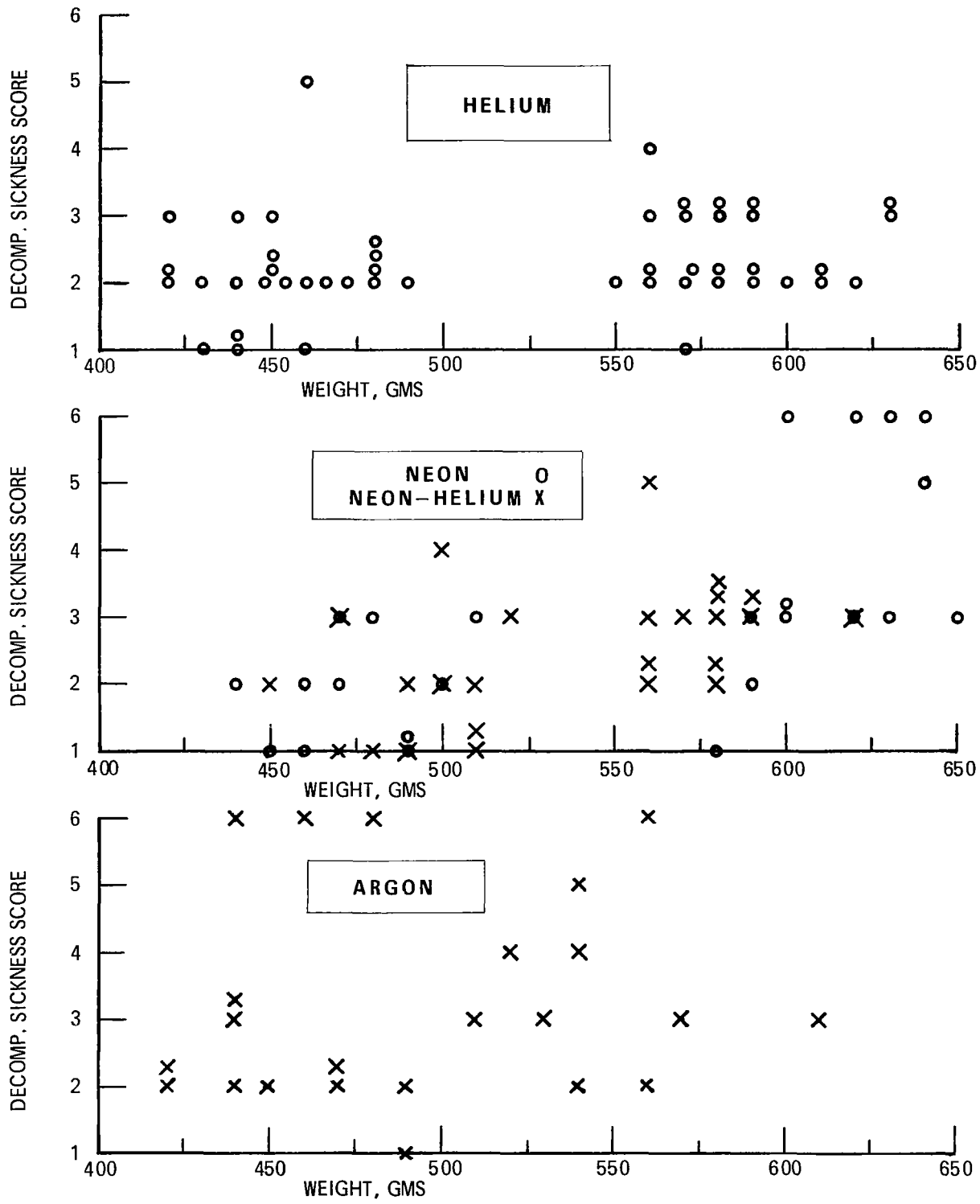
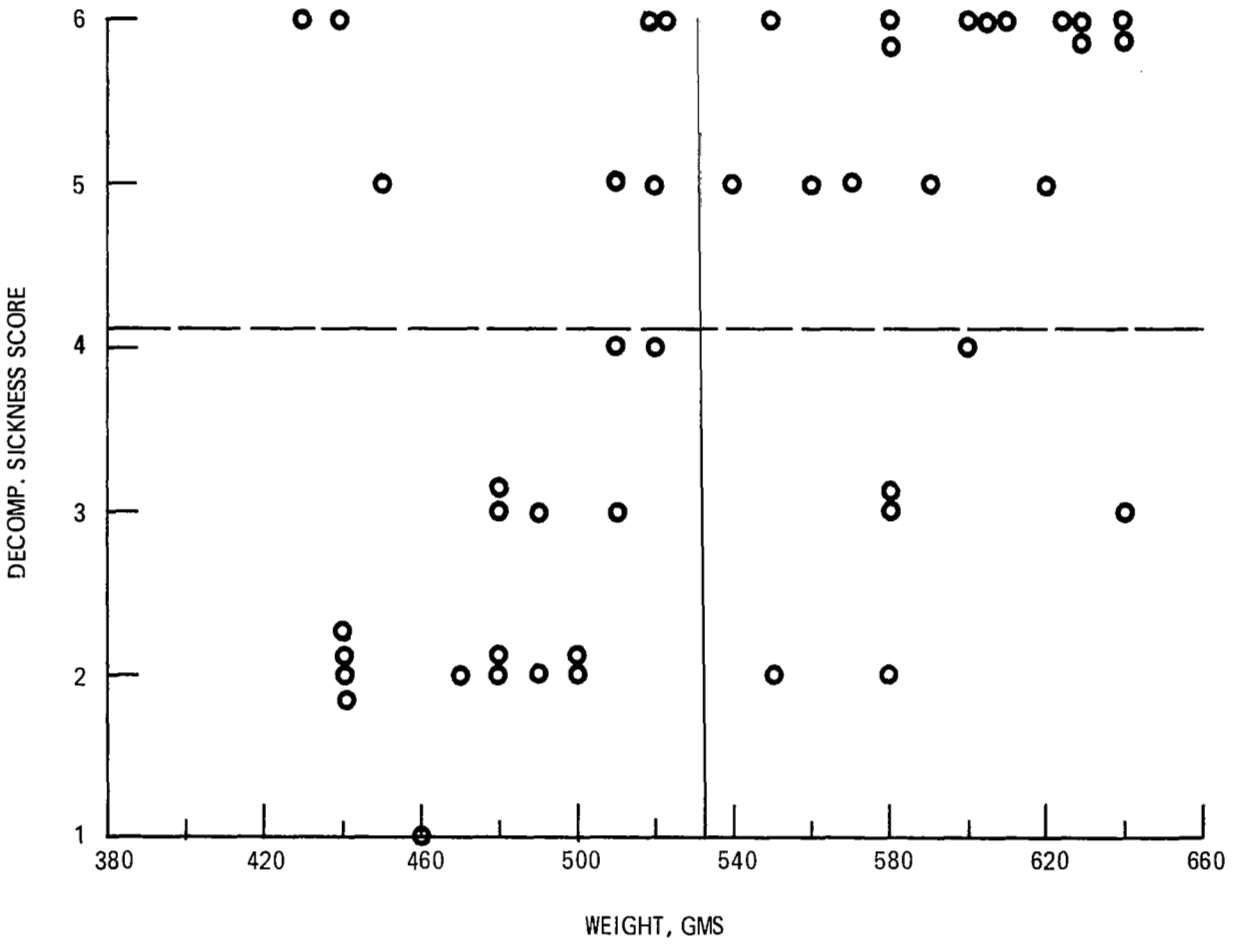


Figure 10. Relationships of Body Weight to Decompression Sickness Scores

Figure 11. Correlation of Whole Body Weight to Decompression Sickness Score for Rats Decompressed after Nitrogen Saturation



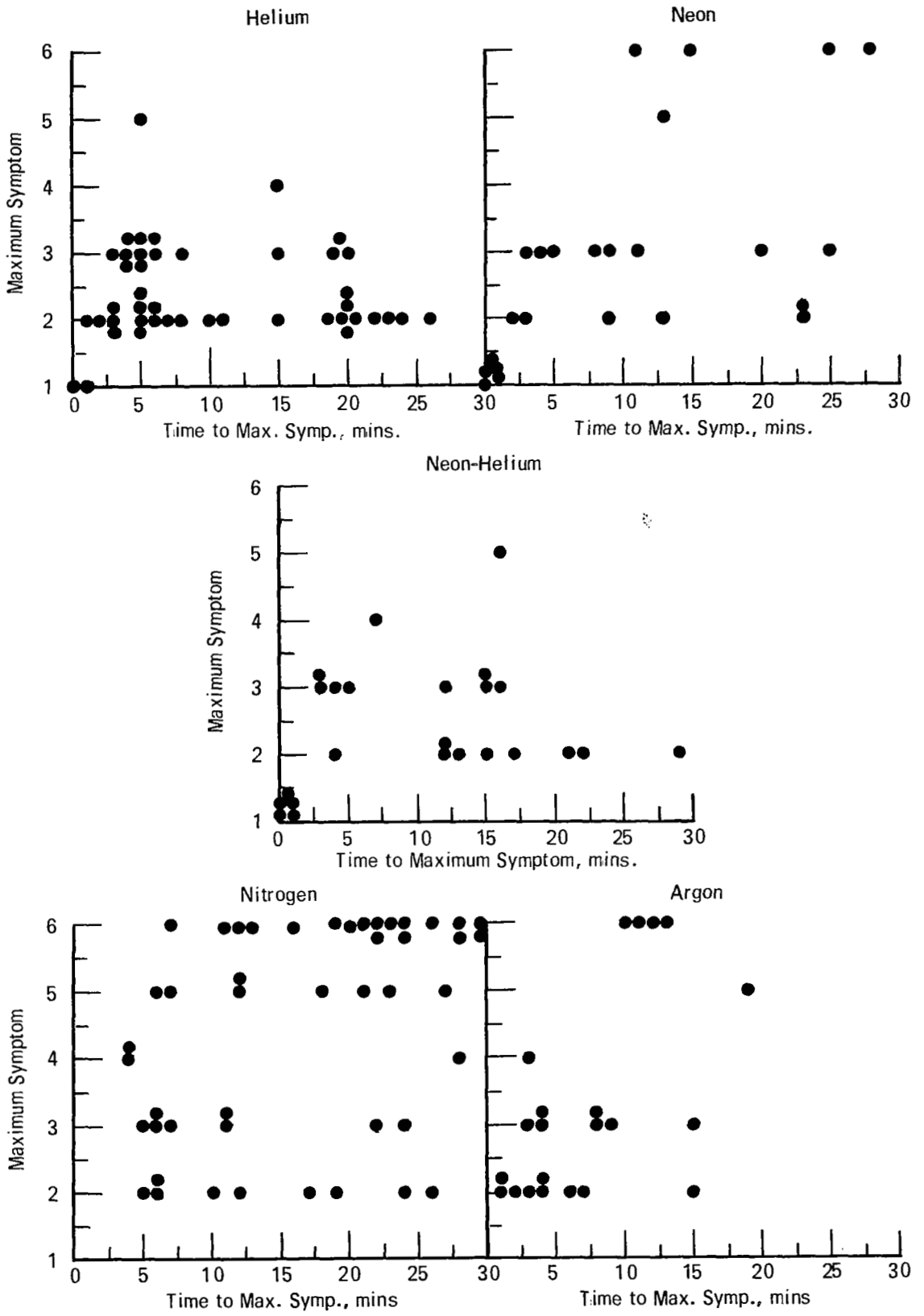


Figure 12. Maximum Symptoms and Time of Appearance

TABLE 7

Comparison of Gases on Basis of Time of Appearance of Maximum Decompression Sickness Symptoms

Time Appearance Max. Symptoms	% of Animals *				
	He	Ne	Ne-He	N_2	Ar
0 - 14 mins.	55	50	42	46	83
15 - 30 mins.	34	29	38	52	13
<10 mins.	53	33	25	28	70
>10 mins.	36	46	54	67	26
<5 mins.	36	21	21	9	43
>20 mins.	21	25	12	41	0

* Animals exhibiting no decompression symptoms are not included.

2. Analysis of Decompression Results

Our experimental decompression profile (Table 8) was subjected to computer analysis according to a mathematical model of inert gas exchange described in Appendix C. Essentially our model considers a biological system as composed of 15 inert gas exchanging compartments each defined by a value of blood flow and lipid: water composition chosen to cover the spectrum of reasonable physiologic possibility. Gas uptake and elimination is considered to be perfusion limited and exponential for each compartment. Solution of the differential equation expressing the exponential elimination or uptake of all inert gases present for each compartment provides theoretical values for the inert gas content (in terms of equilibrium partial pressure) of each compartment at any times selected in the profile. The sum of inert gas tensions divided by total pressure of the environment gives a measure of the relative degree of supersaturation for each compartment at each time chosen.

This was computed for 5 minute intervals during the course of observation at 100 mm altitude pressure. Computed supersaturation or "surfacing" ratios are tabulated in Table 9 for arrival at altitude and 15 minutes later. Arrival (initial) at altitude values are plotted in Figure 13.

The theoretical calculations show a ranking of decreasing supersaturation ratios:

$$Ar > N_2 >> Ne\text{-}He > He > Ne$$

On the basis of a supersaturation limited determination of decompression sickness this should be the decreasing order of hazard of the gases. Clearly this does not match experimental observations; only a general trend exists between surfacing ratio and decompression sickness score. Figure 14 shows this for two selected compartments (No. 7 and 11). In some previous studies with depth decompression in rats in our laboratory these compartments, especially No. 7, correlated well with decompression sickness scores.

TABLE 8

Decompression Profile Subjected to Computer Analysis According to 15-compartment Perfusion Limited Gas Exchange Model

Time (mins.)	Total Pressure mm	Environmental Composition and Partial Pressure (mm)*		
0	900	IG	748	
1	750	IG	618	
9	750	IG	599	
10	750	N_2	570	IGO
10.5	650	N_2	490	IGO
12	650	N_2	5	
15	100	N_2	5	Observation Period at Altitude
20	100	N_2	5	
25	100	N_2	5	
30	100	N_2	5	
35	100	N_2	5	
40	100	N_2	5	
45	100	N_2	5	

IG = Inert Gas: He, N_2, Ne, Ar, or Ne-He

* Balance of total pressure contributed by oxygen

TABLE 9

Computed Surfacing Ratios of Dissolved Inert Gases in 15 = Perfusion Limited Tissue Compartments Upon Arrival at Altitude and 15 minutes later

Compartment No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
$\dot{Q}$ min $^{-1}$	0.3	0.3	0.3	0.1	0.1	0.1	0.1	0.03	0.03	0.03	0.03	0.0085	0.0085	0.0085	0.0085
% Fat	30	70	100	0	30	70	100	0	30	70	100	0	30	70	100
t = 15 (Arrive at altitude, 100 mm total pressure)															
He	2.11	1.98	2.60	4.16	4.29	4.69	5.03	6.18	6.31	6.47	6.59	7.08	7.12	7.18	7.22
N_2	3.37	4.69	5.24	4.16	5.61	6.35	6.59	6.18	6.86	7.11	7.20	7.08	7.30	7.38	7.40
Ne	2.60	2.82	2.99	4.16	4.23	4.46	4.83	6.18	6.12	6.30	6.44	7.08	7.04	7.12	7.16
Ar	3.37	4.69	5.24	4.16	5.77	6.42	6.68	6.18	6.89	7.14	7.22	7.08	7.31	7.38	7.41
Ne-He	2.11	2.48	3.01	4.16	4.49	4.97	5.34	6.18	6.39	6.60	6.72	7.08	7.15	7.22	7.25
t = 30 (15 minutes after decompression to altitude)															
He	0.15	0.21	0.33	0.97	1.26	1.73	2.17	3.94	4.37	4.78	5.06	6.23	6.42	6.60	6.70
N_2	0.45	1.50	2.22	0.97	2.82	4.33	4.90	3.94	5.63	6.33	6.60	6.23	6.89	7.14	7.22
Ne	0.33	0.75	0.96	0.97	1.67	2.18	2.65	3.94	4.45	4.94	5.25	6.23	6.41	6.63	6.74
Ar	0.45	1.50	2.22	0.97	2.99	4.43	5.04	3.94	5.66	6.39	6.63	6.23	6.91	7.15	7.23
Ne-He	0.15	0.29	0.47	0.97	1.44	2.07	2.61	3.94	4.55	5.06	5.37	6.23	6.48	6.70	6.80

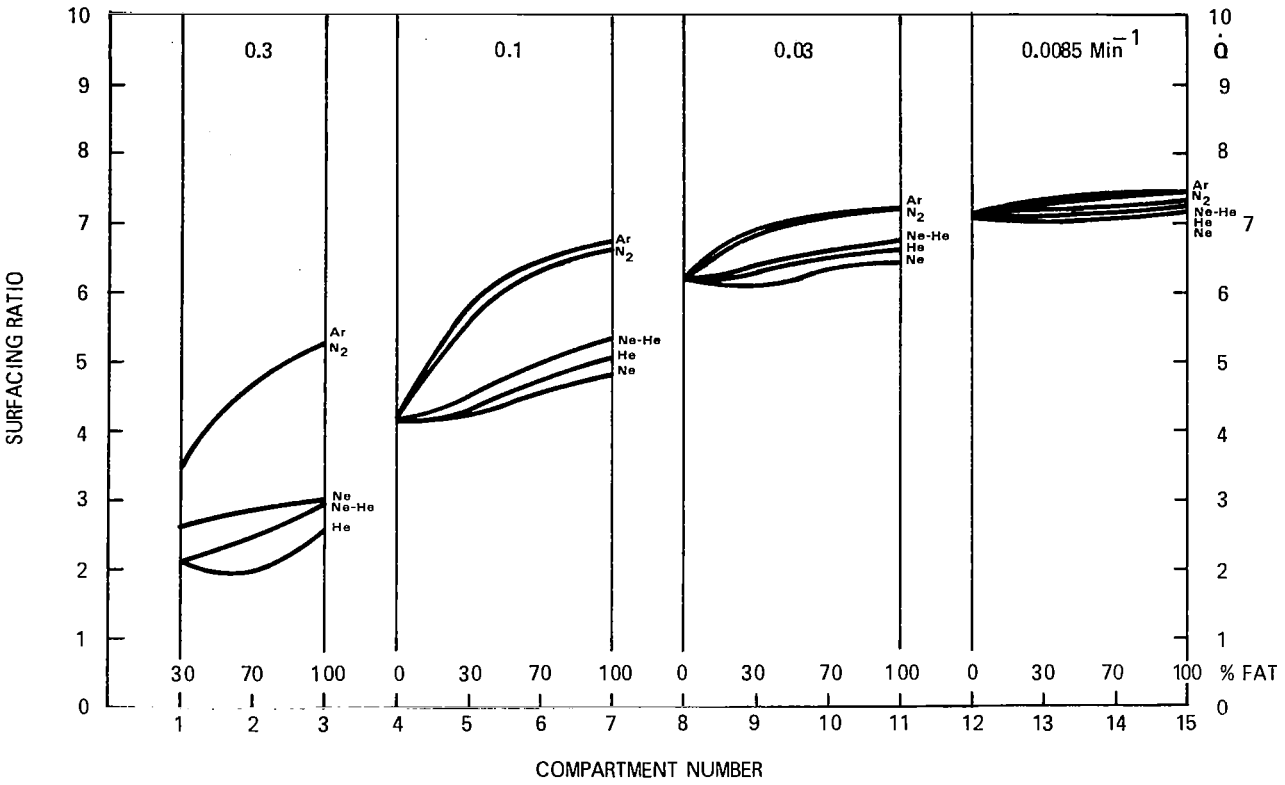


Figure 13. Computed Surfacing Ratios of Dissolved Inert Gases in 15 Perfusion-limited Tissue Compartments Upon Arrival at Altitude (t = 15 mins; P = 100 mm)

Figure 14. Relationships Between Decompression Sickness for Different Inert Gases and Supersaturation in Selected Tissue Inert Gas Compartments.

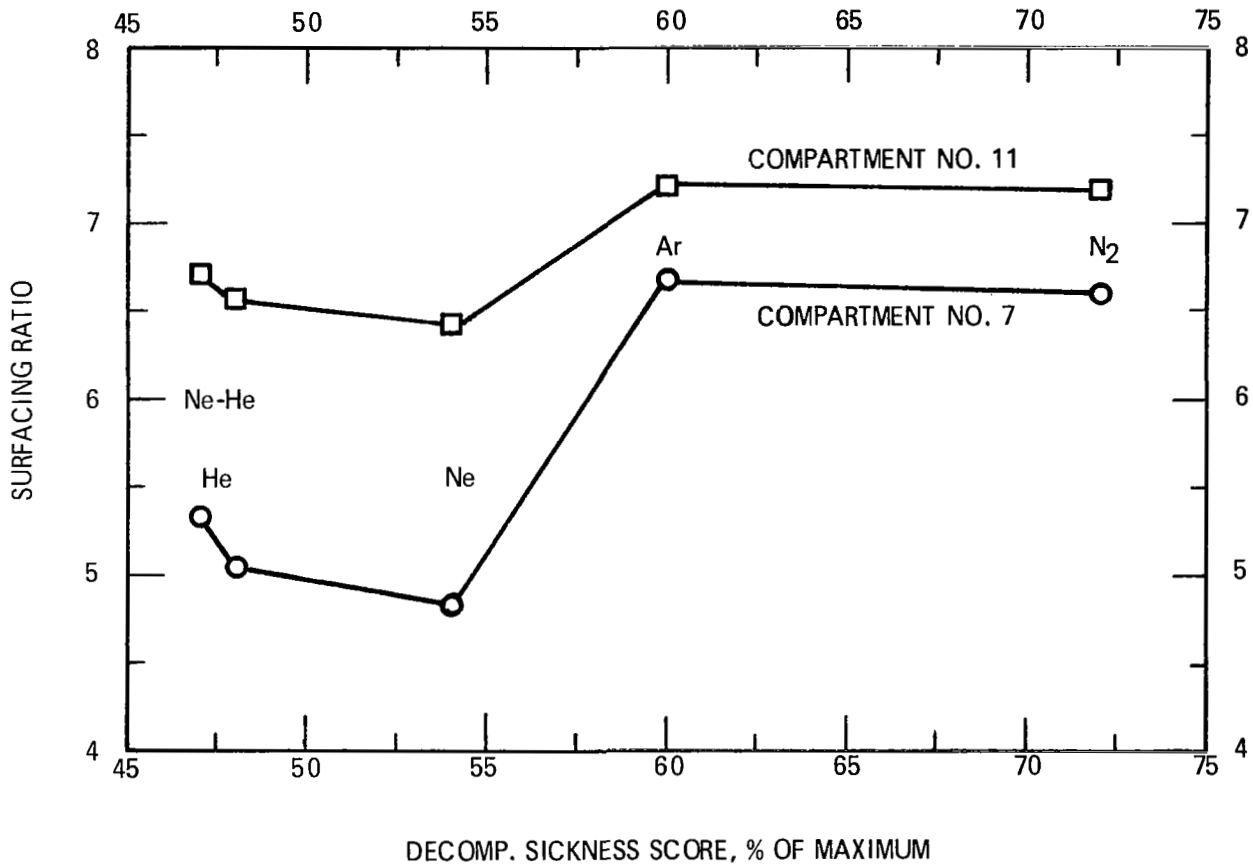


Figure 15 shows for compartment No. 7 the change in relative supersaturation for each gas with time after arrival at altitude. On this basis, neon has a lesser slope than neon-helium or helium; argon and nitrogen have even smaller slopes. It should be noted, however, that supersaturation should be critically important to nucleation while other factors should come into play once bubbles form (e. g. diffusivities in lipid and water, concentrations in lipid and water).

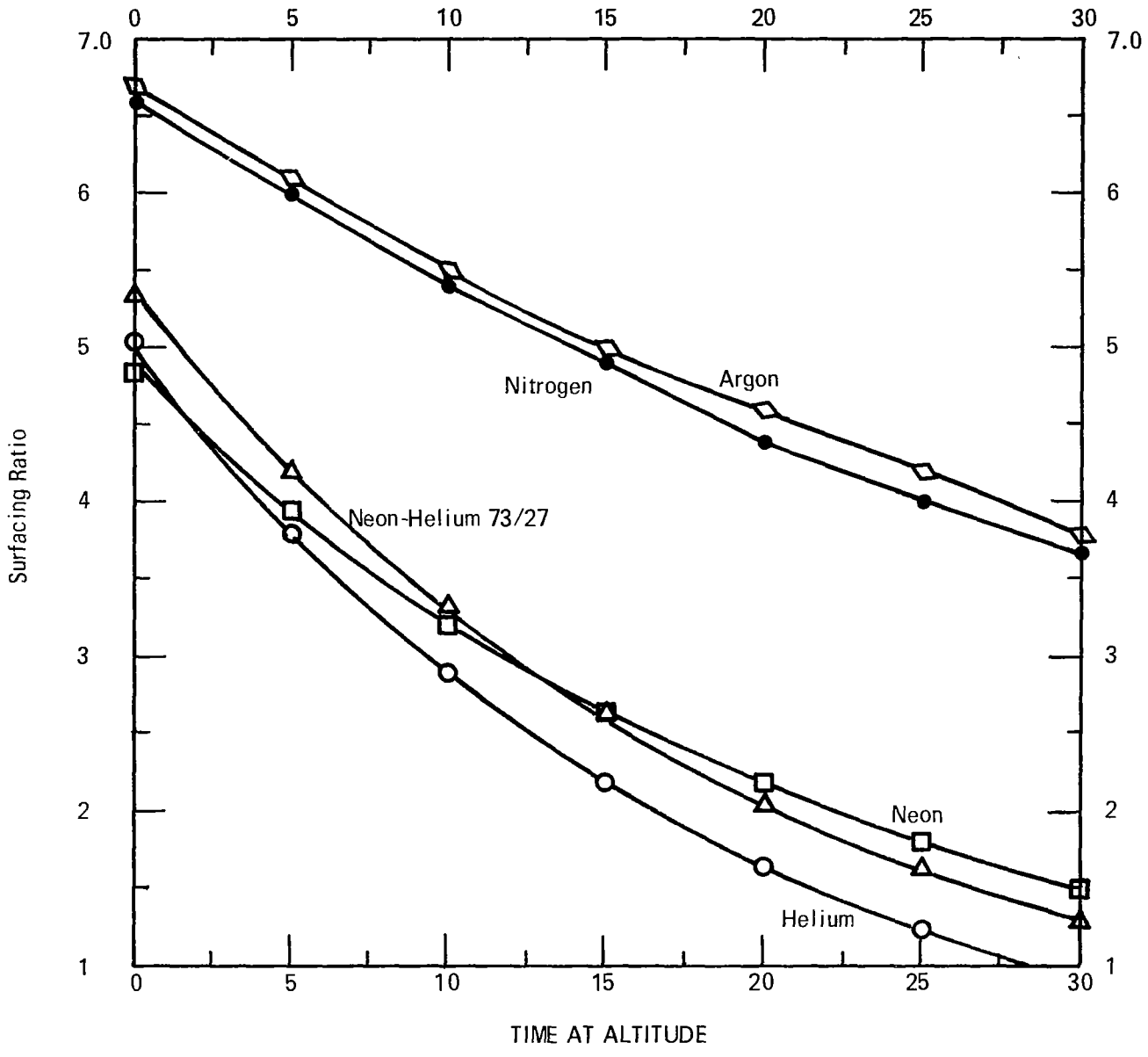


FIGURE 15. Computed Supersaturation in Tissue Inert Gas Compartment No. 7 During a Period at Altitude.

C. Discussion

In terms of (a) a perfusion limited model of gas exchange and (b) considering a positive relation between relative supersaturation of a tissue and decompression sickness incidence and severity, it would be predicted that argon and nitrogen would be identical in decompression hazard and both should be considerably more hazardous than neon, neon-helium, or helium. Neon would be expected to have a slight advantage over neon-helium or helium. Except in the case of comparing the pair nitrogen and argon to the triad, neon, helium, neon-helium, as a group, the expected correlation between supersaturation and bends does not hold. The first assumption above is likely a good one for saturation conditions, as existed in our decompression; the second assumption is probably not valid.

The relative difference and order of experimental ranking of nitrogen versus argon may be rationalized on the basis of factors involved in bubble growth once nucleation has occurred. Thus the ratio of decompression scores for nitrogen/argon is 1.2 in agreement with the ratio of diffusivities for these gases in fat and approximately that of the ratio in water.

With rats we are dealing not with a hit versus no-hit evaluation but with a semi-quantitative evaluation of a spectrum of decompression sickness symptoms. Indeed on a total bends incidence basis (Table 5), nitrogen and argon are indistinguishable and considerably more hazardous than helium, neon, or neon-helium. Neon and neon-helium, while indistinguishable from one another, are less hazardous (on a total bends incidence basis) than helium.

Van Liew, et al (28) found that neon resembled nitrogen with respect to behavior of gas pocket bubble growth and resolution in rats. Bennett and Hayward (38) have called attention to the possible advantage of neon-helium mixtures in decompression, but their data suggest a 50-50 mixture to be most favorable. We would conclude from

our data that neon-helium mixtures, even those available as relatively economic commercial "crude" neon (73:27) should be more fully explored in large animals and man as a potentially advantageous inert gas component for two-gas space cabin environments.

Of perhaps most importance is a comparison of the gases on the basis of incidence of severe bends (paralysis and death). Helium (4%) was found safest on this basis followed closely by neon-helium (8%). Neon (21%), argon (26%) and nitrogen (56%) would be considered unacceptable on this basis of evaluation. Argon perhaps should be more fully evaluated in the rat before our somewhat unusual findings with this gas relative to nitrogen and neon are generally accepted.

V. REFERENCES

1. MacHattie, L., and H. Rahn. Survival of mice in absence of inert gas. Proc. Soc. Exptl. Biol. Med. 104:772-775, 1960.

2. Morgan, T. E., F. Ulvedal, R. G. Cutler and B. E. Welch. Effects of man of prolonged exposure to oxygen at a total pressure of 190 mm. Hg. SAM TDR-63-52. Brooks AFB, Texas: USAF School of Aerospace Med., 1963.

3. Roth, E. M. Space-cabin atmospheres. Part I. Oxygen toxicity. NASA SP-47. Washington: Natl. Aeron. Space Admin., 1964.

4. Roth, E. M. Space-cabin atmospheres. Part II. Fire and blast hazards. NASA SP-48. Washington: Natl. Aeron. Space Admin., 1964.

5. Roth, E. M. Space-cabin atmospheres. Part III. Physiological factors of inert gases. NASA SP-117. Washington: Natl. Aeron. Space Admin., 1967.

6. Roth, E. M. Space-cabin atmospheres. Part IV. Engineering trade-offs of one-versus two-gas systems. NASA SP-118. Washington: Natl. Aeron. Space Admin., 1967.

7. Cook, S. F., F. E. South, and D. R. Young. Effect of helium on gas exchange of mice. Am. J. Physiol. 164:248-250, 1951.

8. Leon, H. A., and S. F. Cook. A mechanism by which helium increases metabolism in small mammals. Am. J. Physiol. 199:243-245, 1960.

9. Hamilton, R. W., Jr., G. F. Doebbler, C. H. Nuermberger, and H. R. Schreiner. Biological evaluation of various space cabin atmospheres. Final Report to the USAF School of Aerospace Medicine, Contract AF 41(609)-2711. Tonawanda, New York: Union Carbide Corporation, 1966.

10. South, F. E., and S. F. Cook. Effect of helium on the respiration and glycolysis of mouse liver slices. J. Gen. Physiol. 36:513-528, 1953.

11. Maio, D. A., and J. R. Neville. The effect of chemically inert gases on oxygen consumption in living tissues. SAM-TR-66-109. Brooks AFB, Texas: USAF School of Aerospace Medicine, 1966.

12. Rodgers, S. H. The oxygen consumption of rat tissues in the presence of nitrogen, helium, or hydrogen. Ph. D. Thesis. Rochester, New York: The University of Rochester, 1966.

13. Grimard, M., and H. S. Weiss. Inert gas effects on the respiration of tissues from normal and nitrogen-free animals. Preprints, 1970 Annual Meeting, Aerospace Medical Association.

14. Young, H. L., and P. R. Lundgren. Stimulation of oxygen consumption of rat tissue by helium and neon. Preprints, 1970 Annual Meeting, Aerospace Medical Association.

15. Fox, E. L., H. S. Weiss, R. L. Bartels, and E. P. Hiatt. Thermal responses of man during rest and exercise in a helium-oxygen environment. Arch. Environ. Health 13:23-28, 1966.

16. Robertson, W. G., and G. L. McRae. Study of man during a 56-day exposure to an oxygen-helium atmosphere at 258 mm. Hg total pressure. VII. Respiratory Function. Aerospace Medicine 37:578-582, 1966.

17. Robertson, W. G., H. J. Zeft, B. E. Welch. Observations on man in an oxygen-helium environment at 380 mm. Hg total pressure. II. Respiratory. Aerospace Medicine 37:453-456, 1966.

18. Hamilton, R. W., Jr., J. B. MacInnis, A. D. Noble, and H. R. Schreiner. Saturation diving at 650 feet. Tech. Memo. B-411. Tonawanda, N.Y.: Ocean Systems, Inc., 1966.

19. Bradley, M. E., J. Vorosmarti, P. G. Linaweaver and W. F. Mazzone. Results of physiologic studies conducted during chamber saturation dives from 200 feet to 825 feet. A preliminary report. Research Report 1-68. Washington: U. S. Navy Deep Submergence Systems Project, 1968.

20. Hargreaves, J. J., W. G. Robertson, F. Ulvedal, H. J. Zeft and B. E. Welch. Study of man during a 56-day exposure to an oxygen-helium atmosphere at 258 mm. Hg total pressure. I. Introduction and General Experimental Design. Aerospace Medicine 37:552-555, 1966.

21. Schreiner, H. R. The physiological effects of argon, helium and the rare gases. Technical Report I to the Office of Naval Research, Contract Nonr 4115(00). Tonawanda, New York: Union Carbide Corporation, 1964.

22. Hamilton, R. W., Jr., J. D. Cohen, G. F. Doebbler, L. F. Exposito, J. M. King, K. H. Smith and H. R. Schreiner. Biochemical and metabolic effects of a six-month exposure of small animals to a helium-oxygen atmosphere. NASA CR-1372. Washington: Natl. Aeron. Space Admin., 1969.

23. Weiss, H. S., J. F. Pitt, E. S. Kreglow, M. Grimard and E. P. Hyatt. Three-week exposure of rodents to a neon enriched atmosphere. Aerospace Med. 39:1215-1217, 1968.

24. Berry, C. A. Preliminary clinical report of the medical aspects of Apollos VII and VIII. Aerospace Med. 40:245-254, 1969.

25. Fischer, C., P. C. Johnson and C. A. Berry. Red blood cell mass and plasma changes in manned space flight. J. Amer. Med. Assoc. 200:99, 1967.

26. Fischer, C. Personal communication.

27. Landaw, S. A., H. A. Leon and H. S. Winchell. Effects of hyperoxia on red blood cell survival in the normal rat. Aerospace Med. 41:48-55, 1970.

28. Van Liew, H. D., and M. Passke. Permeation of neon, nitrogen, and sulfur hexafluoride through walls of subcutaneous gas pockets in rats. Aerospace Medicine 38:829-831, 1967.

29. Schreiner, H. R. Advances in decompression research. J. Occupational Med. 11:229-237, 1969.

30. Duffner, G. J., and H. H. Snider. Effects of exposing men to compressed air and helium-oxygen mixture for 12 hours at pressures of 2-2.6 atmospheres. Research Report 1-59. Washington: U. S. Navy Experimental Diving Unit, 1959.

31. Gersh, I. H., G. E. Hawkinson, and E. H. Jenney. Comparison of vascular and extravascular bubbles following decompression from high pressure atmospheres of oxygen, helium-oxygen, argon-oxygen, and air. J. Cell. Comp. Physiol. 26:63-74, 1945.

32. Doebbler, G. F., R. G. Buchheit, and H. R. Schreiner. Effect of helium, neon, nitrogen, and argon on the relative susceptibility of animals to depth decompression sickness. Presented at the 38th Annual Meeting of the Aerospace Medical Association, Washington, D. C., 10-13 April 1967.

33. Beard, S. E., T. H. Allen, R. G. McIver, and R. W. Bancroft. Comparison of helium and nitrogen in production of bends in simulated orbital flights. Aerospace Medicine 38:331-337, 1967.

34. Kellett, G. L., K. R. Coburn, and E. Hendler. Investigation of decompression hazards following equilibration in a simulated spacecraft atmosphere of 50 per cent O_2 - 50 per cent He at 7 psi. Rept. NAEC-ACEL 540. Philadelphia: U. S. Naval Aerospace Crew Equipment Laboratory, 1966.

35. Maio, D. A., T. H. Allen and R. W. Bancroft. Decompression sickness in simulated Apollo space-cabins. Aerospace Med. 40:1114-1118, 1969.

36. Bondarev, E. V. Use of a two-gas artificial atmosphere in manned spaceships. In: Space Biology and Medicine, Vol. 3, No. 2. Washington: Joint Publ. Research Serv., 1969.

37. Schreiner, H. R. Decompression procedures for the safe ascent of aerospace personnel from ground level to altitude. Final Report to the National Aeronautics and Space Admin., Contract NAS 9-6978. Tonawanda, N.Y.: Union Carbide Corp., 1968.

38. Bennett, P. B. and A. J. Hayward. Relative decompression hazards in rats of neon and other inert gases. Aerospace Med. 39:301-302, 1968.

39. Aldrete, J. A., and R. W. Virtue. Prolonged inhalation of inert gases by rats. Anesthesia Analygesia Current Res. 46:562-565, 1967.

40 Reeves, E., and E. L. Beckman. The incidence of decompression sickness in dogs following 7, 12, 18, and 24 hour saturation dives with "no-stop" decompression. Federation Proceedings 25:400, 1966.

41. Swine in Biomedical Research, edited by L. K. Bustad and R. O. McClellan. Richland, Washington: Battelle, 1966.

42. Rahn, H. and W. O. Fenn. A Graphical Analysis of the Respiratory Gas Exchange. Washington: American Physiological Society, 1955.

43. Doyle, R. E., S. Garb, L. E. Davis, D. K. Meyer and F. W. Clayton. Domesticated farm animals in medical research. Ann. N. Y. Acad. Sci. 147:129-204, 1968.

44. Philp, R. B., and G. W. Gowdey. Decompression sickness in rats during exercise at simulated low altitudes after exposure to compressed air. Aerospace Med. 33:1433-1437, 1962.

VI. APPENDIX

A. Commentary Accompanying the Short Film Showing Decompression Symptoms in Miniature Pigs

The first scene shows the treadmill, and our method of luring the pig into same. This step has caused no difficulty at all, to our great surprise. Note the wires attached to the swinging gate. They are connected to a fence charger controlled outside the chamber, so that the animal may be shocked if he allows himself to slide along on the moving belt to the rear of the cage. Unfortunately the belt is not reversible, so if a pig turns himself around the experiment is more or less ruined, since his walking behavior is different when going backwards.

Huff and Puff is our most obese subject, and seemed to be far more susceptible to bends than some of the others. His walking at sea level seems normal.

After 11 minutes at altitude he seems most reluctant to use his hind legs, sitting on the treadmill and at times lying down.

Even when he receives several shocks he still prefers not to walk. This we consider to be typical signs of moderate decompression sickness, equivalent to 2 or 3 on our six-item scale for rating rats.

During recompression to sea level the pig turned around. He seems still to have some difficulty in using his hind legs. (Most pigs walk quite easily on the treadmill when it is going backwards.)

The next experiment (Hitler) is to show a pigs response to hypoxia. Here we see normal walking at sea level, occasional pawing and rooting -- a typical behavior pattern.

At 75 mm Hg of inspired oxygen tension, moderate hypoxia, there is increased nervousness, more pawing and rooting than before.

At 60 mm Hg inspired oxygen the pig seems to stagger occasionally, and though it definitely does not seem normal its behavior is quite different from that of the one exposed to altitude. This animal is at one-half atmosphere pressure, not enough to cause bends. We have not attempted to measure the effective alveolar oxygen tension in these animals, although in the work proposed for next year it might be necessary to do this.

Back at sea level it is difficult to see any changes, confirming that at least in this individual hypoxia symptoms do not seem to overlap those of decompression to any great extent.

In the third experiment it was our intention to give a pig a definite case of decompression sickness, in the absence of hypoxia, to observe the symptoms. The first scene shows normal walking.

Following this the pig was exposed to two atmospheres of pressure, mostly nitrogen, for three hours, then decompressed to 180 mm Hg. Within two minutes of arrival at that pressure the animal had a convulsion, which is the first thing seen after the title. Next the animal sits and apparently cannot get up, and to verify this we shocked him. The remainder of this sequence shows him in various positions reflecting his disability. This pig would be rated 5 out of a possible 6 in severity of symptoms.

On return to surface he walked on all four feet for a while, but was by no means normal. Later he demonstrated that he could not stand, though he was able to drag himself along by his front feet. This pig died within two hours after being taken out of the chamber. The same pig had been in a similar condition in an earlier experiment, but on that occasion was given treatment similar to the U.S. Navy Oxygen Treatment Table and recovered without any ill effects.

APPENDIX

B. Description of Closed Environmental System (CES-2) Used to Saturate Rats with Various Inert Gas-Oxygen Mixtures

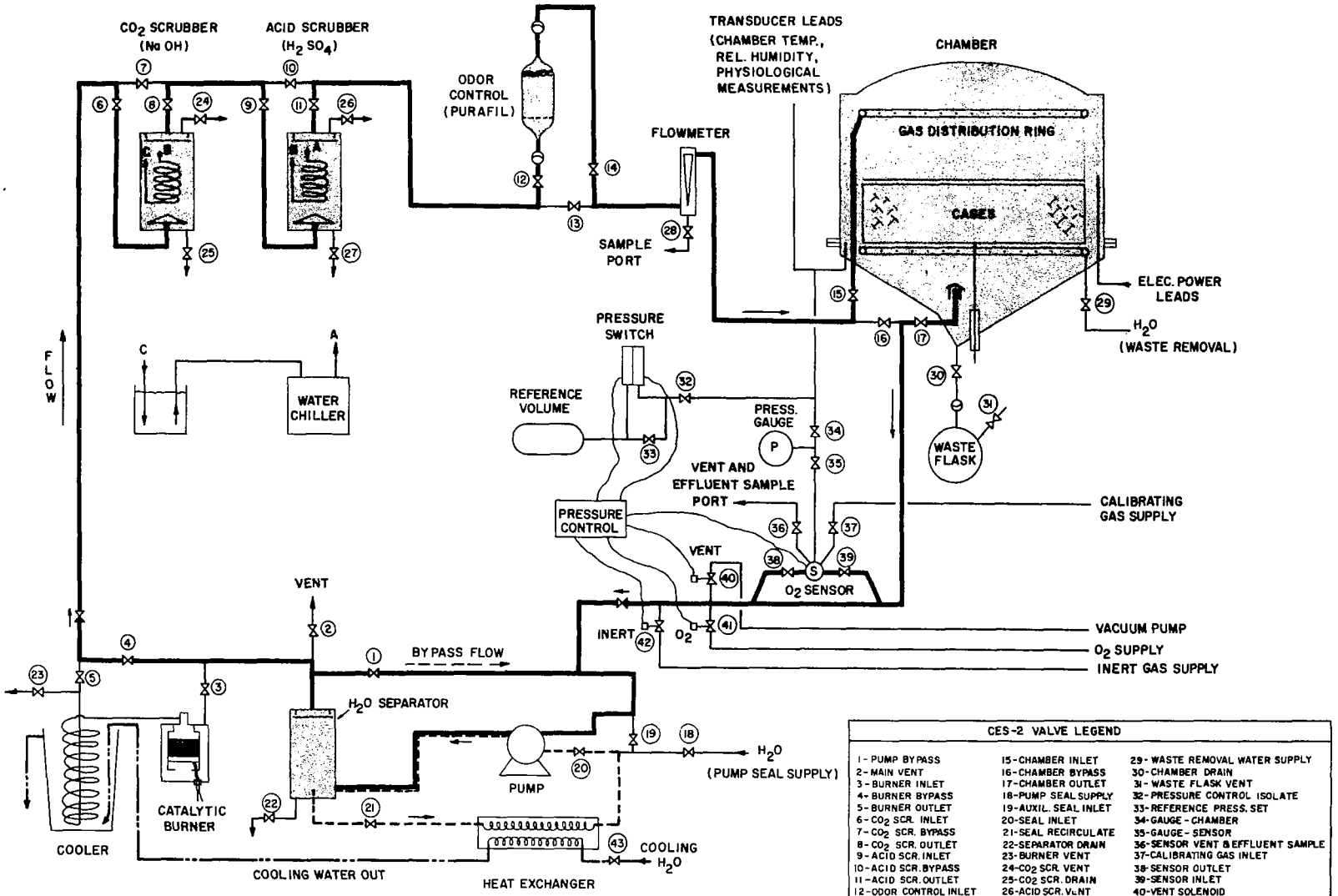
The closed environmental system used in the rat experiments was designed to permit exposures of small animals for as long as several weeks, in a controlled gaseous environment. The original design criteria called for a system that would be conservative of inert gas, would be safe for use with 100% oxygen, would permit accurate control of pressure and gas composition but which called for less precise control of temperature and humidity. The system has been used successfully for many exposures of rats and rabbits.

An overall view of the chamber and its associated life support system is shown in Figure 4. Figure 16 is a schematic diagram of the gas flow system.

The chamber proper is a vertically oriented cylinder 42 inches in diameter, with a conical bottom and a plexiglass dome on top. Several ports are welded into the cylinder, containing gloves, a lock and a window. Standard "dry-box" gloves are used for handling the animals inside. These take no pressure differential, so must be used only when the chamber atmosphere is at ambient pressure. The glove ports are covered with plastic covers when not in use. These covers, the main hatch, the lock, and most other joints are sealed with "O" rings. For access to the animals the entire cover is raised with an electric hoist.

The animals are contained in six pie-shaped cages. The entire cage shelf rotates so that all animals can be reached with the same set of gloves. Water is provided from a centrally located bottle via nipples in each cage. Hoppers are provided for feed. Waste drains into the conical bottom and into a collection flask which can be isolated and emptied without disturbing the chamber composition.

To maintain a suitable gaseous environment free of



CES-2 VALVE LEGEND

1-PUMP BYPASS	15-CHAMBER INLET	29-WASTE REMOVAL WATER SUPPLY
2-MAIN VENT	16-CHAMBER BYPASS	30-CHAMBER DRAIN
3-BURNER INLET	17-CHAMBER OUTLET	31-WASTE FLASK VENT
4-BURNER BYPASS	18-PUMP SEAL SUPPLY	32-PRESSURE CONTROL ISOLATE
5-BURNER OUTLET	19-AUXIL. SEAL INLET	33-REFERENCE PRESS. SET
6-CO_2 SCR. INLET	20-SEAL INLET	34-GAUGE-CHAMBER
7-CO_2 SCR. BYPASS	21-SEAL RECIRCULATE	35-GAUGE-SENSOR
8-CO_2 SCR. OUTLET	22-SEPARATOR DRAIN	36-SENSOR VENT & EFFLUENT SAMPLE
9-ACID SCR. INLET	23-BURNER VENT	37-CALIBRATING GAS INLET
10-ACID SCR. BYPASS	24-CO_2 SCR. VENT	38-SENSOR OUTLET
11-ACID SCR. OUTLET	25-CO_2 SCR. DRAIN	39-SENSOR INLET
12-ODOR CONTROL INLET	26-ACID SCR. VENT	40-VENT SOLENOID
13-ODOR CONTROL BYPASS	27-ACID SCR. DRAIN	41-O_2 SOLENOID
14-ODOR CONTROL OUTLET	28-INFLUENT SAMPLE	42-INERT GAS SOLENOID
		43-COOLING WATER SUPPLY

Figure 16. Schematic Diagram of CES-2 Gas Recirculation System

animal-produced contaminants the chamber is provided with a gas recirculation system. Gas is introduced into the chamber by a distribution ring and is exhausted out the bottom. It is pumped by a "water-piston" type of pump, the flow of which is controlled by a bypass flow valve. This type of pump was chosen because of its oxygen compatability and the fact that it cannot introduce contaminants into the gas stream. To use such a pump requires a separator and a heat exchanger, both of which are indicated in Figure 16. Just downstream of the pump is a catalytic burner. This was not used in these experiments because the rats did not generate enough methane during the short exposure to be a problem. (Rabbits generate methane at a much higher rate, and it was for them that this burner was provided.)

The gas next enters a pair of liquid-filled scrubbers. The first contains 4 gallons of 2N sodium hydroxide solution and the second the same amount of 0.01M sulfuric acid. The first scrubber removes carbon dioxide, the second removes ammonia and any NaOH that may have been entrained by the gas stream. Both are provided with spargers to separate the incoming gas into bubbles, and each suitable valves to permit changing of the solutions and a vacuum connection to facilitate degassing of new solutions before putting them on stream. A glass cannister for odor absorbent (Purafil) and a flowmeter complete the circuit. Bypass valves are provided for all components. Flow through the system as used here is about 4.5 scfm of air. The system was designed for constant mass flow, so at pressures other than one atmosphere and for gases other than air the masses are equivalent.

The gas control system uses two sensors, a pressure switch and an oxygen electrode. The pressure switch is set by opening its bypass valve once chamber pressure has been manually adjusted to the desired value. When system pressure exceeds this preset value the pressure switch opens (via a relay) a vent solenoid valve. When pressure drops below the preset value, which it continuously does since the animals are consuming

oxygen all the time, the pressure switch sends a signal to a relay connected to the oxygen control system. Depending on the oxygen level and the set point, this system then opens the appropriate valve to add either oxygen or inert gas. In normal operation, once the system has stabilized only oxygen will be added, unless there has been a leak or a planned venting of inert gas.

The oxygen control system consists of a Beckman 777 oxygen analyzer in which the meter has been replaced by a meter relay. The electrode is located in a sidearm of the main gas stream, and is provided with valves so that calibration gases can be used when necessary, normally once a day.

Humidity is controlled by means of a water chiller connected to coils inside the scrubber cans. By controlling the temperature of the scrubber liquids (to about 10 C) the relative humidity of the chamber can be maintained at about 50%. Humidity was not measured in the present series of exposures, but previous experience indicates that it never should have exceeded the 40-60% range.

Chamber temperature is normally controlled by adjusting room temperature, but to supplement this several turns of 3/8" copper tubing was wrapped around the chamber, and the whole thing was insulated with an aluminized mylar blanket. Water from the chiller or from a thermostatically controlled bath could be circulated as needed by means of a small pump through these coils.

We wanted to maintain a temperature that would be comfortable for the animals, since these exotic atmospheres have different heat transfer properties from air. Based on oxygen consumption values in previous experience (9) we tried to estimate a comfortable temperature of each run. But we soon became convinced that the animals' behavior was a better indicator of comfort than any other information we had. We noticed whether they huddled together or stretched out separately and their individual appearance, and adjusted the temperature accordingly. The

ranges used for the various gases, with a plus-or-minus variation of about 1 C, were as follows:

Nitrogen	25 C
Helium	28 C
Neon	27 C
Argon	23 C
Neon-helium	27 C

APPENDIX

C. Mathematical Analysis of Gas Exchange

A digital computer program was written for the calculation of the partial pressures of inert gases dissolved in various body compartments as a function of total pressure, time and composition of the breathing gas mixture. For the purpose of this program we have made the assumption that the respiratory quotient of all experimental animals was 0.8 and that their alveolar P_{CO_2} equaled 40 mm. Hg throughout each decompression run. On the basis of these assumptions and the alveolar nitrogen equation (Rahn and Fenn, 1955)

$$P_{A_{N_2}} = \frac{(1 - F_{I_{O_2}}) \; P_{A_{CO_2}} \; (1 - R)}{R} + P_{I_{N_2}} ,$$

alveolar inert gas partial pressure $P_{A_{IG}} = F_{IG} \; (P_B - 37)$,

where F_{IG} is the fraction of inert gas in the dry breathing gas.

In accordance with the most reliable experimental data available (Jones, 1950) we are assuming that the transport of inert gases into and out of the tissues of the body is limited by perfusion. On this basis an inert gas exchange "compartment" represents all those regions of the body for the product of blood flow, $\dot{Q}$, and the distribution of inert gas between tissue and blood,

$$\frac{\alpha \text{ tissue}}{\alpha \text{ blood}} ,$$

equals a particular constant. This constant, k, is the spacific time constant of inert gas exchange of that "compartment". It relates to compartment

half-time $t_{\frac{1}{2}}$ (a terminology employed chiefly by the U.S.Navy) by the expression:

$$k = \frac{\ln 2}{t_{\frac{1}{2}}} = \frac{0.693}{t_{\frac{1}{2}}}$$

Since the solubility ratio

$$\frac{\alpha \text{ tissue}}{\alpha \text{ blood}}$$

differs for different inert gases, the value of k and $t_{\frac{1}{2}}$ (of a particular inert gas exchange compartment) differs also, except for tissues with a blood-like affinity for inert gas (TABLE 10). The specific time constant, k, for each inert gas considered is:

$$k = \dot{Q} \cdot \frac{\alpha \text{ blood}}{\alpha \text{ tissue}}$$

The 15 inert gas exchange compartments chosen for our program represent perfusion rates ranging from 0.3 to 0.0085 ml./min./ml. and tissue affinities for inert gases ranging from 100% blood-like to 100% fat-like.

The basic gas transport equation (Schreiner and Kelley, 1967)

$$\frac{d\pi}{dt} = k\,(P - \pi)$$

is used for all calculations [(π = partial pressure of inert gas dissolved in a gas exchange compartment with a specific time constant k and P = alveolar inert gas partial pressure ($P_{A_{IG}}$)].

The computed π-values for all inert gases present in each compartment at any desired time in the decompression profile are summed and divided by the total pressure then prevailing to give a "surfacing ratio" or supersaturation ratio.

TABLE 10

Description of Inert Gas Exchange Compartments Employed in Computer Analysis of Decompression Profiles

Compartment No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Q, min^{-1}	0.3	0.3	0.3	0.1	0.1	0.1	0.1	0.03	0.03	0.03	0.03	0.0085	0.0085	0.0085	0.0085
Fat Content of Tissue, %	30	70	100	0	30	70	100	0	30	70	100	0	30	70	100
$t_{\frac{1}{2}}$ - He, min	3	3	4	7	8	10	12	23	28	34	39	81	99	122	139
$t_{\frac{1}{2}}$ - Ne, min	3	4	5	7	9	12	15	23	31	41	49	81	108	145	171
$t_{\frac{1}{2}}$ - N_2, min	5	9	12	7	15	27	35	23	52	89	118	81	182	315	416
$t_{\frac{1}{2}}$ - Ar, min	5	9	12	7	16	28	37	23	53	93	122	81	187	327	432

APPENDIX D

TABLE 11

Some Physical Properties of Inert Gases Relevant to Tissue Gas Transport

	He	Ne	Ar	N_2
Solubility in Water *	0.0086	0.0097	0.026	0.013
Solubility in Lipid *	0.015	0.019	0.14	0.061
Solubility Ratio, oil/water	1.7	2.1	5.3	5.1
Diffusivity in Water **	63.2 (79.2)	(34.8)	(25.2)	30.1
Diffusivity in Lipid **	(18.6)	(8.34)	(5.92)	7.04

* Bunsen Coefficient at 38°C.

** Diffusivity $cm^2 \quad sec.^{-1} \times 10^{-6}$ at 37°C.

Values in parentheses are calculated

Reference: Roth (5)

NASA-Langley, 1970 —— 4