

LITERATURE REVIEW OF THE EFFECTS OF HELIUM  
ON THE MECHANICS OF RESPIRATION,  
WITH CLINICAL CORRELATIONS

by

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## SUMMARY PAGE

### THE PROBLEM

To review and abstract the pertinent literature relating to the physiology of ventilatory dynamics with helium-oxygen mixtures, and to include in this review relevant studies in diving medicine.

### FINDINGS

Thirty-one bibliographic references are presented. These are representative and not intended to be all-inclusive. Discussion is provided concerning indications and contra-indications for the use of helium-oxygen mixtures in clinical medicine.

### APPLICATIONS

The material presented in this review is intended for use by Qualified Submarine Medical Officers and by prospective Submarine Medical Officers who are students in the School of Submarine Medicine. It will also be of interest to medical officers and physicians interested in the use of helium-oxygen mixtures in diving and in clinical medicine.

### ADMINISTRATIVE INFORMATION

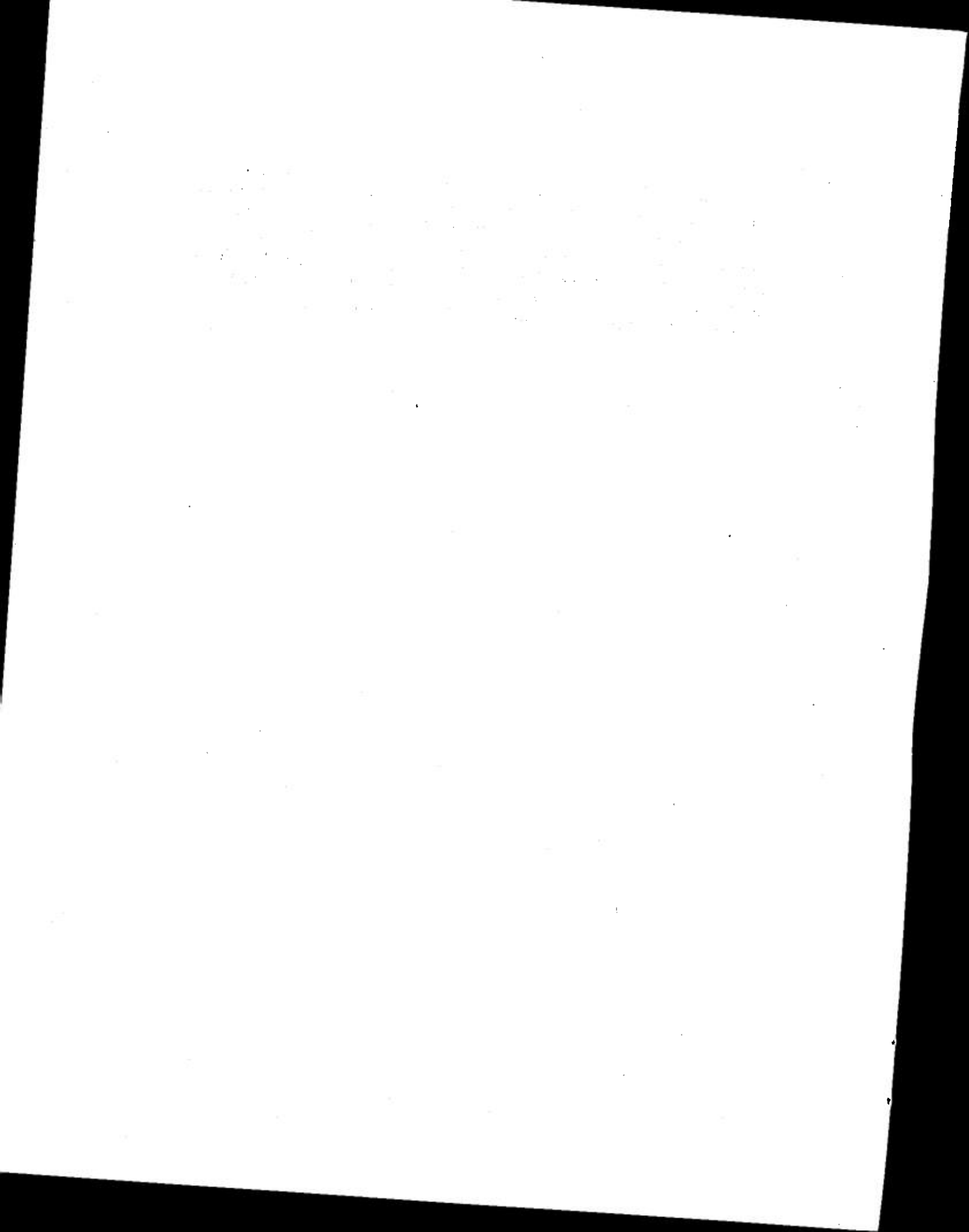
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## ABSTRACT

A review of the pertinent literature relating to the physiology of ventilatory dynamics using helium-oxygen breathing mixtures is presented together with conclusions regarding the indications and contraindications for their use in clinical medicine. A review of relevant studies in diving medicine is included because of the clarification which these investigations lend to problems of pulmonary ventilation. The bibliography is representative but not all-inclusive.



LITERATURE REVIEW OF THE EFFECTS OF HELIUM  
ON THE MECHANICS OF RESPIRATION,  
WITH CLINICAL CORRELATIONS

One of the earliest studies of the therapeutic uses of helium was that of Barach in the 1930's.<sup>1</sup> The basis for the clinical use was the reduced specific gravity of helium compared to nitrogen, the intention being to reduce the work of breathing in patients with obstructive respiratory disease. Since this first optimistic clinical application, studies have shown variable results in the relief of respiratory distress; as more experimental data accumulated it became possible to establish more precise physiological effects of helium-oxygen mixtures and suggest more limited, rational clinical uses. Much of the data arose from studies connected with diving medicine; other data originated from experimental use of helium as a diagnostic rather than therapeutic tool. A review of the pertinent literature in these fields will permit a balanced evaluation of the current clinical applications utilizing this gas.

Helium was discovered in the sun's atmosphere in 1868 and on earth in 1895. It was found in the United States in 1905, but commercially available quantities were not available until 1937.<sup>2</sup> Its presence in the air is in a constant ratio of five parts per million (ppm). It has the lowest solubility in water and oil and the highest diffusibility of the noble gases; air in which helium has been substituted for nitrogen has one-third the density of normal air.<sup>1,5</sup> It is non-explosive and, though chemically inert, has physiological effects which are well-established. Helium is much less

soluble than nitrogen and diffuses much more rapidly, characteristics which as early as 1923 suggested it be used to reduce decompression times in diving operations.<sup>3</sup>

Some of the known effects upon living organisms of the so-called "inert gases" in sufficient concentration include narcosis, depression of responses to stimuli, alteration of development and metabolism in animals, and decreased oxygen-dependent sensitivity to radiation. There are marked differences among the members of this group. Xenon, for example, is a strong anesthetic in 80% xenon-20% oxygen mixtures at one atmosphere, while helium-oxygen mixtures will not become anesthetic until at least 36 atmospheres in men and 122 atmospheres (if at all) in mice.<sup>3,4,5</sup> There have been intensive research efforts into the mechanisms of such effects and into the reasons for such marked differences between the various noble gases; such considerations are beyond the scope of this paper but are well-discussed elsewhere.<sup>3</sup>

Current concepts of ventilatory dynamics and respiratory physiology allow an accurate appraisal of the value of helium-oxygen mixtures in clinical medicine and diving. The original studies of the clinical use of helium made little distinction among the various kinds of obstructive respiratory illnesses for which it was of value (laryngo-tracheal obstructive lesions, asthma, emphysema, etc.) Subsequent

clinical trials, however, showed quite variable responses—for example, helium was claimed to be of value in obstruction of the large airways, but not in asthma.<sup>6</sup> The explanation that the advantage of He-O<sub>2</sub> mixtures was due to decreased density was thus shown to be simplistic and in need of clarification; an understanding of the laws governing flow in the lungs was seen to be necessary.

Ventilation is dependent on the flow of air, which in turn depends on pressure differences between the ambient air and alveolar air. Velocity of flow is proportional to the pressure difference, but the exact relationship of the two depends on the type of flow. Two types of flow can exist—laminar and turbulent. Laminar or streamlined flow is expressed by Poiseuille's Law, which relates flow directly to pressure difference and to the fourth power of the radius and inversely to the length of the tube and to viscosity (it is thus evident that flow is very sensitive to changes in the radius).<sup>7</sup> As flow increases, laminar flow gives way to turbulent flow. This may be predicted to occur when the dimensionless Reynolds number exceeds 2,000. This is calculated by the product of density, linear velocity and diameter divided by viscosity. The tendency for turbulence to occur, in other words, is increased with the linear velocity, diameter and density, but is decreased with increasing viscosity.

In the presence of turbulence, in contrast to the case with laminar flow, pressure and flow are exponentially related; that is, a doubling of flow requires a fourfold increase in pressure.<sup>7</sup> Thus, pressure will increase with the

square of the flow rate. Calculation of Reynolds numbers in different parts of the human airways indicates that flow during quiet breathing is primarily laminar, but that in large airways turbulent flow occurs.

In a pioneer study of the kinetics of ventilation with helium, Dean and Visscher in 1941 noted that HeO<sub>2</sub> mixtures had been of dramatic benefit in laryngo-tracheal lesions, but less so in asthma.<sup>8</sup> They observed that explanations which depended on gas density but ignored viscosity, or that invoked diffusibility as important in ventilation, were basically inadequate without attention to types of flow. In contrast to the suggestion of Barach, diffusion was felt to be of little consequence in the mass movement of air in the lung (diffusion is inversely proportional to the square root of the molecular weight, explaining the high diffusibility of helium). This was shown rather conclusively by experimental methods.<sup>8</sup> Turbulent and laminar flows, then, are the critical factors in assessing ventilation.

Since during laminar flow a decrease in viscosity causes an increase in flow rates, helium might be expected to be beneficial under these circumstances; however, the viscosity of helium is about 10% greater than that of nitrogen. Therefore, the opposite is true. where flow is turbulent, however, the pressure necessary to maintain a flow of HeO<sub>2</sub> is much less than that for air, because turbulent flow depends on density but not viscosity and HeO<sub>2</sub> is one-third as dense as air. In sum, then, HeO<sub>2</sub> mixtures would be expected to be useful where flow is turbulent, but actually slightly detrimental where it is laminar. \*

Of further significance is the law governing the type of flow in a given geometrical system, which holds that the critical velocity above which flow is turbulent is proportional to the viscosity divided by the density ( $V/D$  has been given the name "kinematic viscosity" and is important in determining the distribution of turbulence in the lungs).<sup>8</sup> Helium, with its high kinematic viscosity, will flow much faster than air before converting to turbulent flow. Since laminar flow is more efficient than turbulent flow (i.e., pressure and flow are directly related in the former and exponentially related in the latter), mixtures would be useful in reducing the work of breathing insofar as they induce laminar flow where it would be otherwise turbulent.

The ultimate goal, then, in using light gas mixtures is to reduce the work of breathing, and this is accomplished by substituting laminar flow for turbulent flow in some airways and also by increasing efficiency of turbulent flow. Work of breathing is primarily derived from overcoming elastic and non-elastic resistances. Elastic resistances include compliance and viscous resistances of the lungs; these may be increased in emphysema or when the lung is over-inflated.<sup>7</sup> Under normal conditions, elastic work comprises two-thirds of the work of breathing. However, during hyperventilation, obstruction, or with increased gas density, non-elastic work increases while elastic work does not. This increase in flow-resistive work can be quite significant in patients with obstructive disease or in divers working under great pressure. Hence, under these circumstances, the value of

gas mixtures which lower resistance to flow is evident.

A more recent investigation of pulmonary mechanics during HeO<sub>2</sub> breathing corroborated the previous experimental work.<sup>9</sup> It was theorized that differences in the anatomic levels of obstruction in respiratory disease could affect clinical response to low-density gas mixtures. Accordingly, experiments were done using dogs with either mechanical obstruction of the lower trachea or with pharmacologic constriction of the distal airways. The results confirmed the significant reduction in non-elastic work in the former but minimal or no reduction in the latter. These results were consistent with those cited above. It was pointed out that the large total cross-sectional area of distal airways resulted in a low linear velocity, thereby reducing the Reynolds number well below the critical value for turbulence even in cases of generalized constriction down to the level of the alveolar ducts. Turbulence, then, appears to play little part in the increased flow-resistive work of breathing in such cases as asthma or emphysema. Experimental evidence of this is the fact that breathing HeO<sub>2</sub>, a mixture with a 3.3 times the kinematic viscosity of air, fails to reverse the increased non-elastic work of breathing.<sup>9</sup> In contrast, upper airway obstruction is characterized by high linear velocity in the trachea, and the HeO<sub>2</sub> mixtures have a pronounced effect in reducing the work of breathing; this is most likely due to reducing the Reynolds number below the critical value for turbulent flow. Vagal stimulation, which apparently produces constriction

of the medium and larger bronchi, is also relieved by HeO<sub>2</sub>, presumably due to the same mechanism.

Experience with helium mixtures in diving has been extensive, and in addition to direct value in undersea operations has given further information on effects upon ventilatory dynamics of HeO<sub>2</sub> mixtures. Other physiological effects, such as inert gas narcosis, have also been investigated. Lord, Bond and Schaefer in 1966 reported acute effects resulting from exposure to high ambient pressures; they confirmed the fact that compression of a gas causes the same effects as a high density gas at normal pressure, resulting in increased work of breathing.<sup>10</sup> Maximum expiratory flow rates and maximum breathing capacities were reduced similarly by an increase in density of the respired gas or by increasing pressure on a low-density gas. Viscosity, unlike density, does not increase significantly with increased pressure, so that changes in viscosity should not be of significance in diving. It was noted incidentally that there were no untoward clinical effects from extended exposure to high pressure HeO<sub>2</sub> mixtures.

Dougherty and Schaefer, in 1968, extended earlier work by showing that there was some recovery of pulmonary functions after a saturation period at depth, resulting in an improvement in maximal inspiratory and expiratory flow rates.<sup>11</sup> Since increased work of breathing sets the limit for useful exertion at depth, such recovery would be associated with a higher level of capacity for work during saturation dives. Subsequent experiments confirmed these

findings and explained them as most probably due to distal airway collapse during rapid compression with reopening during the saturation period; pulmonary gas exchange was also studied and shown to remain within normal limits under these circumstances.<sup>12,13</sup>

Overfield, Saltzman, Kylstra and Salzano reported on respiratory gas exchange using 99.1%-0.9% HeO<sub>2</sub> mixtures at 31.3 ATA (1000 feet equivalent depth) under saturation conditions.<sup>14</sup> No significant differences from control values were found in expiratory flow rates, tidal volume, oxygen consumption, carbon dioxide production or arterial levels of oxygen and carbon dioxide. There was some increase in mean alveolar-arterial oxygen tension differences. It was concluded that resting gas exchange under these conditions (i. e., with the breathing medium 4.4 times as dense as air at sea level) was essentially normal. This was in spite of the increased airway resistance, decreased expiratory flow rates, decreased maximum breathing capacity and increased work of breathing predicted from previous studies to occur with increased gas density. (It is interesting that work with HeO<sub>2</sub> mixtures at 380 mm. Hg. total pressure show a great increase in maximum breathing capacity, a function of reduction in resistance to gas flow due to decreased density; there was also a poorly understood slight decrease in vital capacity)<sup>15,16.</sup>

One of the most recent saturation experiments showed no change in vital capacity at 31 ATA or 36 ATA of HeO<sub>2</sub>, in consonance with previous studies showing no significant respiratory embarrassment under these conditions.<sup>4</sup> There is still some disagreement on the

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exact effects of hyperbaric mixtures of HeO<sub>2</sub> on specific pulmonary functions, some investigators reporting compromise of certain of these functions while others have not; however, there is universal agreement that the effects are neither clinically significant nor harmful.

\* The studies mentioned above have shown that there are no significant toxic effects of HeO<sub>2</sub> mixtures under saturation conditions at hypobaric, normobaric or moderately hyperbaric conditions.<sup>4,10,11,12,13,14,17,18</sup> There have been some cases of "helium tremors", vertigo and muscle pains noted during compression, and there have been reports of a so-called "high pressure nervous syndrome" characterized by rather severe motor and psychological deterioration; in the light of extensive experience with saturation dives, these effects seem to be part of a compression syndrome and not due to the gas mixture itself.<sup>4</sup> In mice, at a pressure equal to 4,000 feet of seawater (122 atmospheres) helium-oxygen mixtures caused some deviation from normal behavior, but no lethality, unconsciousness or delayed toxicity.<sup>5</sup> It had been previously shown that mice can be kept alive and healthy for at least 10 weeks in a 79% helium-21% oxygen mixture at one atmosphere.<sup>19</sup> Specific elucidation of the narcotic potency of various gases showed that the relative narcotic properties of helium were much less than that of nitrogen, and even hydrogen. However, until actual testing of humans has been done at extreme pressures, it cannot be said that helium-oxygen will definitely be safe under those conditions, since there is evidence of a convulsive

syndrome in some primates at pressures equivalent to 1,600-2,100 feet of seawater.<sup>20</sup>

Historically, helium has also been used in clinical medicine in the evaluation and diagnosis of pulmonary function. It has proved of value in the study of pulmonary infarction, functional residual capacity and diffusion gradients in emphysema, the "first gas into the lung is the last gas out" concept, ventilation distribution in chronic obstructive lung disease, and total lung capacity.<sup>21,22,23,24,25,26,27</sup>

With the knowledge gained from careful study of the investigations mentioned rather briefly in this paper, the various therapeutic indications for the use of HeO<sub>2</sub> mixtures can be placed on firm theoretic grounds. This knowledge also aids understanding of therapeutic failures and irrational applications. For example, Schiller et al in 1955 studied helium-oxygen in bronchial asthma and found no significant improvement in expiratory reserve volume, inspiratory capacity, vital capacity, or speed of flow.<sup>28</sup> They concluded rightly that since this therapy was of little value in asthma, then turbulence was not significant in the dyspnea of asthma; streamline flow impedance appeared to be of greater importance. These conclusions are consistent with what has been discussed above. In fact, if viscosity is important in governing gas flow in asthmatic lungs, helium might be actually disadvantageous because of its increased viscosity as compared to nitrogen. Well-ventilated areas of the lung might become better ventilated whereas poorly-ventilated

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areas might become more so, with possible hypoxia.<sup>28</sup> Exercise-tolerance in patients with chronic obstructive bronchitis was found not to be improved with HeO<sub>2</sub> mixtures, probably for the same reasons operable in asthma.<sup>30</sup>

A rational program for the use of helium in respiratory disease, then, would recognize that the value of helium lies in its ability to convert turbulent flow into the more efficient laminar flow and to reduce the work of breathing in areas where flow is already turbulent; conversely, it is of little value in cases where disease is confined to areas of obligated laminar flow.

Therefore, it could be predicted to be of use in such instances as laryngeal tumors or strictures, superior vena caval syndrome, and large goiters or other extrinsic neck tumors; but it would not be of much use in diffuse airway constriction such as occurs in asthma or chronic obstructive pulmonary disease. The anatomic locus of obstruction, then, is of importance in predicting the clinical value of low-density gas mixtures. It is likely that general lack of familiarity with the potential uses of helium in anesthesia as well as in therapy is responsible for the relative low incidence of its use in hospitals.<sup>31</sup> Useful gas combinations are pre-mixed tanks of 80% helium-20% oxygen or 70% helium-30% oxygen, used in a closed system such as face-mask with Intermittent Positive Pressure Breathing (IPPB) apparatus. Tents or catheters are to be avoided because of excessive waste-rates and leakage. Correction of flow-meters calibrated for oxygen must be made when helium is used because of its increased diffusibility.<sup>31</sup> The bulk of the accumulated

data testifies to the ability of helium-oxygen mixtures to reduce the work of ventilation in certain disease states or where flow resistance is increased by other factors such as hyperbarism; careful analysis of this data affords an understanding of the exact mechanisms involved, without which rational use is not possible.

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