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International Congress of Aeronautical and Space Medicine

Professor R. Grandpierre, President of the 10th European Congress, has announced that the Congress will be held in Paris, France, September 26-30, 1961. Special topics for consideration will include: (1) Psycho-physiological problems resulting from adaptation or lack of adaptation to a space environment, (2) Patho-physiological problems attending flight in modern aircraft, (3) Recent physiological investigations in the field of space medicine, (4) Pathological problems of non-flying personnel responsible for flying safety.

Communications regarding the Congress may be addressed to: General Secretary, 5 bis, Avenue de la Porte de Sevres, Paris XV°.

Hotel reservations should be addressed to: Union Nationale des Agences de Voyage, 18, Avenue de l'Opera, Paris, France.

A Concept of Triple Tolerance Limits Based on Chronic Carbon Dioxide Toxicity Studies

KARL E. SCHAEFER, M.D.

MOST OF THE physiological ranges of atmospheric components were, in the past, studied in acute experiments which lasted usually several hours but did not extend over days. Tolerance limits established on the basis of detected physiologic changes and impairment of performance in single or repeated exposures for eight hours have to be significantly reduced to be applicable to conditions of chronic exposure in the sealed space cabin or in the true submersible. Tamas[32] suggested as a rule of thumb that the maximal allowable concentrations (MAC values) of various agents published in *Industrial Health Reports* which are based on eight hours a day, five days a week exposure, might be lowered by a factor of 4 to be used as guides for prolonged continuous exposure. For example, the MAC value for carbon monoxide is 100 parts per million (p.p.m.) while the Navy proposed figure for nuclear-powered submarines is 25 to 30 p.p.m. In the older literature, 3 per cent carbon dioxide was considered a permissible threshold concentration; however, the experience in submarines during World War II[17,18] and subsequent experiments with prolonged exposure to 1.5 per cent carbon dioxide[2,7,16,19] established the necessity to keep the carbon dioxide concentration in the neighborhood of 1 per cent and preferably below 1 per cent carbon dioxide for conditions of continuous prolonged exposure. This serves to emphasize the existence of an inverse time-concentration relationship in which time can replace concentration.

In addition, a combination of changes in several factors can result in different effects dependent upon acute or chronic exposure. For example, it is well known that addition of carbon dioxide to low oxygen mixtures has, in experiments of short duration, a beneficial effect in alleviating symptoms of oxygen lack and preventing their occurrence.[8,9] This influence of carbon dioxide is based upon stimulation of respiration and circulation with a resulting improvement in oxygen supply. There is, however, evidence that these effects are greatly reduced or not present under conditions of chronic carbon dioxide exposure.[18]

As a consequence of the rapid development in space technology, the design engineer of life support systems in space capsules came up with requirements for a better quantitative description of man's characteristics and more reliable criteria of tolerance limits. This forces us to take a new look at what we call tolerance limits.

It appeared that the results of the extensive studies on chronic carbon dioxide toxicity carried out over the past ten years in the U. S. Naval Medical Research Laboratory, New London, Connecticut, would have some bearing on this problem and indicate a possible new approach.

Review of Experimental Findings:—Experiments in which human subjects were exposed to 3 per cent carbon dioxide in 21 per cent oxygen for periods of three to six days showed a depression of the respiratory response to 3 per cent and, more significantly, to 5 per cent carbon dioxide after several days.[3,22] A large number of physiologic changes were found to be associated with the two phases of uncompensated and compensated respiratory acidosis produced

From the U. S. Naval Medical Research Laboratory, New London, Connecticut.

Presented at the Aerospace Medical Association Meeting, Miami, Florida, May 11, 1960.

by inhalation of 3 per cent carbon dioxide such as alterations in respiratory exchange ratio,[22] decreased oxygen utilization during rest and exercise,[22] cardiovascular capacity and pulse

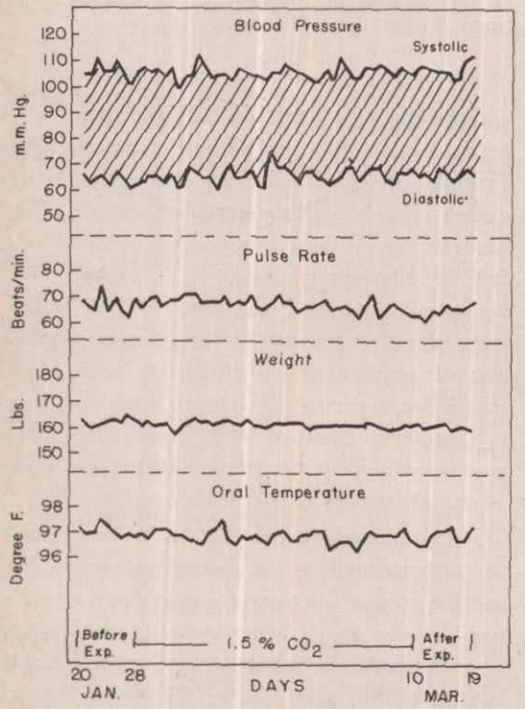

Fig. 1. Effect of prolonged exposure to 1.5 per cent carbon dioxide for forty-two days on systolic and diastolic blood pressure; pulse rate, body weight and oral temperature in twenty-three subjects.

rate,[23,24] response to heat and cold,[24] electrolyte exchange in blood and urine,[22] changes in central nervous system activity as indicated in chronaxia measurements[25] and EEG.[26] A significant impairment of performance was noted during prolonged exposure to 3 per cent carbon dioxide in 21 per cent oxygen.[17,25]

Field tests carried out on submarines during war patrols under conditions of exposure to 3 to 3.5 per cent carbon dioxide and 15 to 17 per cent oxygen also demonstrated significant physiologic changes and deterioration of performance.[17] Laboratory tests, in which subjects were exposed for seventy-two hours to 3 per cent carbon dioxide in 21 per cent oxygen, also demonstrated a decrease in performance.[31] It has been pointed out that the lowered oxygen content does not play an important role in causing the described effects.[18]

In animal experiments in which guinea pigs, rats, mice and dogs were exposed to 3 per cent carbon dioxide in 21 per cent oxygen for prolonged periods biphasic reactions associated with periods of uncompensated and compensated respiratory acidosis were found in body weight, motor activity, blood sugar, alkali reserve and adrenal cortical activity.[6,27,28,31] Excitability of the central nervous system as tested with metrazol seizure activity showed a period of excitation followed by depression during prolonged exposure to 3 per cent carbon dioxide.[4] Histopathologic changes of liver, kidney, heart and striated muscle of guinea pigs exposed for periods up to twenty-one days to 3 per cent carbon dioxide were reported by Zinck.[31] Adrenal hyperplasia and involvement of lymphatic organs were noted in a subsequent study of guinea pigs exposed to 3 per cent carbon dioxide for prolonged periods.[29]

Thus these various effects of chronic exposure to 3 per cent carbon dioxide may be summarized by the statement that these exposures (the level of 3 per cent carbon dioxide) produced alterations in basic physiological functions and were accompanied by performance deterioration, none of which returned to normal during prolonged exposure in spite of developed acclimatization. Animal experiments revealed significant physiological effects and histopathological changes.

Studies of prolonged exposure to carbon dioxide concentration lower than 3 per cent were carried out in recent years at the U.S.N. Medical Research Laboratory in New London, Connecticut. Results of a large scale experiment (Operation Hideout) in which twenty-three subjects were confined in a submarine and exposed to 1.5 per cent carbon dioxide in 21 per cent oxygen over a period of forty-two days with a nine-day control period, prior to and also following exposure, showed that basic performance

preciably affected at this lower level of carbon dioxide.[7]

As shown in Figure 1, weight, pulse rate, systolic and diastolic blood pressure and oral temperature, measured daily in twenty-three subjects at 8 A.M., did not exhibit significant alterations throughout the experiment.[2] Statistical evaluation of these data is described in Table I. The forty-two-day period of exposure to 1.5 per cent carbon dioxide has been divided into two parts corresponding to the phases of uncompensated respiratory acidosis (one to twenty-three days) and compensated respiratory acidosis (twenty-four to forty-two days). The mean values and standard deviations of these five parameters show a remarkable constancy throughout the experiment. Only the diastolic blood pressure shows a slight increase during the exposure to carbon dioxide and during the nine-day recovery period on air.

TABLE I. EFFECT OF PROLONGED EXPOSURE TO 1.5 PER CENT CO_2 ON SYSTOLIC AND DIASTOLIC BLOOD PRESSURE, PULSE RATE, BODYWEIGHT AND ORAL TEMPERATURE

		Control	Exposure to 1.5 Per Cent CO_2 for		9-Day Recovery On Air
			1-23 Days	24-42 Days	
Systolic blood pressure	Mean*	106.4	106.8	106.5	108.1
	S.D.	10.1	8.4	8.7	8.4
	N	23.0	23.0	23.0	23.0
Diastolic blood pressure	Mean	64.8	66.2	67.3	67.3
	S.D.	8.8	8.9	8.1	8.5
	N	23.0	23.0	23.0	23.0
Pulse rate	Mean	67.6	68.5	67.1	67.4
	S.D.	8.3	8.8	9.0	7.3
	N	23.0	23.0	23.0	23.0
Body-weight	Mean	162.0	162.0	162.2	162.0
	S.D.	19.4	24.2	21.7	20.8
	N	23.0	23.0	23.0	23.0
Oral temperature	Mean	97.10	96.90	96.94	97.04
	S.D.	0.89	0.73	0.66	0.46
	N	23.00	23.00	23.00	23.00

*Means of the mean values of data obtained from twenty-three subjects during each experimental period. Measurements were made daily.

Sensory and perceptual processes were not affected during prolonged exposure to 1.5 per cent carbon dioxide. Threshold measurements during adaptation to darkness using a biophotometer did not show significant changes throughout the experiment. Data on visual acuity, amplitude of visual accommodation and depth perception, as well as pitch discrimination, did not reveal any significant alterations during the exposure to 1.5 per cent carbon dioxide.

Studies of psychomotor efficiency as measured by a battery of tests such as Minnesota Manual Dexterity test, letter-cancelling test, McQuarrie test of mechanical ability, strength (maximum hand dynometer readings) and complex coordination test did not exhibit any impairment in psychomotor performance as a result of exposure to 1.5 per cent carbon dioxide.

No decrement was found in the perceptual span and immediate memory as well as in problem solving abilities during the experiment.[7] Eighteen subjects took the Thematic Apperception Test (TAT) and sentence completion test twice: (1) prior to the experiment and, (2) after spending thirty days in the submarine. At this time they had been exposed for twenty-one days to 1.5 per cent carbon dioxide. Results of the second test after confinement appeared to indicate increased uncooperativeness, apathy, heightened sexual needs and a desire to leave.[5]

Psychiatric studies conducted in "Operation Hideout" revealed only moderate increases in anxiety which appeared to be related to the situational factors involved. Subjects who were found to be unstable in a psychiatric assessment prior to the beginning of the experiment showed

more severe and prolonged subjective complaints.[14]

In contrast to the rather negative findings on basic physiologic functions and performance during prolonged exposure to 1.5 per cent carbon dioxide, were the results of studies on respiration,[19] acid base balance and electrolytes.[16] They demonstrated the existence of a phase of uncompensated respiratory acidosis lasting for twenty-three days and a phase of compensated respiratory acidosis from the twenty-fourth to the forty-second day of exposure to 1.5 per cent carbon dioxide. This is indicated in the fall and subsequent rise of blood and urinary pH, the latter changes being associated with alterations in urinary carbon dioxide excretion (Fig. 2). The carbon dioxide excretion of the lungs closely paralleled that of the urine. Furthermore, a significant depression of the respiratory response to 5 per cent carbon dioxide was found after thirty-five days of exposure to 1.5 per cent carbon dioxide (Fig. 2).

During forty-two days' exposure to 1.5 per cent carbon dioxide as well as during the nine-day recovery on air period, sodium content of the red cells was increased and potassium content decreased in nearly equivalent amounts. The carbon dioxide content of the red cells was not only increased during the exposure period but remained elevated during the subsequent nine-day recovery period.

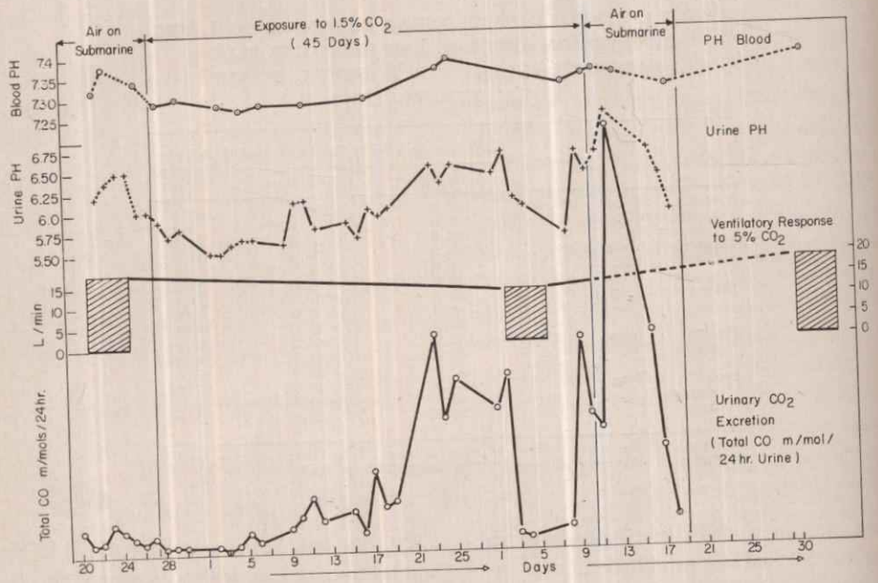

Fig. 2. Changes in acid base balance (venous pH, urinary pH, urinary carbon dioxide excretion) and ventilatory response to 5 per cent carbon dioxide during and after prolonged exposure to 1.5 per cent carbon dioxide for forty-two days (21 subjects).

Data on plasma calcium and inorganic phosphorus obtained during this experiment are suggestive of an altered calcium phosphorus metabolism.[20] Plasma calcium in the venous blood paralleled the changes of the pH depicted in Figure 2 and showed a decrease during the first twenty-three days of exposure, a return to initial levels during the latter part of exposure, followed by a rise above control values during the eight to nine-day recovery period on air following exposure. After four weeks of recovery initial values were reached. Plasma inorganic phosphorus was elevated throughout the car-

dioxide exposure period and remained at this increased level during the nine-day recovery period and even after four weeks of recovery.

Investigations of the cardiovascular capacity and the assessment of stress imposed on the organism during this prolonged exposure to 1.5 per cent carbon dioxide also demonstrated significant effects. Tests of the circulatory system with different degrees of work load, that is (1) postural change from supine to standing position, (2) exercise in the form of twenty-five hops on one foot and, (3) step-up tests, showed an increased pulse rate response under carbon dioxide and an increased time for pulse rate to return to initial levels. These findings were interpreted as a reduction of circulatory reserve under prolonged exposure to 1.5 per cent carbon dioxide which might become important under heavier workloads.[2]

An increased adrenal cortical activity was found during the forty-two days' exposure to 1.5 per cent carbon dioxide and the following ten-day recovery period on air as indicated by a decrease in the absolute number of circulating eosinophils and a significant increase in the 17-ketosteroid output in urine. It is noteworthy that, based on the indices of adrenal cortical response, the "physiological stress" was larger during the compensated phase of respiratory acidosis (twenty-four to forty-two days of exposure) and during the nine-day recovery period on air than during the early phase of uncompensated acidosis.[13] This is the more remarkable in view of the fact that the number of subjective complaints showed the opposite trend.[14] This would indicate that the psychological effects of confinement subsided during the twenty-four to forty-two day period of exposure and the nine-day recovery period which coincided with the greatest physiological stress. In the latter phases, the carbon dioxide tension (pCO_2) was elevated and the pH came back to normal while both pH and pCO_2 were changed during the early phase of uncompensated respiratory acidosis. The results suggest that the elevated pCO_2 level alone (independent of pH change) produces a significant "physiological stress" response. This interpretation is supported by evidence from experiments on rats and guinea pigs carried out simultaneously under the same conditions of exposure to 1.5 per cent carbon dioxide for forty-two days.[12] They also showed a significant increase in adrenal cortical activity during the same two periods in which the pH was not different from control levels and the pCO_2 elevated. The factor of confinement did not play a role in these animal experiments.

Growth curves were obtained in comparable groups of guinea pigs exposed continuously to 1.5 per cent, 3 per cent and 15 per cent carbon dioxide respectively for periods varying from fifty to ninety-three days. These tests showed a depression of growth under 1.5 per cent carbon dioxide which lasted approximately twenty-five days when the normal growth rate was resumed. A similar effect was observed under 3 per cent carbon dioxide for a period of thirty-eight days. Under 15 per cent carbon dioxide, transitory increases in weight were observed around the tenth and twentieth day which were followed by a slight but steady decline during the latter part of the fifty-day exposure period.[21]

Studies of the carbohydrate metabolism in rats and guinea pigs exposed for forty-two days to 1.5 per cent carbon dioxide,[12] showed a fall of liver glycogen and muscle glycogen while the blood sugar was maintained at a constant level.

It seems important to emphasize that these changes in carbohydrate metabolism were still present after twenty-five to twenty-eight days of exposure when a compensation of the respiratory acidosis was attained in animals as well as in men. One has to conclude therefore that under these conditions, the increased pCO_2 tension was the decisive factor rather than the change in pH. This interpretation is supported by recent findings of Hastings[10] who demonstrated that the net glycogen synthesis in liver slices is directly proportional to the logarithm of carbon dioxide tension at a constant pH of 7.40. One of the conclusions of Hastings has an important bearing on the problem of carbon dioxide tox-

icity, namely, that homeostasis of the carbon dioxide tension is just as important as that of pH. During adaptation to carbon dioxide the organism reaches a compensation of the respiratory acidosis (pH) but remains uncompensated as far as the carbon dioxide tension is concerned, since the latter stays at an elevated level as long as the exposure to increased carbon dioxide levels lasts.[29]

Nahas[15] is beneficial in eliminating the effects of a reduced pH but cannot alleviate the effects of increased carbon dioxide tension, since the latter is not reduced by trisbuffer.

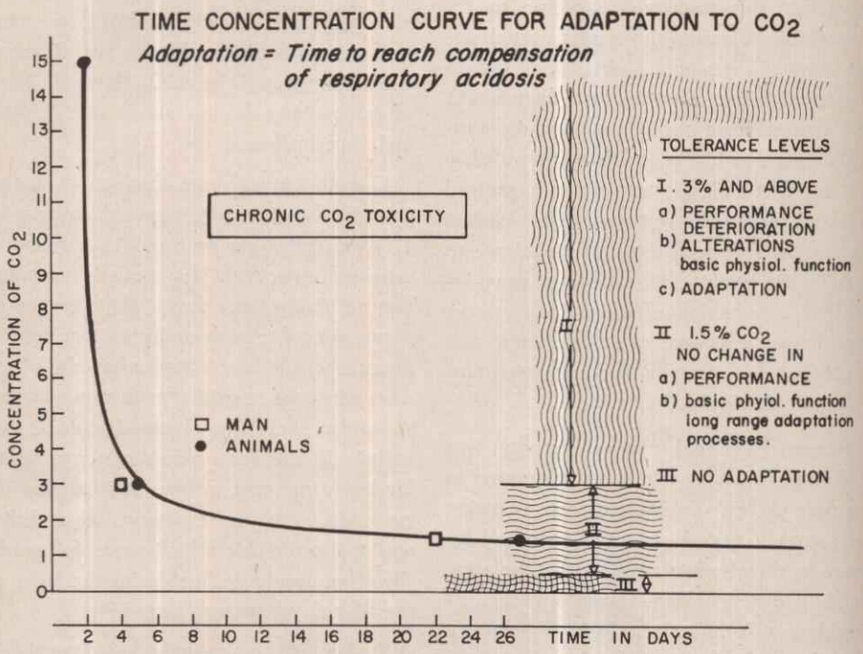

Fig. 3. Time concentration relationship in adaptation to increased carbon dioxide concentration based on experiments in humans and animals and tolerance limits for chronic carbon dioxide toxicity based on three different levels of activity.

Subjects exposed to 1.5 per cent carbon dioxide for forty-two days showed, throughout the whole exposure period, a significantly increased alveolar pCO_2 level in spite of an increased ventilation.[19] The same is, of course, true for higher concentrations such as 3 per cent carbon dioxide and above.[22] In this connection it should be pointed out that the treatment of respiratory acidosis with trisbuffer (tris hydroxymethyl amino methane) as advocated by

Findings with human subjects living in 1.5 per cent carbon dioxide indicate that performance and basic physiologic functions are not affected and that, therefore, this level of carbon dioxide can be tolerated for prolonged periods. However, the long-lasting processes of acclimatization and de-acclimatization, the latter not being completed within twenty-eight days of recovery, suggest that some pathological residues might remain if insufficient time is allowed for recovery. Results of animal experiments and histopathologic findings appear to support this possibility.[21] For example, it was discovered that kidney calcification increased in guinea pigs exposed to 1.5 per cent carbon dioxide for periods

from forty to ninety-three days. These findings of an altered calcium metabolism appear to be in line with the changes in calcium and inorganic phosphorus content of blood plasma in men during exposure to 1.5 per cent carbon dioxide mentioned above.

CONCLUSIONS

In summarizing our data on chronic carbon dioxide toxicity, a time concentration curve for adaptation to carbon dioxide was established which is shown in Figure 3. Time for adaptation is defined as the time to reach a compensation of the respiratory acidosis induced by carbon dioxide. Measurements of pH, carbon dioxide, bicarbonate levels, and electrolytes in blood and urine were used for determination of the two phases in respiratory acidosis. It can be seen that less time is required to reach the compensation at higher carbon dioxide concentrations which is most probably due to a stronger stimulus on the kidney regulation.

Figure 3 also presents three levels of activities which may be used as tolerance limits: (1) The level producing performance deterioration, alterations in basic physiologic functions as expressed in changes of weight, blood pressure, pulse rate, metabolism and finally pathologic changes (3 per cent carbon dioxide and above). (2) The level at which basic performance and physiologic functions are not affected. Under these conditions, however, slow adaptive processes are observed in electrolyte exchange and acid-base balance regulations which might induce patho-physiologic states on greatly prolonged exposure (1.5 per cent carbon dioxide). (3) The level at which probably no significant physiologic psychological, or adaptive changes occur (0.5 to 0.8 per cent carbon dioxide).

The last level is not yet fully established. The main criterion for this level is that no adaptive processes occur. The role of adaptation to different environmental factors in relation to the functioning of the whole organism has been discussed from various aspects by Schaefer,[30] the main argument being that the organism pays for every adaptation. A gain, on one side, is achieved at the expense of a loss on another side.

It is hoped that the concept of triple-tolerance limits may provide stimulation for further refinement of the quantitative characteristics of man's requirements and reactions in normal and artificial atmospheres. The ranges outlined can give the design engineer a framework. He has to know what the human organism pays for compromises in the design. Determination of the ranges also may help to delineate relevant data from theoretical speculations which come up once in a while in regard to tolerance limits. For example, Bartlett[1] made the apparently serious suggestion to use carbon dioxide-rich atmospheres in confined spaces since man, after all, is accustomed to a high carbon dioxide level of 5.5 per cent in the alveolar air and shows a great tolerance to carbon dioxide under conditions of embryonic life. This statement was for obvious reasons based on a misunderstanding of the significance of carbon dioxide gradients between organism and environment, and unawareness of the established effects of chronic carbon dioxide exposure. It emphasized, however, the pressing need for a framework of tolerance limits.

SUMMARY

Results of studies on chronic carbon dioxide toxicity are summarized and a time-concentration curve for adaptation to carbon dioxide is presented which is based on the time to reach a compensation of the respiratory acidosis.

Experimental evidence demonstrating significant effects of elevated carbon dioxide tensions in blood independent of pH changes is reported. Based on these findings, it appears doubtful whether long-term adaptation to even slightly increased pCO_2 is possible without altering normal physiologic processes and producing histopathologic states.

A concept of triple tolerance limits for carbon dioxide toxicity is proposed for three different levels of activity including one at which no significant physiologic adaptive changes to carbon dioxide occur.

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Some Experiments on the Relative Effectiveness Of Various Types of Accelerations On Motion Sickness

W. H. Johnson, Ph.D. and N. B. G. Taylor, M.D., Ph.D.

Although many stimuli (visceral, psychic, visual) may contribute to the incidence, the primary cause of motion sickness is motion. This is sometimes forgotten. Tyler and Bard[10] commented in their excellent review of motion sickness that: "The occasional failure to appreciate the fact that the fundamental cause of motion sickness is motion has led to some conflict of ideas." As Hemingway[3] pointed out, "The patient is sick without being aware of the cause and is therefore apt to attribute his troubles to odors, overheated compartments, visceral sensations, disagreeable sights, distasteful food or anything else unpleasant, unusual, or uncomfortable—which he experienced shortly before or simultaneously with exposure to motion."

Evidence for the close relationships between vestibular stimulation and motion sickness is direct and mainly based on these facts: (1) Animals which are susceptible to motion sickness are immunized by removal of the vestibular organs or by dividing the eighth cranial nerves. This was first done in dogs and subsequently verified in cats by McNally and Stuart[5] and Johnson.[4] (2) Ablation of the vestibular tracts in the cerebellum eliminates motion sickness in dogs as reported by Bard.[10] (3) Deaf mutes with a congenital absence of the non-auditory labyrinth are known to be immune.[10] (4) Patients whose labyrinths had been destroyed by disease are immune as shown by Graybiel.[2]

Furthermore, it is well known that patients, whose labyrinthine sensitivity is being determined by caloric stimulation of sufficient strength to cause marked nystagmus, often also exhibit the pallor, cold perspiration, nausea, and vomiting characteristic of motion sickness.

The first step in an analysis of the etiology of motion sickness should be to determine those characteristics of motion which result in nausea. Observation and demonstration suggest that an essential feature of nausea-inducing motion is repetitive change in velocity—whether it be linear or angular or combinations of these. However, a serious conflict of opinion has been expressed in the literature as to the relative importance of linear and angular acceleration. We consider that this has been the result of failure to realize that unless the head is supported or restrained, it moves in relation to the vehicle[4] thus exposing the non-auditory labyrinth to accelerations which are not only additional to those of the vehicle but may differ from person to person. As examples of opposing conclusions in this regard, Manning[7] was unable to cause motion sickness in an elevator when the heads of his test subjects were fixed to the seat of the elevator, while Wendt[11] and McEachern and his associates[8] were able to make their subjects sick by vertical accelerations. It is the object of this paper to show the relative effectiveness of a 2-pole and a 4-pole swing in producing motion sickness with the head free or fixed to the swing and with or without visual stimuli.

METHODS

The simple 2-pole swing has been established as a reliable apparatus for inducing motion sickness in man and experimental animals.[1,4,9]

From the Defence Research Medical Laboratories, Toronto, Canada.

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