Full Papers

Effects of increased ambient CO_2 levels on human and animal health

by Karl E. Schaefer

U.S. Naval Submarine Medical Research Laboratory, Groton (Connecticut 06340/USA)

This is the last work to have been completed by Karl Ernst Schaefer, who died on December 26th 1981, in Old Lyme, Connecticut. The physiological changes and problems brought on by an excess of carbon dioxide was, for many years, one of the prime research interests of this eminent respiratory physiologist. In the present work, Schaefer explored the physiological limits of diving with varying N_2-O_2 mixtures. The paper contains a wealth of information relevant to the many still unanswered questions in the field and invaluable suggestions with respect to the course of future research. This work yielded, moreover, some interesting disease models for such disturbances as arrhythmia and bradycardia.

H. Mislin

The effects of continuous exposure to increased ambient CO_2 levels have been a cardinal problem of submarine medicine in the past and are still playing a role today.

A comprehensive program of chronic CO_2 toxicity studies was carried out at the U.S. Naval Submarine Medical Research Laboratory in Groton, Connecticut, which consisted of: 1. laboratory studies on human subjects exposed to low levels of CO_2, 2. correlated field studies on patrols of nuclear powered submarines lasting for approximately 2 months and 3. animal studies designed to unravel the mechanisms of CO_2 effects. A partial summary of these efforts has been published in a special issue of the Undersea Biomedical Research Journal under the title 'Preventive Aspects of Submarine Medicine'[1].

The data which have been obtained in this CO_2 research program are useful for an evaluation of the effects of increased ambient CO_2 levels on human and animal health, which has become the particular concern of the Department of Energy and other government agencies. Estimates vary, but it is expected that the ambient CO_2 levels which have risen since the beginning of the industrial revolution may increase up to 8-fold (to 2700 ppm) during the next century due to the continuous increase in fossil fuel consumption.

The lowest ambient CO_2 values which have been tested in chronic animal CO_2 studies are 2000 and 3000 ppm. Preliminary experiments do indicate that under these conditions effects on CO_2 target organs such as the kidneys are produced.

Regulation of respiration and acid-base balance

A summary of physiological studies on 13 Polaris patrols, in which the ambient CO_2 concentrations averaged 0.7–1% CO_2, was made by Schaefer[1]. CO_2 found in the submarine atmosphere in this concentration range was identified as the only environmental contaminant that has a direct effect on respiration. A consistent increase in respiratory minute volume based on an increased tidal volume was found. The CO_2 tolerance curves measured after 2 and 5 weeks of exposure to 1% CO_2 on patrol showed a slight decrease in slope[1].

While the effects of prolonged exposure to low levels of CO_2 on respiration were similar to those known to occur in chronic hypercapnia induced by higher CO_2 concentration ranging from 1.5% CO_2 to 3% CO_2, acid-base changes contrasted markedly[2–5].

Blood pH and bicarbonate exhibited cyclic changes alternating between 'metabolic' and 'respiratory' acidosis in approximately 20-day periods[1]. The term 'metabolic' acidosis has been used to denote a state in which increased P_aCO_2 and decreased pH are found to be associated with a decreased blood bicarbonate level. After 3 weeks of exposure to 0.85–1% CO_2, blood pH, P_aCO_2 and blood bicarbonate began to rise and subsequently declined again after about 40 days.

Data on pH, P_aCO_2 and bicarbonate obtained in 3 patrol studies[1] and 2 laboratory experiments involving prolonged exposure to 1.5% CO_2[6] and 1% CO_2[1] clearly exhibited the cycles in acid-base balance. The long time periods (3 weeks) required to reach a compensation during exposure to low concentrations of CO_2 (0.8–1.5% CO_2) are quite different from the 4–5-day periods needed to accomplish maximal compensation in chronic hypercapnia induced by exposure to 3%–15% CO_2. The presently accepted concepts of CO_2-induced changes in acid-base balance, particularly in regard to clinical conditions, are based on studies of the effects of high concentration of CO_2, mainly those done by Schwartz and co-workers[7–9].

If the times required for maximal compensation of chronic CO_2-induced acidosis produced by different CO_2 concentrations are plotted against arterial or venous CO_2 tension, a graph is obtained that exhibits a systematic difference in response to levels of 3% and above (time for compensation 3–5 days) compared to that at lower levels, where the time periods required for compensation increase with decreasing ambient CO_2 concentration[2] (fig. 1).

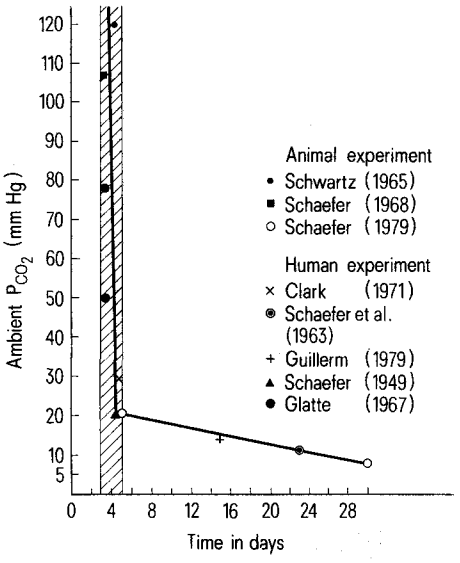

Figure 1. Time to reach maximal compensation of blood pH during prolonged exposure to different ambient CO_2 tensions. Animal and human experiments.

These data suggest that the renal regulation (bicarbonate reabsorption) is fully active during exposure to higher CO_2 concentrations but becomes less and less effective during exposure to lower CO_2 concentrations. Under the latter conditions bone buffering which has a slow time constant appears to become a dominant factor.

Calcium metabolism

The reported 20-day phases in acid-base balance during chronic low-level hypercapnia were found to be reflected in calcium homeostasis, inasmuch as blood calcium levels mirrored the pH changes and urine calcium also exhibited related phasic alterations[1,10,12].

It was suggested in an earlier study on calcium metabolism during exposure to 1.5% CO_2 that the initial 3-week period of decline in blood calcium corresponding to the decrease in blood pH marks a period of deposition of CO_2 in bones[10]. The long time-constant of bone CO_2 storage is an important factor in acid-base regulation during chronic hypercapnia. This has been confirmed by Davies[12,13] and Poyart et al.[14,15]. Davies[16] emphasizes the rapid reduction in calcium excretion following exposure to low level hypercapnia.

The effects of prolonged exposure to low CO_2 concentrations on acid-base balance and the role of bone buffering have received little attention.

Bone CO_2 uptake in chronic hypercapnia has been shown not to follow a P_aCO_2 dependent saturation mechanism. Reichart et al.[17] exposed rats to 8% CO_2 for 2, 4, 6 and 8 weeks and found that total body CO_2 uptake was still increasing after 8 weeks due to a

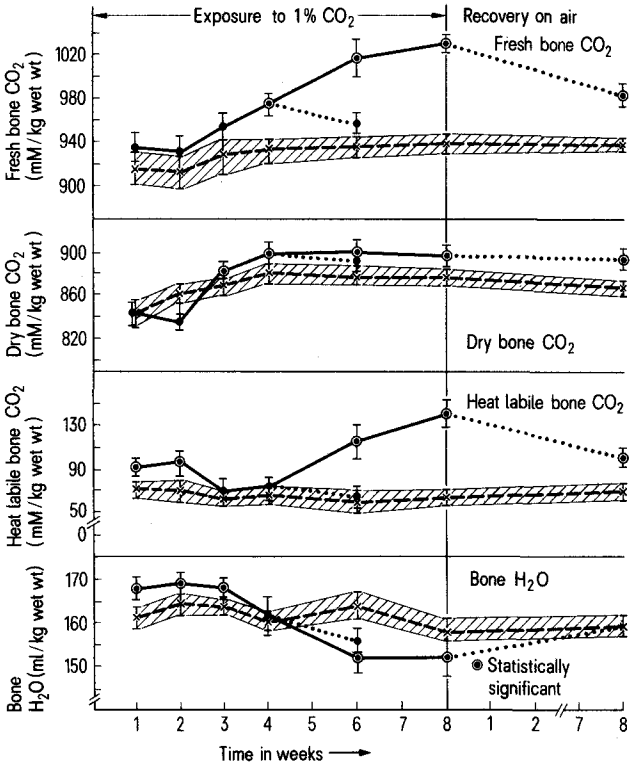

Figure 2. Effect of prolonged exposure to 1% CO_2 on total bone CO_2 content of fresh bone, dry bone, difference between fresh bone and dry bone CO_2 content (heat-labile CO_2), and bone H_2O content. Data represent means and SE, in mmol/kg wet wt. Exposed animals ——, control animals ----; recovery following exposure ·····. Statistically significantly different from controls at 5% level and better. Each group of exposed animals consisted of 6 animals, each control group (littermates of the exposed guinea-pigs) of 3–4 animals (Schaefer et al.[19]).

continuous increase of bone CO_2, while CO_2 uptake in liver and muscle had attained an equilibrium. The authors could not explain the disparity in the CO_2 uptake by different organs. Brown and Michel[18], who studied whole body CO_2 exchange in rats during prolonged exposure to 10% CO_2 also found that the CO_2 uptake did not reach an equilibrium.

During 8 weeks of exposure to 1% CO_2 a continuous rise in bone CO_2 was observed which was particularly marked during the later periods of between 4 and 8 weeks[19]. Bone bicarbonate (heat labile bone CO_2) and bone carbonate (heat stable bone CO_2), determined with a titration method[20], displayed changes during exposure consisting of: 1. an increase in bone bicarbonate associated with a deacrease in carbonate during the first 2 weeks of exposure, followed by a 2nd phase of 2 weeks in which bone bicarbonate decreased and bone carbonate increased. During a subsequent 3rd period of 4–8 weeks of exposure, bone bicarbonate rose sharply while bone carbonate remained stable (fig. 2). The phases of bone bicarbonate increase were found to be associated with bone calcium and phosphorous loss, while the phase

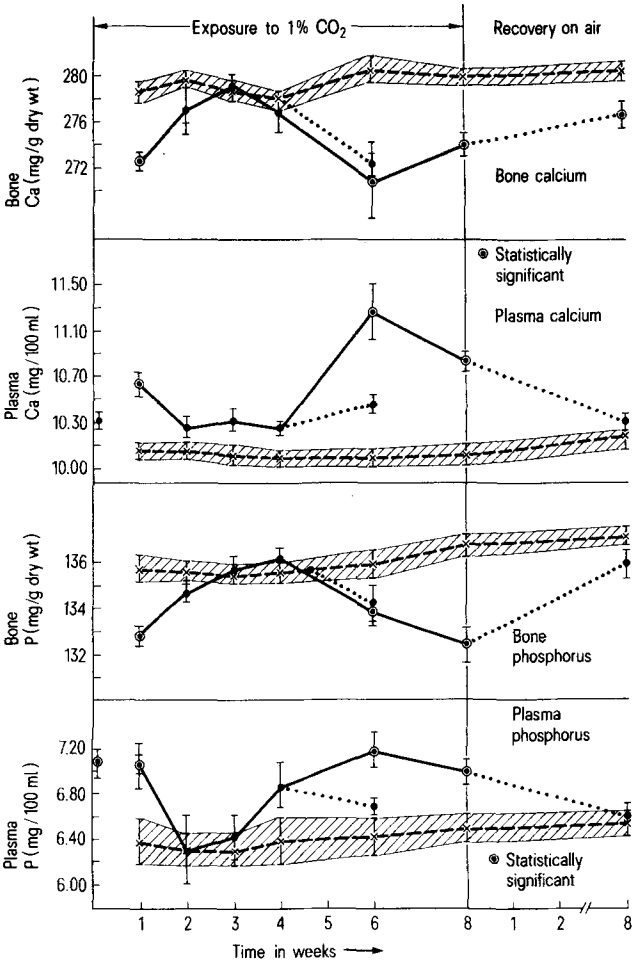

Figure 3. Effect of prolonged exposure to 1% CO_2 on bone and blood calcium and bone and blood phosphorus. Data represent means and SE, in mg/g dry wt. Exposed animals ——; control animals----; recovery following exposure · · · ·. Statistically significantly different from controls at 5% level and better. Each group of exposed animals consisted of 6 animals, each control group of 3–4 animals.

of bone carbonate loss was attended by bone calcium and phosphorous gains (fig. 3). A summary of these phases is shown in table 1. Saturation of the rapidly exchanging pool of bone CO_2 associated with water influx is apparently accomplished during the first 2 weeks of exposure to 1% CO_2 During the subsequent period of the 3rd and 4th week of exposure a reversal takes place showing a dehydration and loss of heat labile CO_2, which must result in a release of gaseous CO_2 from extracellular space. The 2nd rise of the bone bicarbonate fraction after 6 weeks of exposure to 1% CO_2 was apparently based on a process which differs from the first one, because bone water and bone carbonate do not change. The process of CO_2 binding under these circumstances most likely involves deeper layers in the bone and may correspond with the increased CO_2 binding found to occur during aging, which is also associated with the loss of bone H_2O[14].

Table 1. Phasic changes in bone calcium, phosphorus, carbonate, and bicarbonate produced by prolonged exposure of guinea-pigs to 1% CO_2

Exposure to 1% CO_2 (weeks)	ΔCa	ΔP	ΔCO_3^{2-}	ΔHeat-labile CO_2	ΔHCO_3^-	Phases
	(meq/kg wet bone)					
1	−390	−260	0	+21	+ 42	I (initial HCO_3^-
2	−200	− 30	−15	+25	+ 50	uptake; CO_3^{2-} decline)
3	− 30	− 5	+13	+10	+ 20	II (CHO_3^- uptake
4	−196	− 50	+32	+ 9	+ 18	reduced; CO_3^{2-} uptake increased)
6	−320	−100	+23	+62	+124	III (large HCO_3^-
8	−148	−180	+30	+66	+132	uptake; CO_3^{2-} remains stable)

Differences between experimental animals and littermate controls.

These findings suggest that the phasic changes in bone CO_2 fractions are related to the phasic changes in acid-base balance observed in animal and human experiments with prolonged exposure to low levels of CO_2.

Red cell electrolyte changes

Other effects of prolonged exposure to ambient CO_2 concentrations of 0.7–1% CO_2 in the submarine atmosphere included red cell electrolyte changes as reflected by an increase in sodium and decrease in potassium. These alterations indicative of permeability changes in the red cells were accompanied by an influx of calcium into the red cells[1].

In contrast to the effects of higher CO_2 concentrations, plasma potassium and hematocrits were found to decrease on patrols[1], which is in agreement with findings obtained in laboratory experiments[3] during exposure to 2% and to 1.5% CO_2[6].

Gastric acidity

CO_2 has been shown to be a stimulator of gastric-acid secretion in man[21,22]. Moreover, gastric secretion was also found to increase in dogs during chronic hypercapnia[23].

Findings of increased gastric acidity obtained during prolonged exposure to 1% CO_2 on patrols[1] are in agreement with the reported effects of acute and chronic hypercapnia on gastric-acid secretion and have been taken into consideration in evaluating symptoms of pyrosis. The latter show a relatively high incidence during patrols, second only to respiratory symptoms.

Intermittent exposure to CO_2; a model showing the limitations of pulmonary and renal response to CO_2

Intermittent exposure to CO_2 is a snorkel submarine problem that has received very little attention. One pilot study involved a medical student who was on a

liquid diet and exposed for 6 days to increasing ambient CO_2 rising at a constant rate from 0.03% to 3% CO_2 during a period of 15 h[24]. The results of the study provided a model demonstrating limitations of the respiratory and renal response to CO_2. The increase in ventilation produced by intermittent exposure to CO_2 was not sufficient to prevent CO_2 accumulation in the body. The previously accumulated CO_2 was eliminated on the 4th and 5th day during the nightly air-breathing period. The known renal response to hypercapnia, that is, an increased excretion of titratabel acidity, ammonia and hydrogen ions, occurred on the 1st day of exposure. This response was interrupted during the 2nd and 3rd day and finally reappeared again during the 4th and 5th day. This 2nd delayed renal response to CO_2 appeared to coincide with the release of accumulated CO_2 from the CO_2 stores in bone as indicated by a concomitant increase in calcium excretion.

Target organs of CO_2 effects - kidneys, lungs and bones

Previous studies with prolonged exposure to CO_2 concentrations of 15%, 3% and 1.5% CO_2 had demonstrated relatively few significant histopathological changes[25]. However, it was apparent that kidneys and lungs, organs involved in acid base balance regulation, were target organs of CO_2 effects[26,27].

Kidneys. More recent studies involving prolonged exposure of guinea-pigs to 1.5% and 1% CO_2 demonstrated that the incidence of kidney calcification increased with length of exposure[28].

Light microscopic examination of kidney tissue of guinea-pigs exposed to 1.5% CO_2, 21% O_2 and balance N_2 for periods as long as 42 days and rats exposed to the same concentrations for up to 91 days showed that the incidence of focal kidney calcification increased with length of exposure. Calcification occurred primarily in the tubules of the renal cortex. The small but consistent increases in ionized calcium observed during a 4-week exposure to 1% CO_2 may have stimulated the parathyroid, causing an increased blood calcium level independent of the 2 calcium tides in the blood associated with marked bone calcium loss[28] (fig. 4).

The slightly but consistently increased level of ionized calcium found during exposure to 1% CO_2 points towards an involvement of the parathyroid gland. Administration of parathyroid hormone is known to cause kidney calcification[29]. CO_2 has also been shown in increase PTH effects as measured by Ca^{45} release from fetal bones[30].

Moreover, PTH stimulation may have been the cause of the acidosis observed during prolonged exposure to 1% CO_2. The decrease in standard bicarbonate found during the first 4 weeks of exposure indicates a failure of the kidney to reabsorb bicarbonate. PTH has been found to decrease bicarbonate reabsorption and to produce a systemic acidosis[31].

These findings may stimulate research into the clinical significance of slightly increased P_aCO_2 levels in hyperparathyroid states.

The results of the studies of the effects of prolonged exposure to 1% CO_2 demonstrated that kidney calcification could be used as a criterion to establish threshold effects of chronic CO_2 exposure on target organs. Further investigations carried out on guinea-pigs exposed to 0.5% CO_2, 21% O_2 and balance N_2 for periods of up to 8 weeks showed evidence of increased kidney calcification after 8 weeks of exposure. Plasma calcium was increased at that point due to the release of bone calcium. After 8 weeks of recovery on air following 8 weeks of exposure to 0.5% CO_2, values had returned to control levels[32]. In a more recent investigation[33] kidney calcification was also found after prolonged exposure of guinea-pigs to 0.3% CO_2.

Lungs. The lung is another target organ of CO_2 effects. Exposure to higher concentrations of 3% and 15% CO_2 produced pulmonary hyaline membranes in guinea-pigs[27]. The incidence of hyaline membrane formation decreased progressively after compensation of the respiratory acidosis was reached, indicating a nonspecific acidosis effect[17]. Ultrastructural changes associated with the CO_2-induced transient hyaline membrane formation were manifested in the disap-

Table 2. Changes in type II pneumocytes of guinea-pigs

	Experimental			Control		
Duration of exposures (weeks)	Cell diameter (μm)	No. lamellar bodies/cell	Lamellar body diameter (μm)	Cell diameter (μm)	No. lamellar bodies/cell	Lamellar body diameter (μm)
1	9.2 (1.4)	5.1 (1.4)	1.1 (0.13)	9.0 (1.6)	5.0 (1.6)	1.09 (0.13)
2	9.3 (1.2)	5.2 (1.3)	1.1 (0.12)	9.1 (1.5)	5.2 (1.5)	1.2 (0.11)
3	9.2 (1.2)	5.1 (1.5)	1.2 (0.14)	9.2 (1.5)	5.1 (1.6)	1.1 (0.13)
4	12.2 (2.0)**	9.1 (3.2)**	2.1 (0.11)*	9.1 (1.7)	5.1 (1.7)	1.1 (0.14)
6	13.5 (1.7)**	9.2 (2.1)**	2.2 (0.13)**	9.1 (1.6)	5.2 (1.6)	1.2 (0.12)
Recovery on air after 4 weeks exposure						
2 weeks' recovery	13.3 (1.9)**	9.3 (3.1)**	2.2 (0.15)**			
4 weeks' recovery	11.6 (1.9)*	7.8 (2.3)*	1.8 (0.10)*			

Values are means (±SD); experimental n = 6; control, n = 3 or 4; evaluations based on 150 photographs per animal. * Significantly different from controls at the 5% level and ** at the 1% level.

pearance of osmiophilic lamellar bodies (OLBs) of the type II pneumocyte. A decrease in surfactant production, indicated in a rise of minimal surface tension, was associated with these morphological changes.

Electron microscopic studies carried out in guinea-pigs exposed to 1% CO_2, 21% O_2 and balance N_2[34] showed ultrastructural changes in the lungs after 4 and 6 weeks of exposure that consisted of marked increases in the size and number of pneumocyte II cells. These increases were still present 2 weeks and, to a lesser extent, 4 weeks after recovery (table 2). Change in pneumocyte II cells were postulated to be compensatory reactions to impairing effects of CO_2 on the alveolar lining cell (type I cell).

No significant ultrastructural changes were found in the lungs after 4, 6 and 8 weeks of exposure of guinea-pigs to 0.5% CO_2, 21% O_2, and balance N_2[32].

Bones. Studies of the effects of prolonged exposure to 1% CO_2 fraction demonstrated that bone calcium and phosphorus were significantly decreased after 8 weeks of exposure. Bone calcium remained significantly lower after 8 weeks of recovery following 8 weeks of exposure when compared to litter mate control animals, indicating a bone demineralization[11].

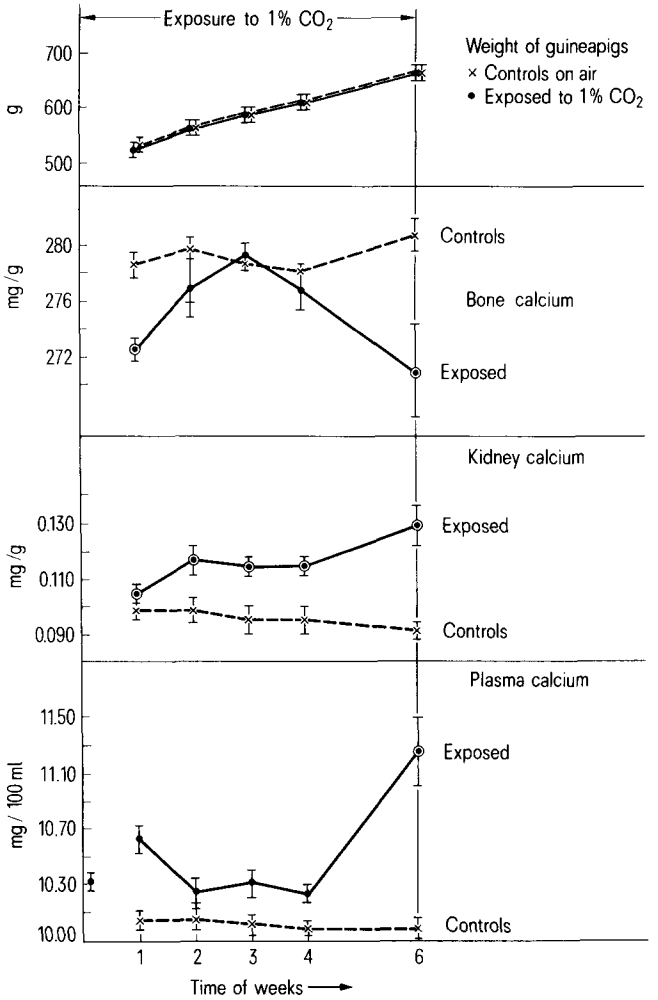

Figure 4. Effect of prolonged exposure to 1% CO_2 on body weight, bone calcium, kidney calcium, and plasma calcium in guinea-pigs. Data represent means ±SEM. ◉ = significantly different from controls at the 5% level or better. Each experimental group consisted of 6 animals, each control group of 3-4 animals (Schaefer et al.)[28].

Discussion

The question has been raised as to whether one can use a backward projection with data on the effects caused by higher CO_2 concentrations to predict effects of smaller CO_2 concentration, assuming a linear hypothesis. Our data demonstrate the existence of concentration-dependent shifts in CO_2 effects on target organs, which rules out any backward projection.

There is a systematic difference in acid-base regulation in response to levels of CO_2 of 3% and above, compared with that observed at lower CO_2 concentrations. In the former conditions, the renal regulation (bicarbonate reabsorption) is fully active and the time to reach maximal compensation of blood pH is short (3-5 days), while in the latter renal regulation becomes less effective and bone buffering, which has a slow time constant, becomes a dominant factor. This results in an extension of the times necessary to accomplish maximal compensation of blood pH to 24-30 days during exposure to 1.5% and 1% CO_2.

Another example of a concentration-dependent shift in CO_2 effects on target organs is exhibited in the ultrastructural changes of the lungs of guinea-pigs exposed to 15% CO_2 and 3% CO_2 on the one side, 1% CO_2 on the other side. The pneumocyte II cells, known to be the source of surfactant production, were found to have decreased during exposure to 15% and 3% CO_2 and to have increased during exposure to 1% CO_2[27,34].

There is a subtle transition from adaptation to CO_2 to adaptive diseases. With increasing length of exposure time, kidney calcification was observed in all experimental conditions with ambient CO_2 concentrations ranging from 15% CO_2 to 0.3% CO_2[1,10,11,26,38,33]. Kidney calcification can be characterized as an adaptive disease in chronic CO_2 exposure. The same is true for bone calcium demineralization observed after 8 weeks of exposure to 1% CO_2[19] as well as for the ultrastructural changes of the lungs[34].

Exposure times to increased ambient CO_2 levels were limited to 60-90 days and under these conditions the adaptive disease states listed above seemed to disappear if sufficient recovery time was provided. It is essential, however, for future studies to definitely establish in what time frame the CO_2 effects become irreversible. For this purpose it is necessary to carry out generation studies of CO_2 effects.

1 Schaefer, K.E., Physiological stresses related to hypercapnia during patrols on submarines. Undersea Biomed. Res., Suppl. 6 (1979) S15-S47.

2 Schaefer, K.E., Hastings, B.J., Carey, C.R., and Nichols, Jr, G., Respiratory acclimatization to carbon dioxide. J. appl. Physiol. *18* (1963) 1071–1078.
3 Guillerm, R., and Radzisewski, E., Effects on many of 30-day exposure to $PICO_2 = 14$ torr (2%): application to exposure limits. Undersea Biomed. Res., Suppl. *6* (1979) S91–S114.
4 Schaefer, K.E., Respiration and acid-base balance during prolonged exposure to 3% CO_2. Pflügers Arch. *25* (1949) 689–694.
5 Clark, J.M., Sinclair, R.D., and Welch, B.E., Rate of acclimatization to chronic hypercapnia in man, in: Underwater Physiology, pp.399–408. Ed. C.J. Lambertsen. Academic Press, New York 1971.
6 Schaefer, K.E., Nichols, Jr., G., and Carey, C.R., Acid-base balance and blood using electrolytes of man during acclimatization to carbon dioxide. J. appl. Physiol. *19* (1964) 48–58.
7 Polak, A., Haynie, G.D., Hayes, R.M., and Schwartz, W.B., Effect of chronic hypercapnia on electrolyte and acid-base equilibrium. I. Adaptation. J. clin. Invest. *40* (1961) 1223–1237.
8 Schwartz, W.B., Brackett, Jr, N.C., and Cohen, J.J., The response of extracellular hydrogen ion concentration to graded degrees of chronic hypercapnia: the physiological limits of the defense of pH. J. clin. Invest. *44* (1965) 291–301.
9 van Ypersele de Strihou, Brasseur, C.E.L., and DeConincok, J., The carbon dioxide response curve for chronic hypercapnia in man. N. Engl. J. Med. *275* (1966) 117–125.
10 Schaefer, K.E., Nichols, G., and Carey, C.R., Calcium phosphorus metabolism in man during acclimatization to carbon dioxide. J. appl. Physiol. *18* (1963) 1079–1084.
11 Messier, A.A., Heyder, E., Braithwaite, W.R., McCluggage, C., Peck, A., and Schaefer, K.E., Calcium, magnesium, and phosphorous metabolism and parathyroid-calcitonin function during prolonged exposure to elevated CO_2 concentrations on submarines. Undersea Biomed. Res., Suppl. *6* (1979) S57–S70.
12 Davies, D.M., Smith, D.J., Leitch, D.R., Morris, J.E.W., and Gray, S.P., The effects on man of continuous exposure to 0.5% carbon dioxide. Inst. nav. Med. Rep. 1976. No.22/76. Alverstoke, England.
13 Davies, D.M., Sixty days in a submarine: the pathophysiological and metabolic cost. J.R. Coll. Physicians *7* (1973) 132–144.
14 Poyart, C.F., Bursaux, E., and Freminet, A., The bone CO_2 compartment: evidence for a bicarbonate pool. Resp. Physiol. *25* (1975) 89–99.
15 Poyart, C.F., Freminet, A., and Bursaux., E. The exchange of bone CO_2 in vivo. Resp. Physiol. *25* (1975) 101–107.
16 Davies, D.M., and Morris, J.E.W., Carbon dioxide and vitamin D effects on calcium metabolism in nuclear submarines. Undersea Biomed. Res., Suppl. *6* (1979) S71–S80.
17 Reichart, E., Caludon, F. and Sabliere, S., CO_2 storage in various organs during chronic experimental hypercapnia. Bull. Eur. Physiopath. Resp. *12* (1976) 19–32.
18 Brown, Jr, E.B., and Michel, C.C., Whole body CO_2 exchange. Proc. XXIV Int. Congr. physiol. Sci. *6* (1968) S185–S186.
19 Schaefer, K.E., Pasquale, S., Messier, A.A., and Shea, M., Phasic changes in bone CO_2 fractions, calcium, and phosphorus during chronic hypercapnia. J. appl. Physiol; Resp. envir. Exercise Physiol. *48* (1980) 802–811.
20 Pasquale, S., Messier, A.A., Shea, M.L., and Schaefer, K.E., Bone CO_2 titration curves in acute hypercapnia. J. appl. Physiol, Resp. envir. Exercise Physiol. *48* (1980) 197–200.
21 Tenney, S.M., and Naitove, A., Effects of alveolar oxygen and carbon dioxide on gastric secretion. Fedn Proc. *19* (1960) 190.
22 Blakemore, W.S., and Wolfson, S.K., Respiratory insufficiency as a factor in postoperative gastrointestinal bleeding. J. thorac. cardiovasc. Surg. *44* (1962) 494–505.
23 Phil, B.G., Pohl, A.L., Dickens, R.A., and Glotzer, C.J., Effect of chronic hypercapnia on gastric secretion in the dog. Ann. Surg. *165* (1967) 254–265.
24 Schaefer, K.E., Carey, C.R., Dougherty, J.H., Messier, A.A., and Morgan C., Effect of intermittent exposure to 3% CO_2 on respiration, acid-base balance and calcium metabolism. Undersea Biomed. Res., Suppl. *6* (1979) S115–S134.
25 Schaefer, K.E., Niemoeller, H., Messier, A.A., Heyder, E., and Spencer, J., Chronic CO_2 toxicity: Species difference in physiological and histopathological effects. NAVSUB-MEDRSCHLAB Report 1971, No.656.
26 Schaefer, K.E., Hasson, M., and Niemoeller, H., Effect of prolonged exposure to 15% CO_2 on calcium and phosphorus metabolism. Proc. Soc. exp. Biol. Med. *107* (1961) 355–359.
27 Schaefer, K.E., Avery, M.E., and Bensch, K., Time course of changes in surface tension and morphology of alveolar epithelial cells in CO_2 induced hyaline membrane disease. J. clin. Invest. *43* (1964) 2080–2093.
28 Schaefer, K.E., Pasquale, S.M., Messier, A.A., and Niemoeller, H., CO_2 induced kidney calcification. Undersea Biomed. Res., Suppl. *6* (1979) S143–S153.
29 Cohn, D.V., Bowden, R., and Eller, G.J., The effect of parthyroid hormone in vivo on the accumulation of calcium and phosphate by kidney and on kidney mitochondrial function. J. biol. Chem. *242* (1967) 1253–1255.
30 Mahgoub, A., and Stern, P., Carbon dioxide and the effect of parathyroid hormone on bone in vitro. Am. J. Physiol. *226* (1974) 1272–1275.
31 Crumb, Ch.K., Martinez-Muldonado, M., Eknoyan, G., and Suki, X., Effect of volume expansion, purified parathyroid extract and calcium on renal bicarbonate absorption in the dog. J. clin. Invest. *54* (1974) 1287–1294.
32 Schaefer, K.E., Douglas, W.H.J., Messier, A.A., Shea, M.L., and Gohman, D.A., Effects of prolonged exposure to 0.5% CO_2 on kidney calcification and ultra structure of lungs. Undersea Biomed. Res., Suppl. *6* (1979) S155–S161.
33 Shea, M.L., Messier, A.A., and Bondi, K.R., Effect of prolonged exposure to low levels of CO_2 concentration on kidney calcium and lung ultra structure. Fedn Proc. *40* (1981) 675.
34 Douglas, W.H.J., Schaefer, K.E., Messier, A.A., and Pasquale, S.M., Proliferation of pneumocyte II cells in prolonged exposure to 1% CO_2. Undersea Biomed. Res., Suppl. *6* (1979) S135–S142.

Modulation of dopaminergic transmission by alpha-noradrenergic agonists and antagonists: Evidence for antidopaminergic properties of some alpha antagonists[1]

Peter C. Waldmeier[2], Rainer Ortmann and Serge Bischoff

Research Department, Pharmaceuticals Division, Ciba-Geigy Ltd, CH-4002 Basle (Switzerland), 27 May 1982

Summary. The effects on dopamine (DA) metabolism, on ^{3}H-spiperone binding and on amphetamine-induced stereotypies of a variety of drugs with different actions on $alpha_1$- and $alpha_2$-noradrenergic (NA) receptors have been investigated.

The preferential $alpha_2$-antagonists yohimbine, rauwolscine, piperoxane and esproquin as well as the preferential $alpha_1$-antagonists corynanthine and WB4101 increased homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) in the rat striatum, mesolimbic area, and cortex. Prazosine and clonidine tended to