

INVOLVEMENT OF CO<sub>2</sub> AND CALCIUM STORES IN  
DECOMPRESSION SICKNESS

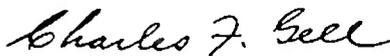
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## SUMMARY PAGE

### THE PROBLEM

In previous investigations of saturation excursion diving, it was observed that symptoms of decompression sickness manifested themselves in poorly localized muscle ache and stiffness which did not respond to recompression and oxygen treatment. This appeared to be associated with a large CO<sub>2</sub> excretion in the urine. The possible physiological mechanisms need evaluation.

### FINDINGS

Detailed analysis of the urine electrolytes of 4 divers participating in saturation excursion dives to 800 and 1000 FSW demonstrated that in all cases an increase in urinary CO<sub>2</sub> excretion and calcium excretion occurred during certain periods of decompression. In two subjects who developed symptoms of decompression sickness of the type which did not respond to recompression and oxygen treatment, the carbon dioxide excretion in the urine was more pronounced and was preceded or followed by a calcium tide. These observations point to the bone with its large CO<sub>2</sub> and calcium store as a target organ in decompression sickness. The hypothesis is presented, that during compression a greater influx of calcium and carbon dioxide occurs into the fast exchanging bone carbon dioxide and calcium stores followed by a greater outflow of calcium and carbon dioxide during decompression in relation to increased and decreased bone-blood flow, respectively. Recent advances in bone physiology seem to support this hypothesis.

### APPLICATION

These findings are of interest to Medical Officers involved in diving operations and research personnel concerned with decompression problems. The hypothesis appears to offer new avenues of approach to the study of decompression sickness and aseptic bone necrosis.

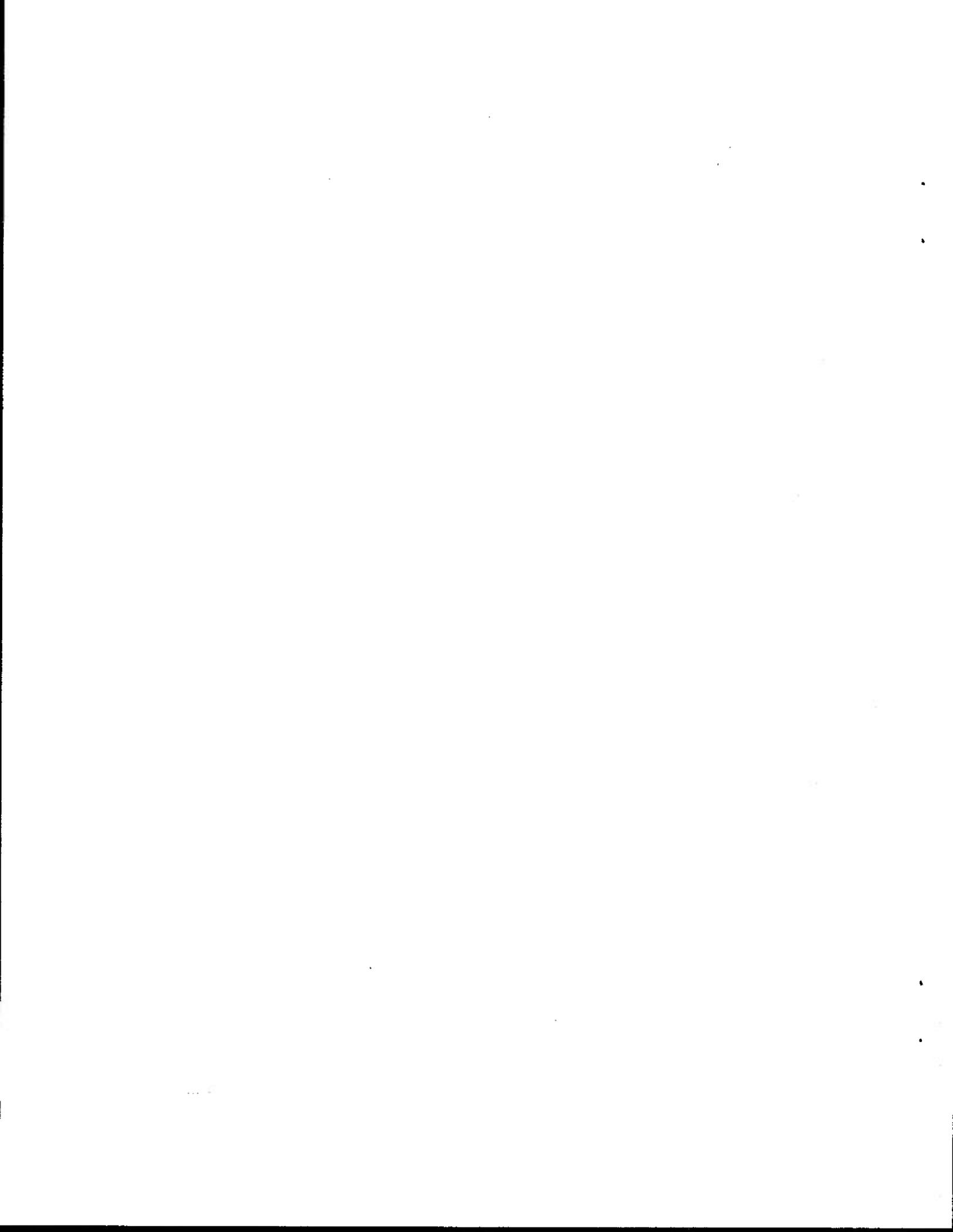
### ADMINISTRATIVE INFORMATION

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## ABSTRACT

Analysis of urine electrolytes obtained during saturation excursion dives of four divers to depths equivalent to 800 and 1000 feet of sea water showed in all cases during decompression an increase in urinary CO<sub>2</sub> excretion and calcium excretion. In two subjects who developed symptoms of decompression sickness manifested in poorly localized muscle aches and stiffness of joints which did not respond to recompression and oxygen treatment, the carbon dioxide excretion in the urine was more pronounced and was preceded or followed by a calcium tide. These observations point to the bone with its large CO<sub>2</sub> and calcium store as a target organ in decompression sickness. The hypothesis is presented that during compression a greater influx of calcium and carbon dioxide occurs, into the fast exchanging bone carbon dioxide and calcium stores related to an increase in bone-blood flow. During decompression a greater outflow of calcium and carbon dioxide seems to develop corresponding with a decreased bone-blood flow. Recent advances in bone physiology appear to provide a fitting framework for this hypothesis.



## INVOLVEMENT OF CO<sub>2</sub> AND CALCIUM STORES IN DECOMPRESSION SICKNESS

### INTRODUCTION

In a previous communication, Schaefer et al.<sup>17</sup> reported that symptoms of decompression sickness manifested in poorly localized muscle aches and stiffness which did not respond to recompression and O<sub>2</sub> treatment appeared to be associated with fluid and electrolyte shifts and a large CO<sub>2</sub> excretion in the urine.

Further analysis of urine electrolyte data revealed that in these cases the carbon dioxide tide was preceded or followed by a calcium tide in the urine. These observations which point to the bone with its CO<sub>2</sub> and calcium sink as a target organ in decompression sickness are presented in this report.

### METHODS

Four subjects participated in saturation excursion dives to pressure equivalent to 800 and 1000 feet of seawater (FSW). Details of these experiments and decompression schedules have been described previously.<sup>17</sup>

Twenty-four-hour urine specimens were collected in polyethylene bottles. A cover of liquid silicone (Dow Corning 200) was used to prevent CO<sub>2</sub> from escaping from the urine into the chamber atmosphere. Aliquots were frozen until

analyzed. Total urine CO<sub>2</sub> was determined by the manometric method of Van Slyke. Urine pH was measured with the Beckman pH meter.

Inorganic phosphorus in the urine was determined by the method of Fiske and Subbarow as modified by Roe and Whitmore.<sup>13</sup>

Calcium in the urine was measured according to the method of Clark and Collip,<sup>4</sup> a modification of the procedure of Kramer and Tisdall.

### RESULTS

Data obtained during the saturation excursion dive to depth equivalent to 800 feet of seawater are shown in Figures 1 and 2.

The dive profile is presented in the lower part of the figures. CO<sub>2</sub> excretion and calcium excretion are plotted together. In the first case the diver developed bends during the 800 FSW saturation excursion dive. During the same day, the CO<sub>2</sub> excretion rose to a peak 6 times above the initial value, while the calcium excretion rose to a level twice normal during the subsequent day (Figure 1). The other diver, who did not experience bends during the decompression from 800 feet, showed

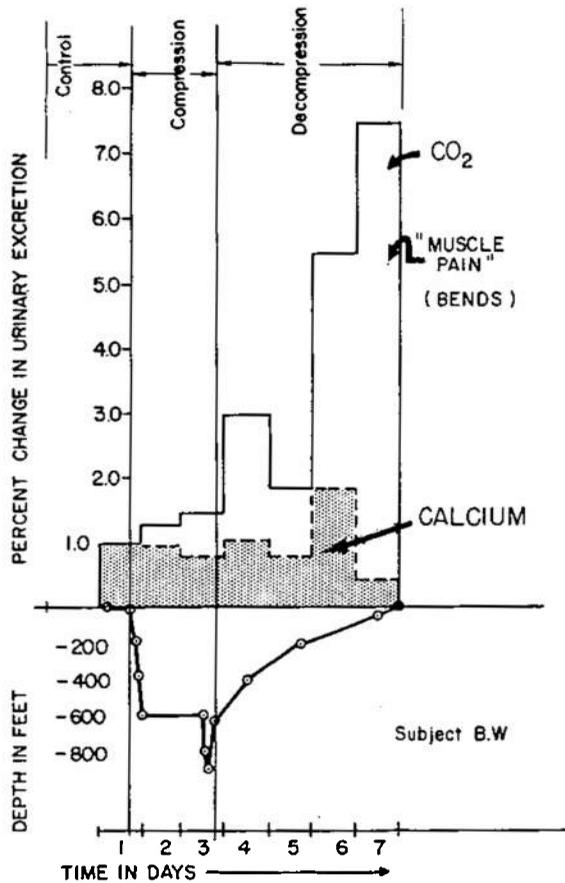


Fig. 1. Carbon dioxide and calcium excretion in the urine during saturation excursion dive to 800 FSW (Expressed in percent change from control values). Subject B. W.

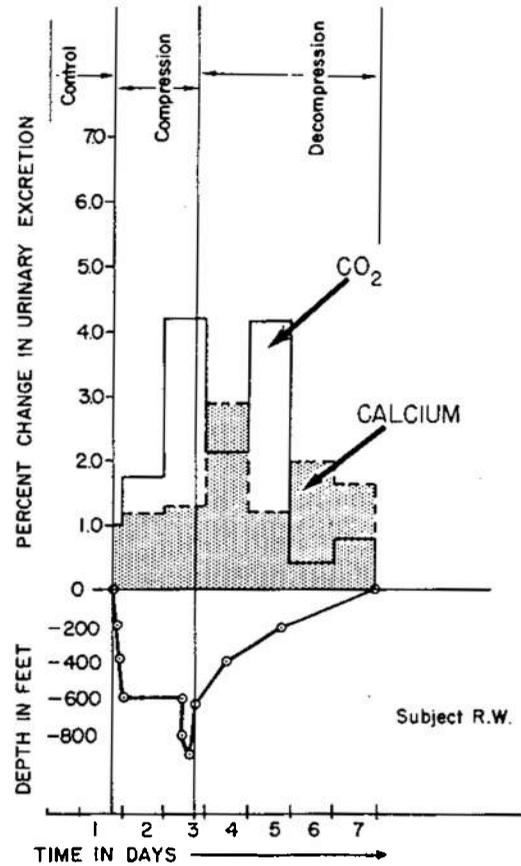


Fig. 2. Carbon dioxide and calcium excretion in the urine during saturation excursion dive to 800 FSW (Expressed in percent change from control values). Subject R. W.

smaller elevations of  $\text{CO}_2$  excretion and calcium elimination during the decompression period (Figure 2).

In the second saturation excursion dive to 1000 FSW, both divers experienced symptoms of decompression sickness during decompression at 30 FSW. Recompression to 60 FSW relieved the

symptoms in one diver but not in the other. Subsequent recompression to 165 FSW and 527 FSW had no success either in relieving the symptoms in the second diver. After staying two hours at the depth of 521 feet, the diver received one tablet of Bufferin, which had an immediate effect. The diver could sleep without pain and the subsequent decompression was uneventful.

Figure 3 shows the CO<sub>2</sub> and calcium excretion of the diver who experienced severe bends during the decompression from 1000 FSW saturation excursion dive.

CO<sub>2</sub> excretion is increased 7 fold during the 24 hours preceding the appearance of bends in which the divers were decompressed from 200 to about 50 FSW and shows only a small elevation during the day at which the bends occurred. However, calcium excretion exhibits a peak, 3-fold above normal, during the day the symptoms of decompression sickness occurred, and the massive recompression to 527 FSW was instituted.

The second diver who had only temporary intermittent pain in both knees

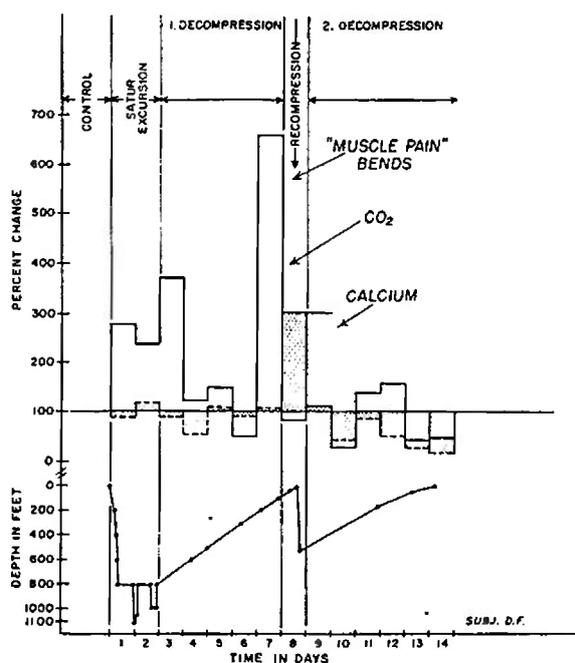


Fig. 3. Carbon dioxide and calcium excretion in the urine during saturation excursion dive to 1000 FSW' (Expressed in percent change from control values). Subject D. F.

between 50 and 40 FSW exhibited throughout the decompression period, in intervals of approximately two days, large increases in CO<sub>2</sub> excretion and only one time was such a large peak in CO<sub>2</sub> excretion preceded by a marked rise in urinary calcium reaching a level 3 times higher than initial values. This occurred on the second day of the decompression period following the recompression to 527 FSW (Figure 4).

The calcium tides in the urine observed in association with large CO<sub>2</sub> excretion during decompression were found to have no correlation with alterations in the excretion of inorganic phosphate at the time of the tidal phase as seen in Figures 5 and 6 for the two divers participating in the 1,000 FSW dive.

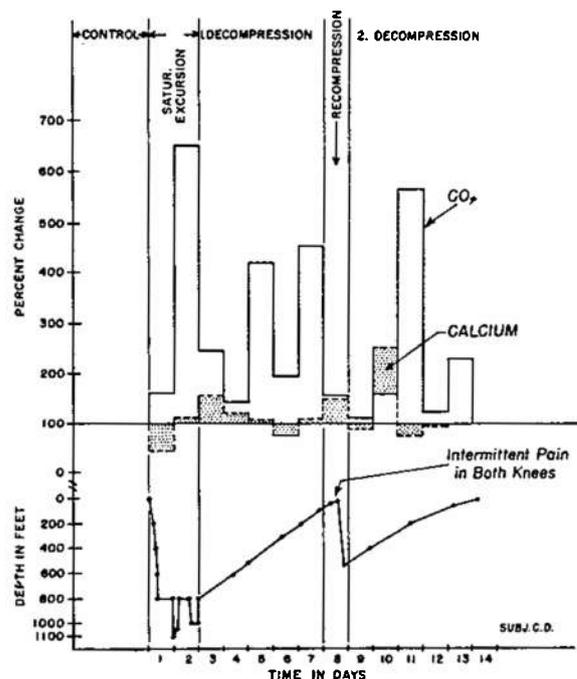


Fig. 4. Carbon dioxide and calcium excretion in the urine during saturation excursion dive to 1000 FSW' (Expressed in percent change from control values). Subject C.D.

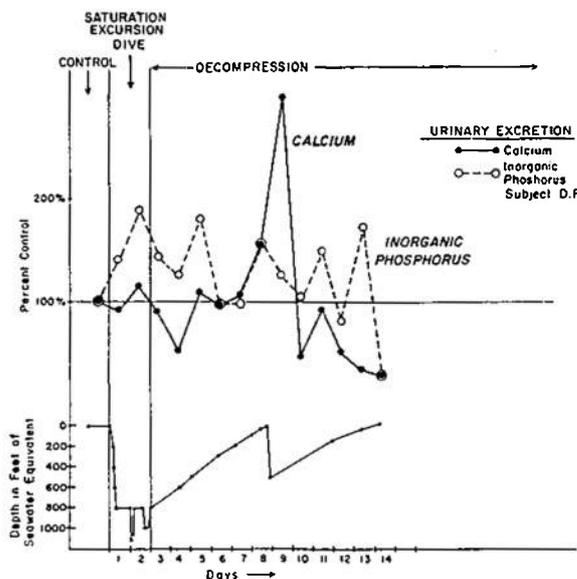


Fig. 5. Calcium and inorganic phosphorus excretion during saturation excursion dive to 1000 FSW (Expressed in percent change from control values). Subject D. F.

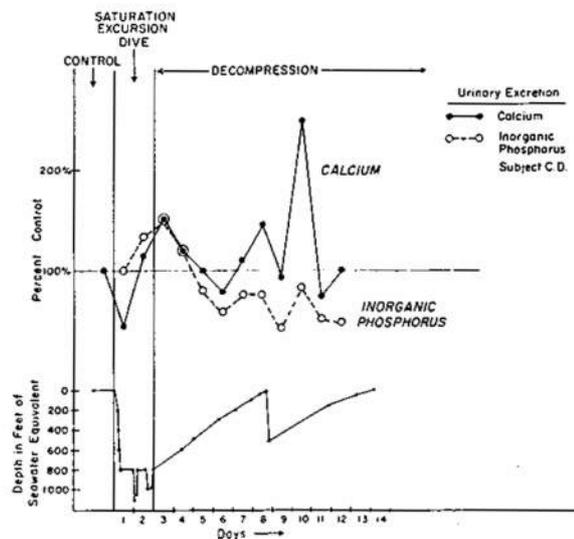


Fig. 6. Calcium and inorganic phosphorus excretion during saturation excursion dive to 1000 FSW (Expressed in percent change from control values). Subject C. D.

The excretion of inorganic phosphate generally increased during compression and tended to decrease during decompression.

Similar behavior was found in the two divers during the 800 FSW saturation excursion dive.

## DISCUSSION

The observations made in this study point to the bone with large carbon dioxide and calcium sinks as a target organ in decompression sickness. But this would involve rapidly exchangeable calcium and carbon dioxide pools, in the bone.

Recent findings of Bursaux<sup>3</sup> and Neumann<sup>11</sup> demonstrating that over 40% of the bone CO<sub>2</sub> store consists of rapidly exchanging bicarbonate provide a better understanding of the interaction of bone CO<sub>2</sub> and calcium stores.

It was originally shown by Neumann<sup>10</sup> that a significant amount of bone CO<sub>2</sub> is released by heating the bone. After a single injection of C<sub>14</sub> bicarbonate, Neumann found the specific activity of CO<sub>2</sub> lost on heating the bones, was more than twice that of the remaining CO<sub>2</sub>. He concluded that the rapidly exchangeable bone CO<sub>2</sub> pool was mainly represented by bicarbonates.

Bursaux<sup>3</sup> investigated the exchangeability and relation between blood bi-

carbonate and bone bicarbonate by ventilating mechanically paired rats for one hour with air and different CO<sub>2</sub> mixtures. In this way he produced hyper- and hypocapnia of one-hour duration. He found a good correlation of CO<sub>2</sub> content of mixed venous blood obtained with a catheter and bone CO<sub>2</sub> content. The average slope was 1.27 m, CO<sub>2</sub>/Kg bone per mm PCO<sub>2</sub>.

This rapidly exchangeable CO<sub>2</sub> pool in the bone must play a major role in the maintenance of acid-base balance. At any rate the bicarbonate pool in the bone is large enough and can apparently be released fast enough to account for the large CO<sub>2</sub>-bicarbonate excretion observed during decompression.

What is the evidence for a coupling of CO<sub>2</sub> and calcium exchange in the bone, which would be necessary to explain the calcium tides following the bicarbonate tides?

We know from the studies of Freeman and Fenn<sup>7</sup> in 1953 on the effects of chronic hypercapnia and hypocapnia, that the accumulation of bone CO<sub>2</sub> during chronic hypercapnia produced by exposure to 10% CO<sub>2</sub> is accompanied by an increment in bone calcium. Moreover, our studies of calcium metabolism in chronic hypercapnia in men exposed to 1.5% CO<sub>2</sub> for 42 days<sup>16</sup> indicated that Ca and CO<sub>2</sub> are stored in bone during acclimatization to CO<sub>2</sub> and bone Ca, and CO<sub>2</sub> are released from bone on de-acclimatization.

During exposure the pH showed a biphasic response, a decrease lasting for 23 days during the period of uncompensated respiratory acidosis and a re-

turn to normal levels during the subsequent period of 24-42 days of compensatory respiratory acidosis. Pulmonary and urinary CO<sub>2</sub> excretion showed corresponding biphasic changes. The plasma calcium mirrored the pH changes. Plasma inorganic phosphorus levels were markedly increased during the initial 23 days of uncompensated respiratory acidosis. The behavior of the plasma inorganic phosphorus level may have had a particular significance for calcium storage. Recent studies of Nichols et al<sup>12</sup> have demonstrated that increased phosphate concentrations in the medium of bone cells causing an increase in calcium influx into the bone cells - or block Parathyroid Hormone (PTH) stimulated calcium movement out of the cell. This effect of increased phosphate concentration has also been observed by Nichols in bone cells obtained from clinical cases. Based on these findings, the elevated phosphate concentrations during the first 23 days of exposure to 1.5% CO<sub>2</sub> could have contributed to the calcium storage by blocking the outflux of calcium.

During the recovery on air following 42 days of CO<sub>2</sub> exposure a calcium tide occurred after 8 days in the blood associated with a peak pulmonary CO<sub>2</sub> excretion. These findings lead to the conclusion that storage of carbon dioxide and calcium in the bone and release from the bone are correlated.

In studies of Gray et al<sup>8</sup> with prolonged exposure of submariners to 1% CO<sub>2</sub>, the findings of Schaefer et al<sup>16</sup> on calcium phosphorus changes were confirmed.

The evidence cited so far for the coupling of CO<sub>2</sub> and calcium exchange in

bones involves the slow CO<sub>2</sub> compartment and the slow calcium compartment. There are, to our knowledge, no studies reported in which the fast exchangeable CO<sub>2</sub> store bicarbonate in bone and the fast exchangeable calcium fraction were simultaneously measured under conditions of acid base alterations or hyperbaric conditions.

We assume that the fast exchangeable CO<sub>2</sub> and calcium fractions have a similar relationship as seems to exist for the slow exchangeable compartments of carbon dioxide and calcium.

Our studies of saturation excursion dives to 800 and 1,000 FSW produced evidence showing a release of carbon dioxide and calcium during decompression which appeared to be correlated in time. In subjects with symptoms of decompression sickness, the peaks in urinary CO<sub>2</sub> and calcium excretion were more pronounced.

Taking into account the findings of Bennett<sup>2</sup> on calcium retention during compression and increased calcium excretion during decompression from saturation dives to 1500 FSW in human subjects and those of Adams<sup>1</sup> showing a decrease in bone density in rats following decompression from 600 FSW simulated dives, and the recent observations of Hills and Straley<sup>9</sup> demonstrating an increased bone blood flow during compression and a decreased bone blood flow during decompression, the following hypothesis is suggested:

- (1) During compression there is a greater influx of calcium and carbon dioxide into the fast exchanging bone carbon dioxide and

calcium stores related to an increased bone blood flow.

- (2) During decompression there is a greater outflow of carbon dioxide and calcium, corresponding with a decreased blood flow in the bones.
- (3) Symptoms of decompression sickness which do not respond immediately to recompression and oxygen therapy occur when the outflow of carbon dioxide and calcium is accelerated.
- (4) Other factors may influence this hypothetical mechanism in various ways.

There were two considerations which led to the presentation of this hypothesis of involvement of CO<sub>2</sub> and calcium stores in decompression sickness, even if the evidence is scanty at the present time. First, we still have a largely taxonomic descriptive approach to the problem of decompression sickness and aseptic bone necrosis, as any survey of literature can show. There are great difficulties in establishing adequate experimental models and we do not have a real understanding of the physiological mechanism underlying the development of decompression sickness and aseptic bone necrosis.

The second consideration is related to some newer aspects in bone physiology, which provided the framework for the proposed hypothesis. Bone is the major CO<sub>2</sub> store of the body which comprises 80% of the total CO<sub>2</sub> store or 110 liter out of 130 liter in a 70 Kg man, (Rahn<sup>13</sup>). Bone is also a major

reservoir for electrolytes and plays a very important part in the maintenance of normal acid-base balance. Recent findings of Neumann<sup>10,11</sup> and Bursaux<sup>3</sup> have demonstrated that about 40% of the bone is present in form or rapidly exchangeable bicarbonate. A rapid turnover of CO<sub>2</sub> in the bone would require rapid changes in bone-blood flow. It was found by Shim and Paterson<sup>18</sup> that the metabolic control mechanism of bone-blood flow is the most potent one.

Breathing mixtures of increased CO<sub>2</sub> or low O<sub>2</sub> increased bone blood flow by about 20%.<sup>4</sup> Acid metabolites had similar effects. The bone blood flow is about 10% of the total cardiac output in younger people and 6-8% in older people. In bone diseases like Recklinghausen's disease and Paget's disease, an enormous increase in cardiac output has been observed (Cournand).<sup>5</sup>

The metabolic control of bone blood flow might play a role in the recently reported increases in bone blood flow during compression and decreases during decompression found by Hills and Straley.<sup>9</sup> Moreover the increasing evidence indicating that bone has a membrane function, Neumann<sup>11</sup> give further support for rapid exchanges of calcium and carbon dioxide. The K distribution between bone fluid, 140 mEq/L and serum, 4 mEq/L gives a good proof for the compartmentalization of bone.<sup>3,11</sup> Large fluxes of ionic calcium into and out of the skeleton are, according to Neumann<sup>11</sup>, continuously maintained and are several orders of magnitude greater than the fluxes related to resorption that are under the control of PTH.

Moreover recent studies of acetazolamide action on calcium metabolism in rats suggest a role of carbonic anhydrase and thereby CO<sub>2</sub> on bone demineralization (Waite and Kenny<sup>19</sup>).

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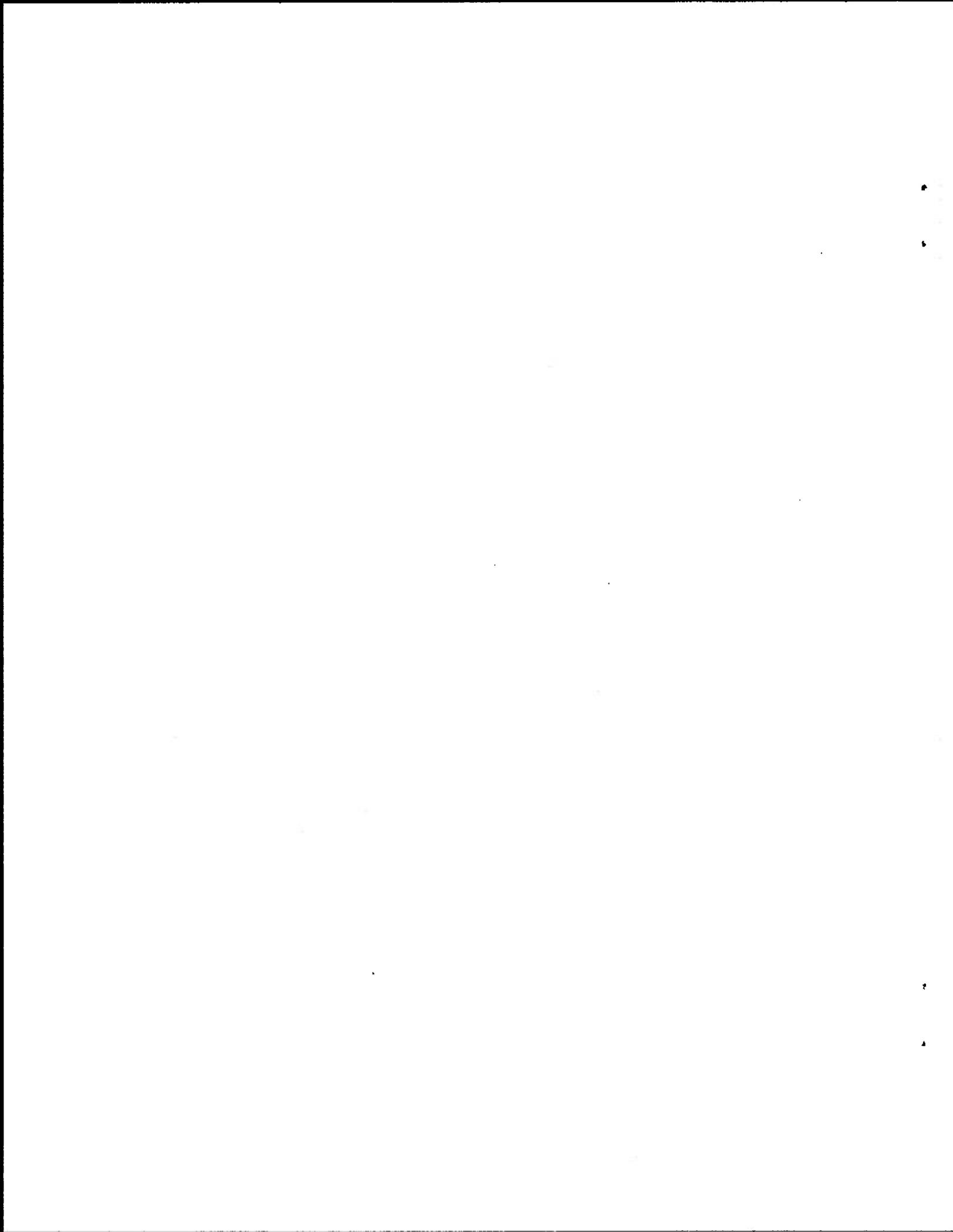
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