1967

Hypercoagulability in the pathogenesis of dysbarism

William Harte Northwall
University of Nebraska Medical Center

HYPERCOAGULABILITY IN THE PATHOGENESIS OF DYSBARISM

William Harte Northwall

Submitted in Partial Fulfillment for the Degree of

Doctor of Medicine

College of Medicine, University of Nebraska

February 1, 1967

Omaha, Nebraska

TABLE OF CONTENTS

Dysbarism is the term for the symptoms and signs resulting from all changes in barometric pressure. Decompression sickness is a syndrome, exclusive of hypoxia and airsic ness, resulting from a rapid reduction in barometric pressure and characterized clinically by a variety of symptoms thought to be caused by two chief mechanisms, evolution of dissolved gases from solution, and the expansion of trapped gases.

The symptoms of dysbarism are many. The following list excludes those symptoms presumably caused by the expanion of trapped gases, for example, abdominal distension and painful paranasal sinuses. This is done so that attention can be focused on the subject of this thesis; namely, hypercoagulability in dysbarism.

The symptoms are:

Joint pains, especially knees and shoulders (the bends)

Cough, chest pain, dyspnea (chokes)

Skin disturbances such as rash, mottling, paresthesia, and edema (the itch)

Various CNS symptoms; visual field defects, aphasias, paralysis, confusion, sensory losses, vertigo (the staggers)

In this analysis of the basic mechanisms responsible for the syndrome associated with decompression, evidence will be presented to support the thesis that the pain and other symptoms, not directly accounted for on the basis of expansion of trapped gas in various tissue spaces of the body, are the result of a decrease in blood flow caused by altered blood coagulability rather than by simple gasseous emboli in the form of bubbles as currently believed. The more complete understanding of the mechanism of blood stasis in this syndrome provides a basis for new approaches to prophylaxis and therapy.

LITERATURE REVIEW ON THE ETIOLOGY OF DYSBARISM

I. Formation of Bubbles

II. Changes in the Circulation

1. Intravascular Agglutination Theory
2. Angiospasm Theory
3. Electrolyte Shift Theory

I. Formation of Bubbles. Very extensive evidence favors the concept that gaseous bubbles within the blood and tissue fluids of the body constitute the primary etiologic agent of dysbarism. In general, but not always, there is a correlation between the symptoms of dysbarism and the presence of bubbles as seen by

x-ray. The higher the altitude attained, the greater is the incidence of the bends, chokes, and other symptoms, and this is correlated with the fact that more and larger bubbles are formed in man and animals as higher altitudes are reached.[2]

Obese individuals are more susceptible to the symptoms of dysbarism. This finding is correlated with the fact that nitrogen is 5.3 times more soluble in fatty tissues than in other body tissues.[3] The importance of nitrogen needs to be emphasized. The main elements of air are oxygen, carbon dioxide, and nitrogen. However, oxygen in a bloodborn bubble quickly diffuses into surrounding cells to be metabolized and carbon dioxide is rapidly picked-up by adjacent RBC's. Therefore, it is the nitrogen which is left in the bubble for lack of a transport system to eliminate it. Breathing air at high pressure during compression increases the plasma tensions of oxygen, carbon dioxide, and nitrogen, but it is only the metabolically inert nitrogen left dissolved in the plasma to later bubble out of solution during decompression. Further, as nitrogen is very soluble in fat, the major proportion of body nitrogen is stored in fatty tissue to be released and returned in large amounts to the blood stream upon decompression. Therefore, breathing 100% oxygen before

and during compression to denitrogenate the body reduces bubble formation and offers excellent protection against the bends in both divers and pilots..

The bubble theory is further supported by the widely observed effectiveness of recompression in the treatment of bends in caisson disease in divers, and also the relief of high altitude bends of aviators upon descent from from altitude.[1]

In 1955, a symposium on underwater physiology was convened to discuss the cause of pain experienced in the bends.[19] There were two main considerations. (1) Air, that is, principally the metabolically inert nitrogen, is released into the various body tissues, hollow viscera, and body cavities. (2) Emboli in the blood stream, gaseous or of blood constituents, produce ischemic pain by either obstructing blood flow, or by producing vascular irritation and vasospasm. Although phenomena number, (1) has been demonstrated most consistently as a result of explosive decompression of animals in a laboratory setting, it is the purpose of the author in developing this thesis to stress number (2) as probably most important in divers and jet pilots.

Those participating in the underwater physiology symposium generally felt that the vascular bubbles and

clinical dysbarism go hand-in-hand. However, other theories such as the agglutination of erythrocytes, of the clotting of blood, may not necessarily contradict the "bubble" theory, but may complement it with a more detailed explanation of why the gas bubble does not pass through the vessel.

II. Changes in the Circulation.

(1) Intravascular Agglutionation Theory.

Swindle decompressed kangaroos while observing pouch blood vessels under a microscope and saw non-gaseous emboli in the form of a fragil coagulum occlude the blood vessels. When a vessel was so occluded, the injection of India ink did not stain the area peripheral to this emboli.[34]

Knisely, however, in observing human circulating blood, states that he had never seen decompression to initiate intravascular agglutination.[23] On the other hand, Antopol states that he found several instances of rouleaux formation in decompressed genetically obese mice.[9] Jacobs and Stewart, working with albino rats, found no evidence of rouleaux formation or increased sedimentation rate, but did observe blood platelets to form aggragates about small gas bubbles and later to appear as free aggregates in the blood.[20] Gersh and Catchpole, using a freeze-dry technique which

should have demonstrated such aggregates, failed to find any.[17] Blood sludging related to ischemic hypoxia due to vascular occlusion has been postulated by several investigators.[27,28, 29,30,31]

(2) Angiospasm Theory.

Knisely studied the scleral vessels of humans at altitude with a binocular-dissecting microscope and saw no bubbles in these vessels, but did observe arteriospasm in all subjects above 30,000 feet. In those with overt bends pain the arteriospasm was sufficient to obliterate arteries. Return to ground level resulted in the return to normal-sized vessels in a variable period of time.[23]

Knisely used nail bed and arm vein refilling tests and found that subjects with the bends pain had a noticeably slower refilling time than those without the pains.[23] In addition, he had 36 subjects at altitude raise their hands to decrease blood flow to the extremity and found that this either initiated the pain or, if already present, made the pain more severe. However, pretreatment with aminophylline prevented pain in this arm raising test.[4]

Apparently, aminophylline increases tissue perfusion by blood. It is well documented that the bends

are associated with a decrease of circulation in the affected limbs. For example, temperature is lowered, pulse volume in fingers is decreased, and the digital blood flow, as measured by an impedance technic, is decreased.[4] Factors causing the most severe decrease in local blood flow in the extremities during the bends are exercise and failure to prophylactically desaturate the body of nitrogen. The reduced blood flow often occurred before any symptoms of decompression sickness, and did not return to normal immediately after return to ground level.[4]

(3) Electrolyte Shift Theory. Larkin and Watts proposed a theory which ascribed bends to a shift of electrolytes in the body so that water was also shifted to the intercellular fluid. This, in effect, produced a syndrome similar to surgical shock presumably because of the loss of circulating volume. The syndrome also resembled "miner's cramps" which are associated with loss of ions and the shift of water into the tissues.[25]

By forcing fluids in those quite susceptible to the bends, the incidence of bends was decreased, and by withholding fluids from those highly resistant to the bends, the incidence of bends increased. However, a second

group of investigators tried to duplicate the above findings and could not do so.[5] The evidence from forcing and with-holding fluids supports a resemblance to shock but not really to "miner's cramps".

DISCREPANCIES IN THE BUBBLE THEORY

Many investigators have recognized that a simple bubble-embolus theory fails to account for some of the experiences related to the bends. If symptoms are caused by bubbles, then why is there often a considerable delay in the appearance of symptoms after decompression? Sometimes these symptoms do not appear until 8 hours after decompression.[15] In addition, subjects at altitude have experienced the bends in an extremity when no bubbles could be seen by x-ray. Conversely, x-ray has demonstrated large collections of bubbles in an extremity when no pain was experienced.[2]

Differences in susceptibility to bends between different individuals and even in the same individual on separate exposures, are often very marked. It is difficult to explain this fact on the basis of physical factors such as the solubility constant of nitrogen in the body tissues, circulation times, and so forth.[1]

In 1908, Haldane recognized the small animals immunity to the bends, and attributed this to their

shorter circulation time which might allow for more efficient bubble removal. Kindwall repeated these experiments and found that the goat and dog react to decompression similarly to the human, and that the rabbit is indeed immune to the bends. Kindwall, on the other hand, showed that the susceptible goat required less time to rid itself of excess nitrogen than the immune rabbit.[21]

Finally, this author has injected bubbles into the arteries of dog extremities and visualized the bubbles returning in the venous stream. For this reason it is conjecture to say that bubbles are always emboli.

FACTORS WHICH AFFECT DYSBARISM

I. Unexplainable Factors. It is important to note that the effect of certain factors to increase the incidence of bends can not be entirely explained. These are age, previous injury to a joint, previous symptoms in a joint, exercise, repeated exposure, and apprehension. Increasing age correlates with more frequent and more severe bouts of dysbarism. If a particular joint of an individual has been injured or previously suffered the pain of dysbarism, it has a greater likelihood of being painful upon future de-

compression. Resistance to bends usually decreases on repeated exposure to decompression, although some become more resistant. Exercise during decompression is not only associated with greater bubble formation, but also with an increased incidence of the bends. Finally, apprehension decreases the tolerance to symptoms and pain.[6]

II. Discussion of Hypercoagulability. It is the purpose of this paper to view the bubble theory in conjunction with hypercoagulability.

Swindle and End[16] using microcinematography, visualized erythrocytes agglutinating upon decompression. Davis[13] feels that decompression is a stress which in turn produces hypercoagulability. This stress is conceptualized by Hans Selye as a single phenomenon resulting from a multitude of factors; bacterial toxins to anxiety, and in the case of decompression sickness, a factor of the physical environment.

In regards to the state of hypercoagulability, ones thinking must not be muddled by the belief that blood is always liquid until clotted and that the clot is irreversible. Plasma itself is a solution of protein macromolecules which behave according to the colloidal physical laws. The largest of the molecules is

the negatively charged fibrinogen, about 350 microns long, which exists in the blood stream in a sol phase. Any positively charged ion, for example H^+ and histamine$^+$, will partially neutralize the fibrinogen's charge, thus destabilizing it and allowing fibrinogen molecules to clump together. The fibrinogen is now in a gel phase.

This mechanism of fibrinogen existing in equilibrium between sol and gel phasis is thought to be continually going on in the body. The state of hypercoagulability is then a shift of the equilibrium toward the gel phase. The idea is expounded upon by McKay, Disseminated Intravascular Coagulation.[28] Please note that the fibrinogen gel referred to is not the same as a fibrinogen polymer (fibrin) existing in an insoluble, irreversible state. Ryan and Godal have done fascinating work on what they call a fibrinogen A to fibrinogen B to fibrin reaction, in which the "B" is a soluble and reversible substance which may circulate in the body in hypercoagulability.[18, 27, 31]

Returning to decompression sickness, there is little doubt that blood born bubbles frequently occur during decompression, but there is a poor correlation between bubble formation and the symptoms of dysbarism

suggesting a more complicated etiology than bubbles per se. The bubble's gas-liquid interface may be an excellent gathering place for the hydrophobic blood constituents such as lipid-rich platelets and protein macromolecules. Thus a bubble in the vascular system might initiate a gel phase surrounding itself, greatly impeding its travel through the vessel until stopped.

End points out that the bubbles alone do not adequately explain all the clinical signs seen in decompression sickness.[15] But the concept of stress-hypercoagulability added to the bubble theory might more fully explain why such a variety of drugs and chemicals act to prevent or relieve decompression.

III. Dysbarism in Humans. A. Recompression. The standard treatment of dysbarism is recompression followed by a slower decompression.[1] Seemingly, this reduces bubble size until dislodged and removed. Previously in this paper it was noted that bubbles may travel from arterial to venous blood, and that the blood-bubble interface may be an excellent gathering place for plasma proteins. Therefore, it is possible that removal of a bubble by recompression may not remove a bubble emboli, but may remove a surface for

a plasma-gel emboli to form on.

B. Non-nitrogen Atmospheres. Obviously, using a non-nitrogen atmosphere such as pure oxygen or an oxygen-helium mixture prevents formation of the bubble in the first place. Helium is much less soluble in the body tissues than nitrogen and therefore does not saturate the tissues to be released later as bubbles. However, breathing pure oxygen for 8 hours followed by air for 2 hours seems to offer protection from the bends.[7] Either this procedure has eliminated nitrogen from the tissues without allowing time for a second build-up of tissue nitrogen, or it has altered something else without preventing bubble formation in the blood stream.

C. Decreasing Blood pH. Decreasing the pH of the blood increases the incidence of the bends. A possible explanation for this is that by lowering the fibrinogen's negative charge, and thereby reducing its colloidal stability, favors hypercoagulability.

Keeping in mind the factors which are procoagulant in the blood, such as the lowering of pH, it is interesting that prolonged compression decreases the CO_2 combining power of blood, and that eventually blood pH falls.[15,10] In line with this, a well constructed

test was performed where NH_4Cl was given to produce metabolic acidosis and blow off CO_2. Some were protected from the bends, but others were not. Then, the subjects deliberately hyperventilated to the point of tingling and numbness to produce respiratory alkylosis. This decreased the symptoms of bends and chokes from 56 to 44%. However, hyperventilation may have decreased body gases and may have lessened the sensitivity to pain. Because of the immediate reversal of symptoms on recompression, it is hard to believe that the pain is due to acid metabolites.[8]

D. Heparin in therapy. Laborit in 1958 used high doses of heparin on individuals in a severe accident resulting in the bends. He was very encouraged by the increased survival rate and the success of this therapy.[24] Heparin is an anticoagulant, probably by several mechanisms. One mechanism is imparting a negative charge to the negatively charged fibrinogen thereby increasing fibrinogen's colloidal stability.

E. Obesity and Cholesterolemia. Both obese individuals and those with high serum cholesterol levels have a higher incidence of dysbarism.[6] It is well known and insurance tables will verify that the obese have a greater propensity to those diseases associated

with hypercoagulability. Possibly more bubbles are formed in fat tissue as N_2 is 5 times more soluble in fat than in other tissues, but is it possible that lean individuals with high serum cholesterol could also form more bubbles in the blood stream?

F. Diet. A high protein diet increases symptoms of the bends and a high carbohydrate diet decreases symptoms of bends.[6]

The obligatory glucose burners (brain, lens, germinal epithelium) can only utilize glucose, thus when blood glucose falls several hours after eating, protein must be degraded, undergoing gluconeogenesis. However, gluconeogenesis does not maintain a high enough glucose level to supply all the body cells. Fortunately, the non-obligatory glucose burning cells can obtain their energy from fatty acids (at body pH exist as ionic fatty acids, or IFA's). IFA's are surfactants and reduce the colloidal stability of fibrinogen, thereby producing a state of hypercoagulability. (Any stress episode will cause mobilization of IFA's.)

G. Fluids and Aminophylline. Both forcing fluids and administering aminophylline decrease the incidence of dysbarism.[6] This apparently is because aminophylline fascilitates blood perfusion through various tissues.

It is doubtful that this drug has any action on the bubble. And forcing fluids may prevent shock-like states, and decreased perfusion of blood with blood slugging, all of which can favor blood coagulation.

IV. Animal Experiments. For the most part, dysbarism experiments reported in the literature use animals as the subjects. A smaller number of experiments are carried out on man. This means that two types of decompression are being used and that the information collected is often difficult to interpret and sometimes contradictory.

The first type is slow decompression on humans simulating the diver surfacing or the pilot ascending to altitude. The second method involves explosive decompression, used on most animal tests, and which usually produces death.

These facts bring up two important questions in the analysis of the following data.

First, the symptoms of dysbarism are mostly subjective and therefore expressed verbally. A human being, slowly decompressed, can express pain. One can not say for sure that an animal undergoing slow decompression is experiencing pain. The rate of decompression can be accelerated so that the animal dies, but

is this really measuring an exaggeration of the dysbarism syndrome?

Second, is the physiology of man wholly comparable with that of animals, and is one animal comparable with another? For example, rabbits and goats both acquire intravascular bubbles upon decompression, but only the goat suffers from dysbarism. The serum and histo-chemistry and blood clotting parameters have not been studied adequately enough in one species, let alone in a variety of species to adequately compare these parameters. Lastly, autopsy material is readily available from animal sources, but humans rarely die from dysbarism.

A. Methysiloxane. One group of investigators treated rats with Methysiloxane (fillerless Dow Corning Antifoam A).[26] These rats were rapidly decompressed-recompressed in a manner which produced a 36% mortality rate in the control group. The test group had an 8% mortality rate. The pathology in both groups was the same. Methysiloxane lowers resistance to flow in the 50ppm range, theoretically, but it may also prevent a "coagulavelum" at the gas-liquid interface. Langmuir stated that protein films at a gas interface undergo denaturation resulting in a strong surface film (coag-

ulavelum). Silicones also tend to prevent blood from clotting.

B. Chlorpromazine. Chlorpromazine subcutaneously has decreased explosively decompressed fatalities in rats and rabbits from 90% in the controls to 30% after the drug. Blood studies showed a marked decrease in clot times of the controls and close to normal clot time in chlorpromazine treated animals. Chlorpromazine can not prevent bubble formation, thus it may either alter an enzyme acting on blood coagulation, or inhibit the stress of rapid decompression.[32] Stress of any variety is known to decrease blood clot times. Again, the state of hypercoagulability is implicated in the pathogenesis of dysbarism.

C. Heparin and PDHA. Philp and Gowday have done an elaborate study of the protective effects of heparin, partially depolymerized hyaluronic acid (PDHA), and of bishydroxycoumarin in decompressed rats.[30] This study is notable in several ways. First, a slow stage-decompression from 5.5 atmospheres to a simulated altitude of 10,000 feet is used instead of an explosive decompression. Second, the rats were placed on a motor-driven treadmill so that progressive difficulties of locomotion were charted as increasing severity of the bends. The scoring system is as follows.

0 No visible signs

1 Indefinite and transient disturbances of gait

2 Stiffness of hind limbs

3 Dragging of hind limbs

4 Complete paresis of hind quarters

5 Complete paresis

6 Death

Third, potential protective agents were either administered before compression or at the end of stage-decompression at a time when the animals contained abnormal amounts of nitrogen but before the onset of altitude induced bends.

Male white rats of selected ages and weights were used. Normal saline, bishydroxycoumarin, heparin and partially depolymerized hyaluronic acid (PDHA) were all injected intraperitoneally in a total volume of 1-2 ml.

The various agents were studied as follows. The effect of heparin and PDHA was determined by the Lee-White clot time on whole inferior vena cava blood. The Quick prothrombin time on inferior vena cava blood determined the effect of bishydroxycoumarin. The lipaemia clearing action of PDHA was assessed by the optical density of plasma from rats who were either

receiving a standerd diet, or from rats which had been made lipaemic by subjecting them to a 36 hour fast and then feeding them a lipid-rich meal.

The first study shows the effect of heparin, PDHA, and saline, injected into old, heavy (*450 g) rats before the 2 hour decompression, The data from the 96 rats in this study were pooled and a chi-square analysis was conducted on the treated versus the control rats. Neither heparin (0.5-1.0 mg/kgm) nor PDHA (50 mg/kgm) produced any significant increase in the incidence or the severity of the bends.

"When heparin (1.0-3.0 mg/kgm) and PDHA (50 mg/kgm) were given to similar heavy rats following the stage-decompression, but before the exposure to altitude, again there was no significant lowering of either the incidence or severity of bends...."

"The administration of PDHA (50 mg/kgm) to moderately heavy rats (*385 g) after the stage-decompression did result in a significant lowering in the incidence of the bends...but not of the severity...."

Heparin and PDHA given to lighter rats(* 350 g) after stage-decompression were much more effective. Heparin significantly lessened the incidence of bends, and significantly reduced the severity. PDHA was not

effective at 2 mg/kgm either in reducing the incidence or the severity of the bends. However, at 10 and 50 mg/kgm PDHA significantly lowered both the incidence and the severity of the bends.

Increasing the dose of heparin did not further reduce either the incidence or the severity of the bends, whereas increases in the dose of PDHA led to a significant reduction in the incidence and severity. Pooling and comparing the data from the heparin experiments with that of the PDHA experiments, and studied by chi-square analysis revealed that the PDHA was significantly more beneficial than heparin in lowering the incidence and severity of the bends.

The effects of various doses of heparin and PDHA on the whole-blood clotting times were studied. Heparin prolonged the clotting time whereas PDHA did not significantly alter the clotting time.

The intraperitoneal injection of 5.0 mg/kgm of bishydroxycoumarin after stage-decompression did not significantly alter either the incidence or severity of the bends as compared with controls, although this dose caused a significant increase in prothrombin times. Administering bishydroxycoumarin 13 hours before compression also did not significantly alter the incidence

or severity of the bends.

Next, the effect of PDHA upon the optical density of plasma was studied. PDHA significantly lowered the optical density of the plasma from normal rats and also lowered that of lipaemic rats to below normal levels.

Philp concluded that three mechanisms of action existed as possible explanation of the results: anti-coagulation, lipaemia-clearing, and surface activity. "Our results indicate that the effects of the compounds tested can not be explained completely by anticoagulant activity for the following reasons: (1) rats whose prothrombin times were markedly prolonged by bishydroxy-coumarin were not protected against the bends; (2) rats whose whole-blood clotting times were elevated only slightly and transiently by heparin were somewhat protected; (3) rats whose whole-blood clotting times were markedly elevated by heparin were well protected, but (4) even greater protection was afforded by PDHA which did not alter the whole-blood clotting times significantly."

Philp speculates that the well known lipemia-clear-action of heparin might be involved in the beneficial effects of using heparin in the treatment of bends. He further states that PDHA also has been re-

ported to have lipemia-clearing properties, which he confirmed in his study. Philp suggests that the rat has the ability to rapidly clear lipids from the blood and that this may be partly responsible for the rat's inherent resistance to the bends. His final conclusion is that body fat may be for more important in the etiology of decompression sickness than by acting solely as a nitrogen reservoir.

This author wishes to make three points in regards to Philp's study. First, this endeaver was of the finest design. Second, some investigators contend that bishydroxycoumarin is a poor anticoagulant. Third, this author considers lipids as procoagulents, and therefore clearing the blood of lipids does not necessarily contradict the author's thesis that the pain symptoms of dysbarism are the result of altered blood coagulability.

D. Endogenous Chemicals. Many investigators have felt that blood-born bubbles can trigger the release of endogenous chemicals which produce the symptoms of dysbarism. Bradykinin, serotonin and histamine have been studied the most.

Bradykinin blood levels are increased in animals following rapid decompression. A bradykinin antag-

onist, 2-(4-phenyl-1-piperazylmethyl)-cyclohexanone, Miles-Ames, in rapidly decompressed mice decreased mortality rate, increased survival time, and prevented histological changes,(increased perivascular space; in the lung, folding of bronchial mucosa, and hyperemia in bone marrow).[12]

Bradykinin is an octapeptide which produces slow contraction of smooth muscle, increases capillary permeability, and increases vasodilatation. Vasodilatation and increased capillary permeability favor blood sludging amd an increased tendency to blood clotting.

Various "anti-histamines" have been tried with no significant results. Kindwall could find no change in rat tissue histamine or serotonin following rapid decompression.[2]

EFFECT OF BUBBLES ON BLOOD VESSELS

It is pertinent to this discussion to discuss the effect of gaseous bubbles on blood vessels. Chase[11] (1934, rabbits) found that air bubbles produced an immediate transient vasoconstriction of muscular arteries, which later fatigued and dilated, resulting in stasis of the blood. He observed that conglutination and rapid and extensive agglutination always occurred in

areas of stasis. Duff, Greenfield, and Whelan[14] (1954, humans) did corresponding experiments and observed vasodilation in forearm vessels following brachial artery injections of various gases. They concluded: 1) dilation was not reactive hyperemia, nor dependent on increased tissue metabolism, 2) was present in chronically sympathectomized and chronically denervated limbs, 3) the action of the gas upon first entering the vessel, rather than the continued presence, produced the dilation, 4) the dilation was unaltered by effective amounts of antihistamines, (tripelennamine HCl).

McGovern[29] studied blood vessel irritation in relation to mast cell degranulation. "The endothelium of the peritoneum, pleura, and blood vessels has a very similar structure. There is a surface layer of argyrophilic protein material and argyrophilic cement lines separating the individual endothelial cells. Underneath the epithelium and closely attached to it are the MCs. When the peritoneum of the rat is mildly irritated by topical application of 1 per cent acetic acid or 48/80, there is increased production of the surface protein film and imbibition with metachromatic substance of both the cement lines and the surface film, this being associated with degranulation of the subendothelial MCs."

DISCUSSION of THE BUBBLE THEORY AND HYPERCOAGULABILITY

The bubble theory per se, not only fails to explain the clinical manifestations of dysbarism, it also fails to explain why such a variety of "drugs" are beneficial in the disease. But the bubble hypercoagulable theory might offer a better explanation for all facets of dysbarism.

It is documented that gaseous bubbles injected into arteries produce vasodilatation with stasis and agglutination. The exact mechanism can not be stated but as it occurred also in sympathectomized arteries, is it not possible that the gas bubble acts as an irritant to the vessel endothelium?

McGovern states that an irritation to the vascular endothelium results in degranulation of the subendothelial mast cells. Human mast cells contain at least heparin, histamine, and eleven enzymes, one of which is trypsin. Histamine causes arteriolar dilatation, increased capillary permeability, may dilate the capillaries or constrict the small venules, and since the molecule is negatively charged, may favor hypercoagulability.

The mast cells are found throughout the human body, up to four types have been identified, and those

in various tissues may discharge their contents by different specific stimuli. Numerous mast cells lie in close proximity to the blood vessels and are thought to play an important role in maintaining the clot-flow equilibrium. Hans Selye states that there is good reason to believe that the mast cells individual active principles can be released selectively.[33]

One experiment concluded that an anti-bradykinin drug was beneficial in decreasing decompression sickness. Bradykinin is formed from a nonapeptide substrate in plasma by the action of trypsin. It produces slow contraction of smooth muscle, increased capillary permeability, and vasodilatation. It may also produce pain. Note that mast cells may release trypsin to the blood stream.

It is the author's belief that a gaseous bubble in a blood vessel irritates the endothelium which in turn allows for the formation and influx of agents which cause the vessel to dilate, (possibly constrict first; vasospasm). Associated hemoconcentration from increased capillary permeability, in combination with decreased blood flow and the collection of surfactants (proteins, platelets, and FFA's) at the bubble surface would favor shift of the plasma gel-sol equilibrium to the gel

phase. This then might be a plasma gel emboli responsible for the ischemic pain of the bends. This whole process conceivably could be reversed by recompressing the individual to decrease the bubble size, allowing flow to re-establish and allowing the plasma gel to return to the sol phase. This process might be prevented by prior anti-coagulant therapy.

SUMMARY Decompression under such conditions as divers surfacing often results in a syndrome of joint and muscle pains known most commonly as the bends. Popular belief is that metabolically inert nitrogen bubbles act as emboli in the smaller vessels thereby producing pain of ischemia in the muscles and joints.

But the formation of bubbles does not adequately explain the symptoms of dysbarism (decompression sickness or the bends). There is often a delay of time between decompression and appearance of symptoms. Subjects have experienced bends in an extremity when no bubbles could be visualized by x-ray; conversely, bubbles have been demonstrated by x-ray when the subjects showed no symptoms of the bends. And with the same controlled physical conditions there is a marked difference in susceptibility to the bends between individuals and even in the same individuals on separate exposures.

A variety of drugs which have no apparent action to decrease bubble formation tend to decrease the symptoms of dysbarism. These drugs include bradykinin antagonists, heparin, chlorpromazine, aminophylline, methysiloxane and PDHA.

These drugs, while working differently, have one common action, which is to favor the sol phase of the plasma gel-sol equilibrium. It is postulated that this action may be achieved by preventing blood sludging, decreasing stress, decreasing the collection of surfactants at gas bubble interfaces, by clearing the blood of lipids, and by acting directly upon fibrinogen. It is suggested that a hypercoagulable state exists in dysbarism which at times may allow plasma gel emboli to form and to decrease blood flow to certain tissues thereby producing the pain of ischemia known as the bends.

CONCLUSION:

1. The postulate that gaseous emboli in the blood stream are the sole etiologic agent of dysbarism fails to explain all the clinical manifestations of dysbarism.
2. Decompression is a stress and any stress can produce a state of hypercoagulability.

3. Drugs which counteract the state of hypercoagulability are beneficial in prophylactically decreasing or therapeutically alleviating the symptoms of dysbarism.

I wish to express deep appreciation to Herbert L. Davis for the inspiration, instruction and support of this paper, and to Dr. A. L. Bennett for his labor in helping this author prepare this paper for presentation.

BIBLIOGRAPHY

1. Adler, Harry F., ed. by Robert G. McIver, Dysbarism, Aeromedical Reviews 1-64, Febr. 1964, 166 pages, p. 17.

2. Ibid. pp. 17-19.

3. Ibid. p. 16.

4. Ibid. pp. 10-14.

5. Ibid. p. 15.

6. Ibid. pp. 53-63.

7. Ibid. p. 84.

8. Ibid. p. 50.

9. Antopol, D.K., and others, Studies on dysbarism I, Development of decompression syndrome in genetically obese mice, Am.J.Path 45:115-27, Jul 64, (Cited in: Adler, H.F., cf. 1.).

10. Bean, J.W., Journ. Physiol., 72:27, 1931.

11. Chase, W.H., Anatomical and experimental observations on air embolism, Surg., Gyn, and Ob., 59:569-577, Oct. 1934.

12. Chryssanthou, D.B., and others, Aerospace Med. 35:741-6, Aug. 1964.

13. Personal communication with Dr. Herbert L. Davis.

14. Duff, F., Greenfield, A.D.M., Whelan, R.F., Clin. Science (Lond) 13(3):365-76, Aug. 1954.

15. End, E., The physiologic effects of increased pressure. Proc. Sixth Pacific Science Congress, 6:91, 1938.

16, Personal communication with Dr. Edgar End.

17. Gersh, I., Catchpole, H.R., Appearance and distribution of gas bubbles in rabbits decompressed to altitude. J. Cell. Comp. Physiol. 28:253, '46.

18. Godal, H.C., A study of the beta naphthal reaction of plasma, (Fibrinogen B-test), Scand. J. Clin. Lab. Invest., 14:203-6. 1962.

19. Goff, L.G., ed., Proceedings of the underwater physiology symposium, Jan. 10-11, 1955, Washington D.C., Prepared for the office of Naval Research, Publication 377, National Academy of Sciences- National Research Council, Wash. D.C., 1955.

20. Jacobs, M.H., Stewart, D.R., Observations on the blood of albino rats following rapid decompression, CAM Report No. 76, Oct. 1942.

21. Kindwall, E., Metabolic rate and animal size correlated with decompression sickness, Am. Journ. Physiol. 203:1, pp.385-8, 1962.

22. Kindwall, E.P., and others, Failure to show change in rat histamine and serotonin after rapid decompression, 203.1:389-390, Am. J. Physiol. 1962.

23. Knisely, M.H., Observations and interpretations of changes in circulation induced by aero-embolism. Eng-M-49-696-1c, Wright Field, 14 Jan. 1943, (Cited in: Adler, H.F., cf. 12, pp.9-10.).

24. Laborit, H., Barthelemy, L., Perrimond-Trouchet, R., (Action of heparin in the treatment of decompression accidents), Agressologie 2(3):229-236,'61.

25. Larkin, J.C., Watts, D.T., A new concept of the bends and a method of increasing one's resistance. CAM Report No. 291, 1 Jan. 1944. (cited in: Adler, H.F., cf. 12, p.15).

26. Lyle, C.B. Jr., Dahl, E.V., Protection of rapidly decompressed rats by pharmacologic and physical means. Am.J. Physiol. 201:759-61 Nov. 61.

27. Lyons, R.N., Thiol-vitamin K mechanism in the clotting of Fibrinogen. Aust. J. Exp. Biol. Med. Sci., 23:131, 1945.

28. McKay, D.G., Disseminated Intravascular Coagulation. N.Y., Hoeber Medical Division, Harper & Row, 1965.

29. McGovern, Mast cells and their relationship to endothelial surfaces, J. Path. Bact. 71:1, 1956, (Cited in: Selye, Hans, cf 61 p.109).

30. Philp, R.B., The ameliorative effects of Heparin and depolymerized hyaluronate on decompression sickness in rats, Canad. J. Physiol. Pharmacol., 42:819-29, Nov. 64.

31. Ryan, E.A., Relationship of Fibrinogen B to Thromboembolic Phenomena, Canad. Med. Assoc. J., 64: 237, 1951.

32. Sautet, J., and others, (Effects of Chlorpromazine on animals exposed to rapid decompression after a sojourn in compressed air), La Presse Med. 69:335-6, 18 Feb. 61.

33. Selye, Hans, The Mast Cells, Butterworth Inc., 1965, 498pp.

34. Swindle, P.F., The possible relationship between intravascular agglutination of erythrocytes and decompression sickness. CAM Report No. 178, 13 Aug. 1943. (Cited in: Adler, H.F., cf. 12, pp.9-10)