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A review of blood changes associated with compression-decompression: relationship to decompression sickness

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Philp, R. B. 1974. A review of blood changes associated with compression-decompression: relationship to decompression sickness. Undersea Biomed. Res. 1(2): 117-150.–Blood cellular and chemical changes associated with compression-decompression of experimental animals and human subjects are reviewed. Existing evidence suggests that diving entails multiple physiological stress factors which probably account for many of the observed changes including elevated levels of isoenzymes, catecholamines, and cortisol as well as leucocytosis and possibly reductions in red-cell count. Decompression of both experimental animals and human subjects is commonly associated with a reduction in circulating platelet count which may persist for 2-3 days postdive. Animal data suggest that this may be due to the adherence of platelets to *silent* bubbles. Some antiplatelet drugs have been shown to reduce the morbidity and mortality of decompression sickness in animals and to retard the postdive loss of platelets in man. Hemoconcentration is a not uncommon finding in clinical bends and limited evidence of associated platelet loss has been obtained. The practical and theoretical potential of pharmacological agents in the treatment of decompression sickness is reviewed. (210 references).

decompression sickness
blood chemistry
platelets and red cells
isoenzymes
pharmacological treatment of bends

"Blood will tell but often it tells too much"

Donald R.P. Marquis

Decompression sickness (DS), variously referred to throughout its history as the bends, caisson disease (in reference to tunnel workers or *sand hogs*), compressed air illness, and dysbarism, is a syndrome which results when people are subjected to an overly abrupt and extensive reduction in environmental barometric pressure. As the various names imply, it has been encountered not only by deep-sea divers but by high-altitude aviators and men employed in underground engineering projects in which compressed air is used to hold back ground water. It also constitutes a potential hazard for astronauts and even for commercial air passengers should an accidental rapid loss of cabin pressure occur. The condition appears to be the result of the formation of bubbles of inert gas (chiefly nitrogen when air is the breathing gas) in fluids and tissues of the body. Inert gases like nitrogen are dissolved in

body tissues and fluids and, with sufficient time, reach a state of concentration equilibrium with the environment. If the reduction in barometric pressure exceeds the rate at which the dissolved nitrogen can diffuse across the various membrane barriers of the body and be eliminated in the expired air, a state of supersaturation occurs and bubbles may form. The situation is analagous to the precipitation of solute from a supersaturated solution and it has frequently been compared to the formation of bubbles which accompanies the removal of the cap from a bottle of carbonated beverage.

The symptoms and signs of DS are protean, ranging in severity from skin rash and joint pain to central nervous system disturbances, respiratory difficulties, paralysis, and acute circulatory shock, depending presumably upon the extent and location of the offending bubbles. Treatment classically has revolved around the principle of recompression of the victim with a view to driving the bubbles back into solution, with moderate, controlled decompression to allow the harmless diffusion and elimination of inert gas. Breathing oxygen toward the end of the therapeutic decompression has greatly expedited treatment, the aim being to produce a more favorable concentration gradient for the elimination of nitrogen across the alveoli of the lungs.

The central position of the gas bubble in the etiology of decompression sickness is by now so widely accepted that it hardly seems necessary to document the supporting evidence here. It has been pointed out (Buckles 1968) that "All the predictive models that are used to compute 'safe' decompression schedules involve some considerations about the formation and growth of bubbles *in vivo*." Behnke (1971) emphasized the importance of the particular location of bubbles even further, stating "Intravascular bubbles form the crux of our discussion and the prime tissue involved is circulating blood."

Agreement as to the principle causative agent of the condition has not always been so universal. The monumental work of Paul Bert (1878) established the central role of the bubble in DS yet disagreements on this point persisted for years. Pioneers in the field of pressure physiology and medicine, hampered as they were by incomplete knowledge both of physics and physiology, often formulated novel and bizarre theories to explain the syndrome of caisson disease (Fryer 1968). One of these was the *congestion* theory which held that blood was forced under pressure from soft, compressible tissues into those protected by rigid structures such as the brain and spinal cord and that the signs and symptoms of the disease resulted either from hemorrhage occurring during the congestive phase or from anemia resulting from the sudden return of the blood to the periphery during decompression (Van Rensselaer 1891a). The frequency of spinal cord lesions in early victims of caisson disease, together with the oft-noted occurrence of clots and thrombi in soft tissues and organs examined post mortem, lent support to this theory (Van Rensselaer 1891b). Deaths in these instances, however, usually occurred days or weeks after the decompression and undoubtedly were secondary to paraplegia resulting from spinal cord injury during decompression. Andrew H. Smith (1894), consulting physician to the New York Bridge Co. during the construction of the Brooklyn Bridge, believed that activation of the clotting process was involved in the pathology of bends. He wrote "But meanwhile, the slowing of the current, or perhaps actual stasis, has brought about more or less serious and permanent results. Thrombi may have formed, affording material perhaps for emboli at more distant points."

Despite Smith's erroneous views on the cause of decompression sickness (he was an exponent of the congestion theory) his words were nonetheless prophetic. On the basis of observations of the fine vasculature of decompressed rats, Swindle (1937) and End (1938) proposed that the sludging of red cells led to the formation of emboli and petechial infarcts

and that these were the primary causative agent in decompression sickness with bubbles being a complicating factor. The hypothesis failed to impress contemporary workers in the field. Coming as it did at a time when new knowledge was accumulating on nitrogen desaturation of the human body (Behnke 1937, 1945; Behnke and Willmon 1941; Willmon and Behnke 1941), and when more effective decompression tables were being developed as well as better treatment procedures including oxygen breathing to assist nitrogen elimination (Behnke and Shaw 1937; Yarbrough and Behnke 1939) such a theory, which relegated the bubble to a secondary role, was bound to encounter skepticism. Research on the effects of decompression on blood languished for a quarter of a century, except for sporadic observations, whilst the advancement of the art and science of diving, and the application of the laws of physics thereto, continued apace.

Despite these advances, a nagging suspicion persisted that other causative factors might be involved in the pathogenesis of DS because certain observations were difficult to reconcile with the hypothesis that the bubble was the sole etiological agent. Among these were the sometimes prolonged lapse of time between the end of decompression and the onset of symptoms, the occasional failure of recompression to relieve the victim, wide variations in susceptibility (even within an individual subjected to the same decompression profile on different occasions), and the great difficulty in demonstrating the presence of bubbles in affected individuals. These considerations were reviewed by Holland (1969).

Regarding the demonstration of bubbles in victims of DS, the advent of the Doppler ultrasonic probe appears to have yielded convincing evidence that intravascular bubbles are indeed associated with decompression, even in the absence of overt signs of the bends (Smith and Spencer 1970; Rubissow and McKay 1971; Spencer and Oyama 1971; Powell 1972; Spencer and Clarke 1972; Shilling and Werts 1972). Thus the central position of the bubble has been reaffirmed. However, in the reaffirmation a further paradox has been revealed—the presence of the etiological agent has been detected frequently in the absence of the disease. Were the bubble to be viewed as a microorganism this would be a clear violation of one of Koch's postulates; namely, in order to be identified as the causative agent of a disease the microorganism must elicit the appropriate symptomatology when it is introduced into a susceptible animal. The significance of secondary biological influences upon susceptibility to decompression sickness becomes readily apparent.

A resurgence of interest in the role of the blood in decompression sickness followed observations of French investigators that compression with air caused a transient reduction in the whole-blood clotting time of rats and that the tranquilizer chlorpromazine prevented this hypercoagulability and afforded some protection against decompression sickness in rats and rabbits (Sautet, Jullien, Leandri, and Rampal 1961). French workers (Laborit, Barthélémy, and Perimond-Trouchet 1961) also claimed that the anticoagulant heparin improved the survival rate of rabbits rapidly decompressed from high pressure. Barthélémy (1963) advocated the use of heparin in the treatment of decompression sickness and described five cases of bends in divers in which heparin appeared to have elicited clinical improvement whereas recompression therapy alone had not. It is from this point in history that your reviewer takes up his task in earnest.

ALTERATIONS IN BLOOD COAGULATION

It would appear that compression-decompression may be associated with the development of a *hypercoagulable state*, evidence of which may be detected in the absence of overt signs of DS, providing the screening procedures are adequate. Such shifts toward increased

activity of the hemostatic mechanism do not usually exceed normal physiological limits in man but they may represent a prodromal state. Early animal experiments suggested that the hyperbaric environment itself might set the stage for hyperactivity of the clotting system which is subsequently triggered by a too-rapid decompression. Experiments with air-injected rabbits, however, indicated that the presence of an air-blood interface alone will activate the hemostatic mechanism. To date, little evidence is available concerning the state of the hemostatic process in individuals suffering from Type I or Type II bends. It may be that the changes are too subtle to detect unless normal, predive baseline values are available.

In 1933 Aggazzoti studied the clotting times in dogs and rabbits before and during decompression from 6-11 ATA. He found accelerated clotting in 12 of the animals but in 4 that seemed to show signs of decompression sickness the clotting time was prolonged. Much later, Jullien, Leandri, and Crozat (1958) found evidence of accelerated clotting using the heparin test and thromboelastography in experimental animals and human subjects decompressed too rapidly from a hyperbaric environment. The changes occurred at the end of decompression and they were not associated with detectable signs or symptoms of DS. Barthélémy (1963) reported a shortening of the clotting time during a sojourn at high pressure, which recovered to normal values provided decompression was relatively slow. The abnormality persisted, however, if the maximum permissible ascent rate was used and also appeared to be aggravated by elevated P_{O_2} or P_{CO_2} levels. Mazza and Pallotta (1963), using rabbits decompressed rapidly (15-20 sec) from 5 or 6 ATA, found evidence of hypercoagulability which was reversible in those which survived. Subsequently, they reported (Mazza and Pallotta 1964) that 8 days of premedication with chlorpromazine reduced clotting activity in rabbits and tended to prevent the hypercoagulability following decompression. Survival, however, was not significantly altered.

Using various animal models of decompression sickness, several investigators have demonstrated evidence of increased clotting activity including decreases in clotting factors (Ehm, Piechotta, and Schimpf 1971) and histopathological evidence of disseminated intravascular coagulation (Philp, Schacham, and Gowdey 1971; Albano, Burrano, Mazzone, LaMonaca, and Scaglione 1971). Wells, Bond, Guest, and Barnhardt (1971) observed increases in partial thromboplastin times in dogs decompressed in 10 min after 1 hr of breathing 95% N_2 and 5% O_2 at a pressure equivalent to 200 fsw (7.3 ATA). Inwood and Philp (1973) used a rat decompression model which yields a spectrum of severity of signs of decompression sickness and found a strong association between the severity of DS and the degree of disturbance in the hemostatic mechanism. Levels of Factors 5 and 8 were significantly elevated in moderately affected animals but greatly depleted in severely affected ones and in those which died (Fig. 1) even as compared to control rats which were killed with an overdose of sodium pentobarbital. Partial thromboplastin time (PTT) (Fig. 2) was significantly shortened in mild to severely affected rats but greatly prolonged in those which died and the Hicks-Pitney thromboplastin generation time and the thrombin time (TT) were prolonged in animals which died from DS (Fig. 3). There was evidence of significant levels of fibrin-fibrinogen degradation products (Fig. 4) in moderately and severely affected animals and in those which died from DS, the levels correlating with the severity of the attack. Similar findings were obtained in our laboratory using anesthetized rabbits injected intermittently with air via the carotid artery, thus suggesting that air-blood contact per se is sufficient to activate the clotting system, independent of the presence of compression-decompression. Earlier workers had noted the formation of fibrin deposits in the hearts of experimental animals with air embolism (Richardson, Coles, and Hall 1937); (Auer and Krueger 1946).

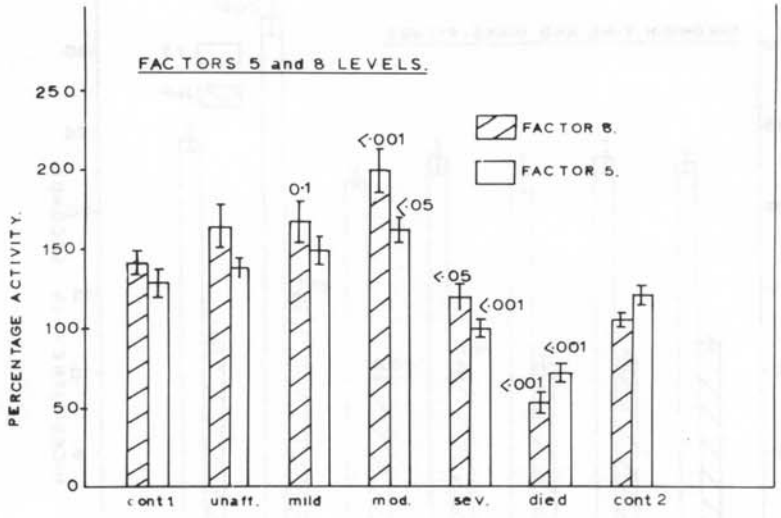

Fig. 1. Levels of Factors 5 and 8 of rats with varying degrees of severity of DS induced by 2 hr at 5.4 ATA, stage decompression in 15 min and treadmill exercise at simulated altitude (10,000 ft). Control group 1 received treadmill exercise at 1 ATA (no compression-decompression). To control the effects of morbid change, rats in control group 2 were similarly exercised after being given a lethal dose of pentobarbital IP. The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

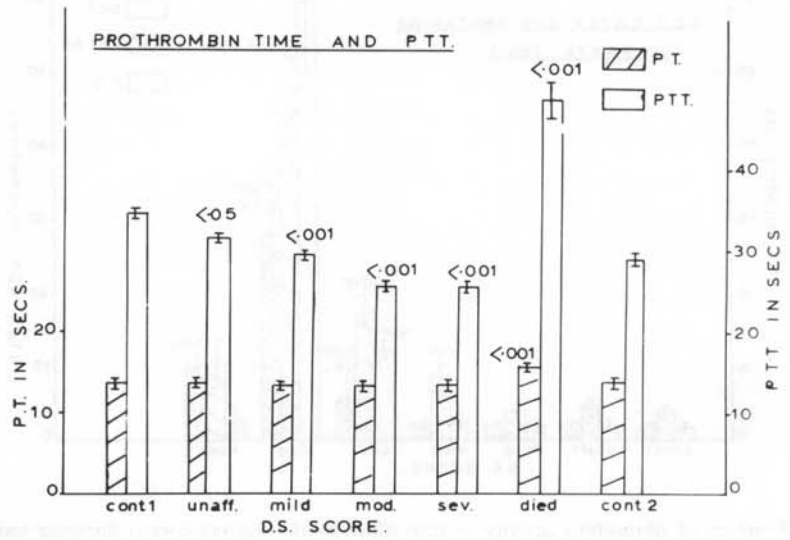

Fig. 2. Prothrombin and partial thromboplastin times, experimental conditions as described for Fig. 1. The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

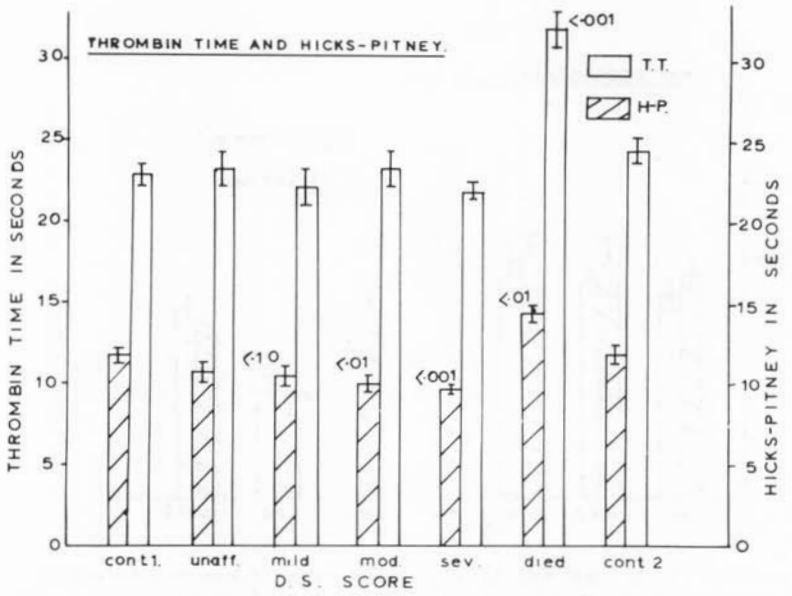

Fig. 3. Thrombin clotting times and Hicks-Pitney thromboplastin generation tests, experimental conditions described in Fig. 1. The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

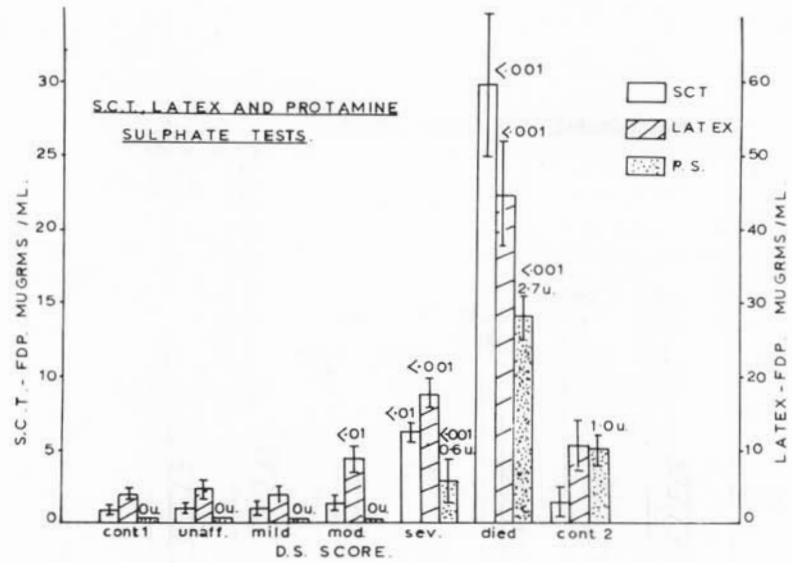

Fig. 4. Evidence of fibrinolytic activity as determined by the staphylococcus clumping test (SCT) and the latex agglutination method and evidence of fibrinogen-fibrin monomer complexes as determined by the protamine-sulfate test (PS). Experimental conditions as in Fig. 1. The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

In recent years, evidence of altered clotting activity after decompression has been observed in human subjects. In 1970 Sicardi reported an increased antithrombin rate of the order of 34% in three divers following decompression from a pressure equivalent to 200 msw (21 ATA) and pointed out that such increases were frequently associated with a hypercoagulable state. Livingstone, Achimastos, and Ackles (1971) using thromboelastography, demonstrated a shortening of the r time and k time after exposure and decompression of human subjects to 7 or 10 ATA, thus again suggesting a hypercoagulable situation. Our group (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972) performed an extensive examination of the hemostatic system in 16 human subjects decompressed on a continuous profile after 10 min at 10.4 ATA on air. There were 4 cases of Type I bends and 12 (including these 4) of *skin bends* (pruritis). When results from samples collected immediately after the end of decompression were compared with predive results, these affected divers showed a significant decrease in prothrombin consumption time, a significant decrease in Antithrombin III activity, and significant decreases in euglobulin lysis time and plasminogen activity (indicative of increased fibrinolytic activity). There was also evidence of increased circulating fibrin-fibrinogen split products. Although the absolute values for these tests remained within normal physiological limits, the changes were indicative of a shift to a more hypercoagulable state. Subsequently we reported (Philp, Inwood, Ackles, Radomski 1974) evidence of altered hemostasis, persisting for 24 hr or more postdive, including prolongation of thrombin generation times up to 24 hr postdive and a reduction in Antithrombin III activity up to 48 hr postdive. Bonin, Straub, Schibli, and Bühlmann (1973) found evidence of fibrinolytic activity and prolongation of the prothrombin time (PT) in divers decompressed after 2 hr at 10 ATA breathing a He-O_2 mixture. The changes in PT were more pronounced in individuals with Type I bends.

CELLULAR CHANGES

PLATELETS

The evidence from animal experiments strongly suggests a role for the involvement of platelets in DS. Adherence and aggregation of platelets to the bubble surface has been demonstrated and platelet microthrombi have been shown to be present in severe cases of DS in experimental animals. A thrombocytopenic response to compression-decompression in man has been observed in conjunction with several dive profiles, largely in the absence of any overt signs of DS. Preliminary evidence indicates that the extent of platelet loss in man may be influenced by the state of the platelet population in an individual, so that subjects with an inherent platelet defect may be less likely to lose platelets while those with highly active platelets (as determined by in vitro tests of platelet function) may lose more than normal subjects. The question of whether the loss of platelets is a compresion phenomenon or is due to decompression per se appears to have been answered. The continuing loss of platelets for 24-48 hr may be due to damage incurred during decompression by a cohort of the platelet population, such that their normal life expectancy is shortened.

Information concerning the disposition of platelets in clinical cases of Type I and Type II DS is virtually nonexistent. In the face of experimental evidence gleaned both from animals and from human subjects, one would be inclined to believe that any sign of DS, however mild, if accompanied by evidence of thrombocytopenia, ought to be viewed as a potentially serious situation.

Although Geller (1941) postulated that platelets could interact with bubbles he provided no supporting evidence. Jacobs and Stewart (1942) may have been the first to observe an effect of bubbles on platelets. Severing the tips of the tails of decompressed rats, they saw bloody froth issue from the vessels and, upon microscopic examination, found that the bubbles were surrounded by platelet aggregates. They speculated that such aggregates might occlude fine blood-vessels. Our laboratory used a standardized animal model for decompression sickness which consisted of a 2-hr exposure to 5.3 ATA followed by stage decompression over 17 min and exercise at a simulated altitude of 10,000 ft (696 millibars or 0.69 ATA). There was a loss of circulating platelets following this procedure, the extent of which correlated with the observed severity of DS (Philp, Gowdy, and Prasad 1967; Inwood and Philp 1973). Other experiments (Philp and Gowdey 1969; Clark, Philp, and Gowdy 1969a) demonstrated that rats rendered thrombocytopenic by an immunological procedure were not protected against DS, and those which were thrombocytotic during the rebound recovery phase had a significantly higher incidence of DS than control rats. Moreover, rabbits which were slowly infused with air intravenously showed a progressive fall in the circulating platelet count. Others (Ehm et al. 1971) subsequently confirmed this observation in decompressed rabbits. Somewhat earlier Kahn, Suetsugu, Alkalay, Platthy, and Stein (1966) found that the increased resistance to blood flow through the lungs, which followed the injection of a large air embolus, was largely absent in dogs rendered thrombocytopenic. They speculated that pulmonary vasoconstriction was due to serotonin released from platelets.

Histopathological evidence of platelet involvement in experimental DS has also been accumulating. In 1963 Clay reported on a series of dogs decompressed in 10 min after 1 hr at a pressure of 6 ATA and found 14 of 31 dogs had platelet microthrombi in blood vessels of the lungs. Adebahr and coworkers (Adebahr and Kupffer 1967; Adebahr and Stack 1969; Adebahr 1971) saw platelets and platelet aggregates surrounding intravascular bubbles in rabbits killed by the intravenous injection of air.

Philp et al. (1971), using the rat decompression model described above, showed that there was a positive correlation between the extent of lung pathology (microthrombi) and the severity of DS and that the intravenous infusion of air into rabbits produced multiple microthrombi in lung vessels consisting of air bubbles, platelet aggregates, and sludged red cells. Direct, visual evidence of platelet-bubble interactions was provided by our laboratory (Philp, Inwood, and Warren 1972; Warren, Philp, and Inwood 1973). We were able to develop a method for the in situ fixation of tissues which permitted the examination of blood and bubbles by electron microscopy. Using explosively decompressed rats with massive intravascular bubble formation, we showed that bubbles acquired a coating, approximately 200 Å in thickness, which appeared to consist of fibrinogen primarily. Lipid micelles also became entrapped at the air-blood interface, and platelets appeared to be selectively attracted to the interface with platelet adhesion progressing to platelet aggregation (Fig. 5). A striking similarity between this reaction and blood-foreign surface reactions in general was noted. Stegall, Smith, and Hildebrandt (1972) reported a marked (> 50%) reduction in circulating platelet counts of minature swine 24-48 hr after decompression from a hyperbaric environment. This was preceded by a significant increase in platelet adhesiveness immediately postdive.

Sicardi (1970) was the first to note a loss of platelets in human subjects following decompression. He reported a 37% reduction in the circulating platelet count of three divers following decompression from a simulated depth of 200 msw (21 ATA). The following year Bennett and Gray (1971), reporting on a 1500 fsw (46.5 ATA) dive, found that two of the

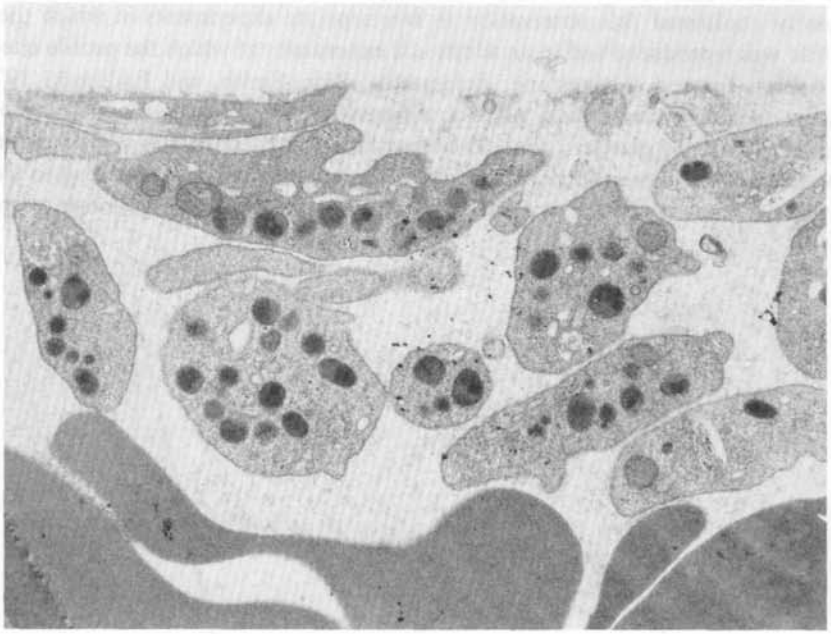

Fig. 5. Electron micrograph (x15,000) of platelets adhering to a blood bubble interface and to each other. The bubble is the clear area at the top of the photo. Deformed red cells can be seen at the bottom of the photo (courtesy Prof. B.A. Warren, Dept. Pathology, U.W.O.).

diving subjects lost 78,000 and 135,000 platelets/mm^3 of blood; the latter diver developed Type I bends near the completion of decompression. Not all investigators have confirmed a platelet loss following decompression. Bühlmann, Matthys, Overrath, Bennett, Elliott, and Gray (1970) found no significant change in platelet count immediately following a saturation exposure of divers to 31 ATA on a HeO_2 breathing mixture. Philp, Ackles, Inwood, and Livingstone (1972) found a mean decrease in circulating platelet count of 11.9% ± 3.35 (SEM) in 16 divers decompressed on a continuous, pneumatic analogue computer profile after 10 min at 10.4 ATA of air. There was, however, no correlation between the degree of platelet loss and the occurrence of Type I bends or skin bends. In addition, the adhesiveness of platelets to glass beads was significantly increased in 12 of the diving subjects who displayed decompression-associated signs and symptoms which included pruritis and skin rash and four cases of Type I bends. Such an increase was not observed in the four unaffected individuals. The megathrombocyte index (i.e. those platelets having a transverse diameter $>2.5\mu$ when examined microscopically in stained smears) was significantly increased in all divers but much more so in those affected with skin bends or Type I bends. These large platelets are believed to be young, newly released ones (Garg, Amorosi, and Karpatkin 1970).

Martin and Nichols (1972) recorded the unique observation that the circulating platelet count continued to fall for about 72 hr after a 1-hr exposure to a simulated depth of 100 fsw (4.1 ATA). These authors used a stage decompression procedure proven to be exceptionally free of any incidents of DS in nearly 200 open-sea dives. The platelet loss

averaged about 30% at the lowest point. Philp, Inwood, Ackles, and Radomski (1974) subsequently confirmed this observation in two separate experiments in which the British dive profile was reproduced and in an additional experiment in which the profile cited above (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972) was used. Again, postdive increases in platelet adhesiveness were observed which preceded the major fall in circulating platelet count. The megathrombocyte counts rose progressively after decompression, with a steep increase at a time (96 hr postdive) corresponding to the return of the platelet counts toward normal levels (Fig. 6). Platelet aggregation in response to

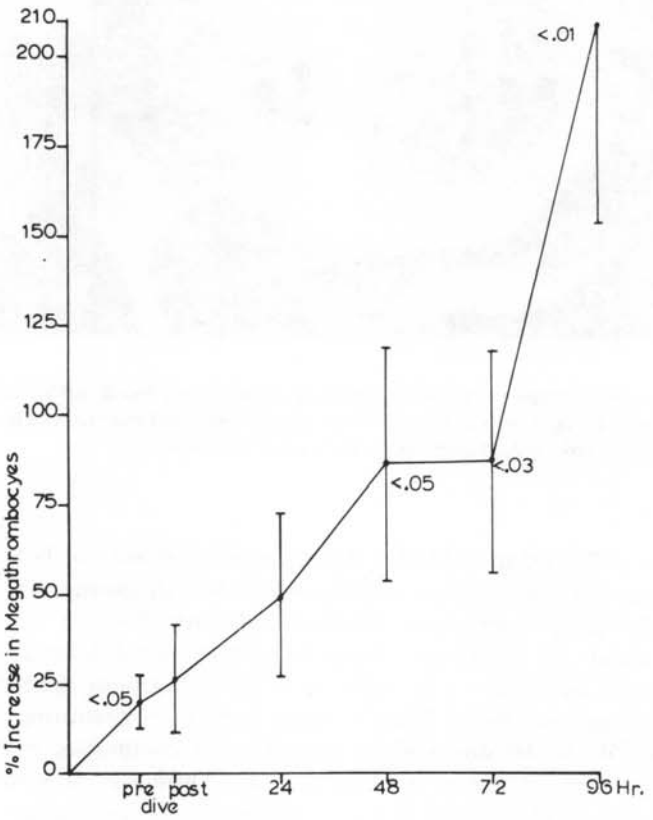

Fig. 6. Megathrombocyte indices before and after a simulated dive to 100 ft (air). The megathrombocyte index rose sharply at 96 hr postdive, a time corresponding to the return of platelet counts toward normal values. Megathrombocytes (platelets with a transverse diameter $> 2.5\mu$) are believed to represent newly released platelets. The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Philp, Inwood, Ackles, and Radomski 1974).

adenosine diphosphate (ADP) was also studied but no significant changes were noted in association with decompression. The progressive fall in circulating platelet count has also been seen under operational diving conditions. Philp, Freeman, Francey, and Ackles (1974)

performed platelet function and hematological studies on seven divers before and after a 6-7 day saturation exposure in an underwater habitat located in 50 ft of seawater off Freeport, Grand Bahama Island (Wicklund 1972). Two subjects were worthy of special note in that they both lost over 50% of their circulating platelet count 24 hr after surfacing. One of these divers had been engaged in a series of daily decompression dives to 150 fsw for several days prior to the experiment. He had not dived for the immediate 2 days preceding it. During this control period his platelet count showed an increase, thus indicating that it was probably recovering from the previous diving activities and that he had a high percentage of young platelets which are believed to be more biologically active (Zbinden, Grimm, and Muheim 1971; Karpatkin 1972). The other subject was shown to have spontaneous platelet aggregation, a phenomenon reported to be sometimes associated with idiopathic, peripheral thrombosis (Vreeken and Van Aken 1971; Friedlander, Cook, Hawkey, and Symons 1971; Biermé, Boneu, Guiraud, and Pris 1972). It is conceivable that these two individuals lost more platelets than most subjects because they both had a highly-reactive platelet population. Again, an increase in platelet adhesiveness preceded the loss of platelets as did an increase in platelet aggregating activity in response to ADP. Megathrombocyte indices increased markedly at a time when the platelet count was returning toward normal values. One other subject was mildly thrombocytopenic before the dive, possibly because of recent drug medication. His platelet count doubled while under pressure, suggesting that thrombopoiesis was not seriously compromised.

This laboratory has previously observed platelet abnormalities which appeared to influence the extent of platelet loss (Philp, Inwood, Ackles, and Radomski 1974). Two diving subjects were studied whose platelets lacked the release reaction in response to ADP or epinephrine. This anomoly appears to be present in about 10% of the population and is sometimes associated with a mild hemostatic defect such as easy bruising and it is similar in appearance to that caused by the ingestion of aspirin (Weiss, Chervenick, Zaluski, and Factor 1969). Neither of these subjects lost significant numbers of platelets after decompression, in contrast to their companions. Kindwall (1972) compared the platelet counts of two groups of tunnel workers, one of which had been operating at about 3.4 ATA for 1 week while the other had been working in free air. The mean platelet count of the compressed air workers was the same at any acceptable level of significance.

Recent experiments with the rat decompression model in our laboratory (Inwood and Philp 1973) showed that platelets collected from rats with moderate-to-severe DS were less senstive to ADP-induced aggregation than those of control rats (Fig. 7). We postulated that this was likely due to the consumption of the most active platelets in a peripheral, microthrombotic process so that the remaining platelets consisted of a less reactive, possibly senescent, cohort. A significant reduction in the circulating platelet count was also seen in these rats (Fig. 8). French workers (Broussolle, Stoltz, Mainart, Hyacinthe, and Pietrini 1973) likewise studied platelet aggregation in rats following a decompression accident and reported similar findings, reaching the same conclusion as we did.

RED CELLS

Very few observations have been made on the effects of decompression on red-cell function. Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski (1972) noted a significant increase in the number of reticulocytes seen in a group of subjects with skin bends or Type I bends occurring after decompression. This was not observed in

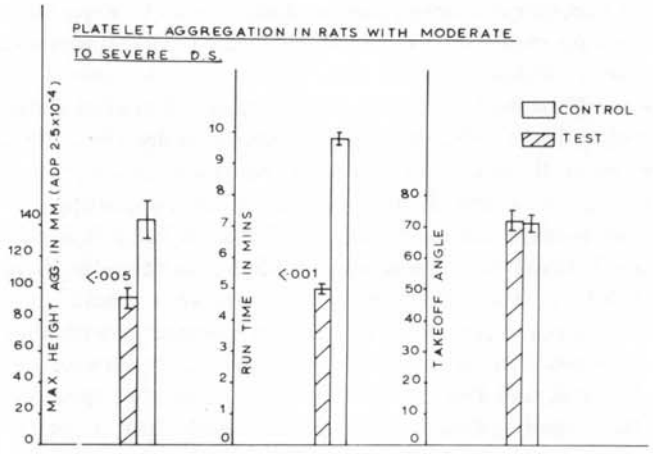

Fig. 7. Platelet aggregation in response to adenosine diphosphate in rats with moderate to severe DS as compared to control rats. A significant decrease in aggregating activity, as evidenced by a decrease in curve height and an increase in the time to onset of aggregation (run time) was observed in the rats with DS. This was felt to be due to the disappearance of the more active platelets from the circulation (see Fig. 8). The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

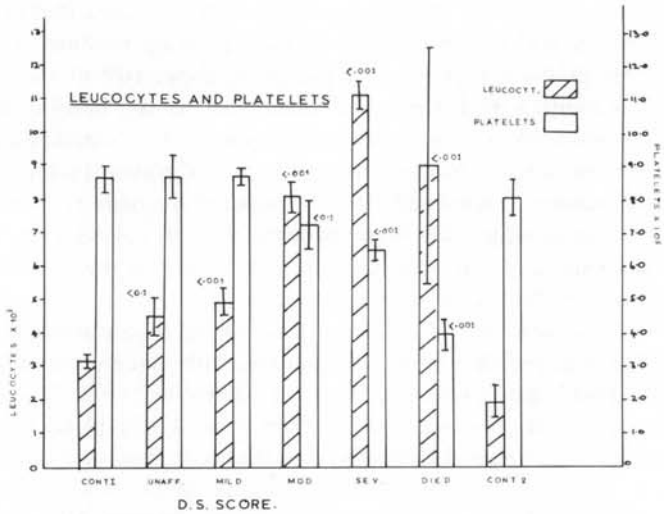

Fig. 8. Changes in platelet and leucocyte counts of rats with varying degrees of severity of DS. Platelet counts tended to decrease with severity whereas leucocytes increased (experimental conditions as in Fig. 1). The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

unaffected individuals. Analysis by this author of data presented by Beckman and Smith (1972) concerning TEKTITE II aquanauts suggested that a slight (0.25% of red cells) but statistically significant ($p < 0.02$) increase in reticulocyte counts occurred postdive. This was not related to any signs of decompression sickness nor to any evidence of hemoconcentration. Conversely, Hock, Bond, and Mazzone (1966) reported no significant changes in

reticulocyte counts during a HeO_2 saturation dive (SEALAB II). Similarly, Hamilton, MacInnis, Noble, and Schreiner (1966) reported no significant changes in red-cell counts or hemoglobin concentration during a HeO_2 saturation dive to 650 fsw (21.7 ATA). Linaweaver (1969) did not find any significant changes in red-cell counts or hemoglobin concentration either during or after saturation HeO_2 chamber dives. Kemph and Hitchcock (1948) found no significant changes in red-cell morphology or mean corpuscular hemoglobin concentration following explosive decompression of dogs to simulated high altitudes.

Barthélémy (1963) observed an increase in red-cell sodium and a decrease in red-cell potassium in divers breathing air at simulated depths of 30 msw (3.9 ATA) and 60 msw (6.8 ATA). The potassium depletion tended to persist after decompression whereas the sodium returned to normal values. Philp, Inwood, Ackles, and Radomski (1974) found no change in red-cell sodium, as compared to predive values, following decompression after 1 hr at a simulated depth of 100 fsw (4 ATA). Investigations of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) generally have not revealed changes associated with compression-decompression (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972; Philp, Inwood, Ackles, and Radomski 1974). Kindwall (1972), however, noted a slight but statistically significant reduction in MCHC in a group of tunnel workers who had been working daily for 1 week at about 3.4 ATA, as compared to a similar group working in free air. Hemoglobin concentration was not significantly different in the two groups. In conjunction with the reduction in MCHC there was a slight but significant increase in MCV. This latter observation is suggestive of a fluid shift into the red cells and this subject will be discussed in greater detail under *Fluid and Electrolyte Shifts*.

Since the pioneer observations of End and Swindle on blood sludging and red-cell aggregation following decompression, several authors have confirmed the existence of this phenomenon. Wagner (1945) noted the passage of sludged red cells through the pial vessels of cats rapidly decompressed from high pressures, as have other investigators using various animal models of DS (Heimbecker, Lemire, Chen, Koven, Leask, and Drucker 1968; Buckles 1968; Wells et al. 1971; Philp et al. 1971). The formation of red-cell aggregates appears to be invariably associated with stasis of flow but the aggregates may persist after flow has been restored. We have observed red-cell fragmentation and deformation (i.e. helmet cells) in association with intravascular bubbles following rapid decompression of rats (Inwood and Philp 1973; Warren et al. 1973).

Collecting blood samples from divers while they are at simulated depth (for subsequent examination at the surface) is fraught with difficulty because a technical error may be introduced by the formation of bubbles during decompression, resulting in hemolysis. Moreover, calculation of MCV, MCH, and MCHC are only as reliable as the initial measurements. Since the counting of red cells by whatever technique involves considerable chance of variation, these values must always be viewed with some suspicion. Nevertheless, existing data suggest that changes in hemoglobin concentration, red-cell size, and reticulocyte numbers are more likely to be encountered when air is the breathing mixture rather than HeO_2. Whether this is related to a greater propensity for bubble formation or to a membrane-related effect of nitrogen (as will be discussed later) remains open to question.

LEUCOCYTES

Kemph and Hitchcock (1948) failed to detect any change in the leucocyte counts of dogs subjected to explosive decompression. Smith and Brown (1951) did an extensive study of

leucoctye changes in normal and splenectomized cats exposed for 30-40 min to simulated high altitude after rapid decompression (36,000 ft in 5 min). They found that acute decompression stress produced a rapid doubling of leucocytes in both normal and splenectomized cats, with increases in eosinophils and neutrophils. Lymphocytes did not change significantly. Leucocytes have been observed adhering to the periphery of intravascular bubbles following the intravenous injection of air into rabbits (Adebahr and Kupffer 1967; Adebahr and Stack 1969; Adebahr 1971) and the rapid decompression of rats from high air pressures (Philp, Inwood, and Warren 1972). Inwood and Philp (1973) used the standardized compressed-air, rat decompression model developed in their laboratory and showed that there were significant increases in the total leucocyte counts of rats moderately or severely affected with DS (see Fig. 8). These increases were due largely to increases in the numbers of polymorphonuclear leucocytes.

Masland (1948) observed leucocytosis in aviators suffering from acute neurological DS. Analysis of TEKTITE II air saturation dives (Beckman and Smith 1972) revealed significant increases in total white-cell and neutrophil counts, after decompression, in three of the six missions reported. The authors felt, however, that these changes were more likely related to skin and ear infections than to decompression stress since previous data collected during TEKTITE I dives did not show changes in leucocytes either during the dive or after decompression. Other investigators have not been able to show significant changes in total leucocytes or differential counts immediately following decompression (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972) from a simulated air dive or up to 96 hr later (Philp, Inwood, Ackles, and Radomski 1974).

Helium-oxygen saturation dives have yielded conflicting results. Some authors reported no significant changes in leucocytes either during the exposure or thereafter (Linaweaver 1969; Hamilton et al. 1966; Bühlmann et al. 1970). Vorosmarti, Bradley, Linaweaver, Kleckner, and Armstrong (1970) however, found that HeO_2 saturation dives were associated with significant increases in monocyte counts which became evident on the 3rd day of the dive and which persisted for 2 to 3 days postdive. Eosinophil counts became significantly elevated 7 to 8 days postdive. Somewhat earlier, Waldvogel and Bühlmann (1968) observed a marked increase in the leucocyte counts of four divers following a saturation exposure to 23 ATA of HeO_2 (2.5-3.5% O_2) and Bennett and Gray (1971) also observed leucocytosis after a HeO_2 saturation dive. Bonin et al. (1973) saw increased leucocyte numbers in divers following a HeO_2 dive (2 hr at 10 ATA).

To date, no author has proposed a satisfactory explanation for these various changes. In some cases the presence of infection might be responsible, but this cannot account for the leucocytosis in all cases. Animal experiments have indicated that leucocytosis can be observed fairly soon after decompression from high pressures or to simulated high altitude. The variety of gas mixtures and dive profiles used in experiments in which leucocytosis has been observed in man, and the absence of observable leucocytosis in other, similar experiments make it unlikely that hyperoxia or inert gas effects could account for these changes. Bennett (1972) reported that sudden, severe exercise resulted in a significant increase in circulating leucocytes and pointed out that these changes correlated with increases in circulating velocity, which appeared to flush sequestered white cells into the blood. This effect could also occur in response to the hemodynamic changes induced by increased epinephrine output. It is of interest to note that Waldvogel and Bühlmann (1968) saw increased urinary output of epinephrine during the last 24 hr of decompression from a HeO_2 saturation dive. Using two of the same subjects, Bühlmann et al. (1970) observed only a transient increase in urinary catecholamines which occurred shortly after maximum

pressure was obtained. Slight decreases were detected during decompression and no leucocytosis occurred. Urinary catecholamines were not altered following an air dive in which leucocyte counts did not change significantly (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972).

Thus it is possible that leucocytosis might relate more to the degree of stress, either physical or emotional, experienced by a particular diver than to any other factor. The inconsistencies observed in white cell differential counts could be due to the influence of subclinical infection, the adherence of white cells to *silent* bubbles and their subsequent removal, or to local hemodynamic or cellular influences which might result in the selective washout of certain cell types.

CIRCULATING ENDOTHELIAL CELLS

Philp, Inwood, and Warren (1972) found that the number of free, circulating endothelial cells increased in direct proportion to the severity of DS in afflicted rats. They felt that the isolation of endothelial cells by gas bubbles and capillary stasis probably resulted in cell hypoxia with the subsequent sloughing off of these cells. The authors pointed out that such denuded areas could serve as foci for platelet aggregation and thrombus formation. In electron microscopy studies Warren et al. (1973) found that intravascular bubbles caused pressure damage to endothelial cells which subsequently herniated through fenestrations in the more rigid structures of the arterial wall. Deposits of fibrin were noted on the vessel wall after endothelial damage, as well as layering of platelets over the endothelium.

FLUID AND ELECTROLYTE SHIFTS

Hemoconcentration as indicated by an increase in packed-cell volume (PCV) or by estimates of blood volume has been a frequent observation associated with DS in animals decompressed from high pressures (Carson 1942; Cockett, Nakamura, and Franks 1963; Cockett and Nakamura 1964a; Cockett, Nakamura, and Franks 1965; Philp et al. 1967; Heimbecker et al. 1968; Wells et al. 1971; Inwood and Philp 1973). Similar increases in PCV have also been seen in experimental animals following rapid or explosive decompression to simulated high altitude (Kemph and Hitchcock 1948; Smith and Brown 1951) and the intravenous injection of nitrogen (Hetherington and Miller 1946).

Hemoconcentration has commonly been associated with clinical DS in man (Masland 1948; Malette, Fitzgerald, and Cockett 1961, 1962; Cockett and Nakamura 1964b; Brunner, Frick, and Bühlmann 1964; Barnard, Hanson, Rowton-Lee, Morgan, Polak, and Tidy 1966; McCallum 1968; Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972a; Saumarez, Bolt, and Gregory 1973).

Although changes in PCV have seldom been seen following nonsaturation dives in which no incidence of bends existed (Barthélémy 1963; Philp, Freeman, Francey, and Ackles 1974), a reduction in PCV has been a frequent observation during or after saturation diving. Chouteau (1969) reported a loss of red cells in the CONSHELF I and II projects. A significant reduction in PCV was observed in one of six dive groups in TEKTITE II (Beckman and Smith 1972). In TEKTITE I dives, however, they observed an increase in postdive PCV which they attributed to dehydration. Widell, Pilmanis, Chapman, Pilmanis, and Given (1973) reported that both PCV and hemoglobin concentration decreased significantly during a 7-day sojourn in the HYDRO-LAB habitat located in 50 fsw. The parameters remained depressed for some days postdive. This observation was subsequently

confirmed by Philp, Freeman, Francey, and Ackles (1974) under nearly identical diving conditions.

Blood studies during HeO_2 saturation diving have also yielded conflicting results. Schaefer, Bond, Mazzone, Carey, and Dougherty (1968) saw no significant changes in PCV or hemoglobin concentration during a 12-day saturation at 7 ATA. In the SEALAB II experiments (MacInnis and Bond 1969) red-cell count and PCV fell during the first few days of the saturation dive, with recovery about the 9th day. In a dry-chamber saturation dive to 650 fsw Hamilton et al. (1966) found no significant change in red-cell count, PCV, or hemoglobin concentration during the exposure. No changes were seen in GENESIS E (a dry-chamber saturation dive at about 7.0 ATA) or in SEALAB (an in-sea saturation dive at 6.8 ATA).

In CONSHELF III (Chouteau 1969), carried out at a depth of 328 fsw (11 ATA), no hematological data was included, but a preliminary dry-chamber saturation dive at a similar pressure did not induce any significant change in hematological parameters. Bühlmann et al. (1970) noted a slight fall in PCV following decompression from a saturation dive at 31 ATA. In earlier experiments at 22 ATA (Waldvogel and Bühlmann 1968) no changes in PCV, hemoglobin, or red-cell count were noted during or after the dive. Similarly Vorosmarti et al. (1970) found no significant changes in red-cell count, reticulocyte count, hemoglobin concentration, or PCV during HeO_2 saturation dives (dry-chamber) to 450 fsw (14.6 ATA) although there was a significant reduction in PCV immediately postdive. In a 600 fsw (19.2 ATA) chamber dive, PCV rose on the 3rd day of saturation and fell thereafter to significantly low levels during the decompression phase. Hemoglobin concentration was also depressed significantly in the postdive samples. These authors felt that the repeated blood sampling contributed to this "anemic" response. In an earlier publication (Bradley and Vorosmarti 1968) they reported that a 30-min exposure to 1.9 or 2.8 ATA of pure oxygen caused a depression in PCV and hemoglobin 7 days after the exposure in student divers, but not in experienced ones. They felt that a transient depression or erythropoiesis was the most likely explanation for the response. In a series of saturation dives at pressures ranging from 7 to 19.2 ATA, Linaweaver (1969) found no significant changes in hemoglobin PCV or red-cell counts either during or after the dives.

These frequent observations of reductions in PCV, red-cell count, and hemoglobin concentration during or after saturation dives could be the result of depressed erythropoiesis, increased red-cell destruction, or increased plasma volume (hypervolemia). Should the first two causes pertain, this discussion would rightly belong to the section on red-cell changes. Certainly these possibilities cannot be discounted.

Hyperoxia is known to increase red-cell destruction and may depress erythropoiesis as an adaptive response to the increased oxygen tension in the blood (Mengel, Kann, and Horton 1964; Mengel, Kann, Lewis, and Horton 1964; Mendel, Kann, Smith, and Horton 1964; Mengel, Kann, Heyman, and Metz 1965; Landaw, Leon and Winchell, 1970; Vorosmarti et al. 1970; Widell et al. 1973). Schaefer, Bond, Mazzone, Carey, and Dougherty (1968) and Schaefer, Jacey, Carey, and Mazzone (1968) felt that a PO_2 of 300 mm (0.4 ATA) was probably the threshold for the antihematopoietic effect of O_2. Table 1 summarizes the evidence of reduced PCV, red-cell count, or hemoglobin concentration during or after saturation diving on various gas mixtures and lists the partial pressure of oxygen (insofar as this author could determine) in each situation. There appears to be little relationship between the partial pressure of O_2 in the breathing mixture and the detection of an anemic response either during or after the dive. Rather, the response appears to be associated more frequently with extensive swimming in the sea, especially when air is the breathing gas.

TABLE 1

Summary of hematological data during and after saturation diving*

Project	Total ATA	N_2 ATA	He ATA	O_2 ATA	Days	Swimming	During PCV	During HB	During RBC	After PCV	After HB	After RBC	Reference
CONSHELF I	2.06	1.57	–	0.42	7	in sea			↓			↔	Chouteau (1969)
CHOUTAQUA	12.61	–	12.38(?)	0.23	5	–	↔	↔	↔				Chouteau (1969)
CONSHELF II	1.95	1.56	–	0.39	30	in sea		"discrete anemia"					Chouteau (1969)
CONSHELF III	10.95	0.10	10.62	0.23	30	in sea	↔	↔	↔				Chouteau (1969)
TEKTITE II	2.50	2.00	–	0.50	14-21	in sea				↓	↓	↔	Beckman & Smith (1972)
HYDRO-LAB	2.50	2.00	–	0.50	7	in sea	↓	↓	↓(?)	↓	↓	↓(?)	Widell et al. (1973)
HYDRO-LAB	2.50	2.00	–	0.50	7	in sea				↓	↓	↓(?)	Philp, Freeman, Francey, & Ackles (1974)
GENESIS E	7.00	0.40	6.30	0.27	12	–	↔	↔	↔	↔	↔	↔	Schaefer, Bond, Mazzone, Carey, & Dougherty (1968)
SEA-LAB I	6.80	1.16	5.37	0.27	9	in sea	↔	↔	↔	↔	↔	↔	MacInnis & Bond (1969)
SEA LAB II	7.20	1.30	5.62	0.25-0.35	10-30	in sea	↓	↓	↓	↔	↔	↔	MacInnis & Bond (1969)
MAN-IN-SEA	14.60	0.15	14.02	0.44	1	–				↔	↔	↔	MacInnis & Bond (1969)
MAN-IN-SEA	20.70	–	20.40	0.31	2	–	↔	↔	↔				Hamilton et al. (1966)
	22.00	0.80	21.50	0.56-0.80	2½	–				↔	↔	↔	Waldvogel & Bühlmann (1968)
	31.00†	0.75	29.60	0.43-2.70	3½	wet pot				↓(?)	↔	↔	Bühlmann et al. (1970)
	7.10	1.00	5.80	0.30	9	wet pot	↔	↔	↔	↔	↔	↔	Vorosmarti et al. (1970)
	14.60	1.00	13.30	0.30	9	wet pot	↓	↔	↔	↓	↔	↔	Vorosmarti et al. (1970)
	19.20	?	18.70	0.50	6	–	↔	↔	↔	↔	↔	↔	Linaweaver (1969)
	2.0††	1.60	–	0.40	1½	–	↔	↔	↔	↔	↔	↔	Schaefer, Jacey, Carey, and Mazzone (1968)

*some information in this table was taken from MacInnis, J. B. 1966. The medical and human performance problems of living under the sea. Can. Med. Assoc. J. 95(5):191-200.

† with excursions to 36 ATA †† with excursions to 6 ATA ? indicates data not fully confirmed or not statistically significant

Widell et al. (1973) commented on the known effect of prolonged weightlessness–elimination of the normal gravitational pooling of blood in the lower extremities. This shift of blood to the thoracic organs results in the recruitment of tissue fluid and the subsequent cardiac loading initiates a renal response with increased sodium and water excretion. If the sodium and water loss persists for a sufficient length of time, a true reduction in blood volume may result. Although Widell's group saw increased sodium, potassium, and water excretion and decreased aldosterone output in two of their three subjects, they discounted the effect of weightlessness as an explanation for the reduced red-cell mass. Rather they felt this was due to hyperoxia because cardiovascular and respiratory tests indicated that a blood volume reduction had not occurred. The conditions of the aquanaut, however, differ greatly from those of the astronaut in that the weightlessness is intermittent and of comparatively short duration. The renal response may not persist sufficiently to produce a loss of blood volume and a reduction in red-cell count, hemoglobin concentration, or PCV may thus reflect hemodilution rather than a true loss of cell mass.

Changes in blood and urine electrolytes have likewise been observed in nonsaturation diving conditions. In discussing a statistically significant reduction in serum sodium concentrations in subjects with decompression-related signs and symptoms after a 10-min sojourn at a simulated depth of 300 fsw (10.3 ATA) Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski (1972) speculated (in the absence of clear evidence of sodium diuresis) that sodium was passing from the extracellular space to some intracellular site. They noted that disturbances in normal cell metabolism interfered with the sodium pump mechanism, resulting in intracellular accumulation of sodium. This has been

seen in a number of pathological situations including uremia and shock (Welt, Smith, Dunn, Czerwinski, Proctor, Cole, Balfe, and Gitelman 1967; Cunningham, Wagner, and Shires 1970).

Barthélémy (1963) also noted a reduction in plasma sodium which occurred in divers under pressure and persisted after decompression. Linaweaver (1969) did not observe significant changes in serum electrolytes during or after HeO_2 saturation diving and Bühlmann et al. (1970) noted no significant changes in serum electrolytes after a saturation exposure to 31 ATA, although renal excretion of sodium, calcium, magnesium, and chloride decreased. Radomski and Bennett (1970) observed a significant reduction in urinary sodium and calcium after 30 min at 10.3 ATA in air, as well as significant increases in serum potassium and phosphorus, with a return to normal values within a few hours. These changes were not seen when helium-oxygen was breathed in the same dive profile. No significant changes in serum sodium were observed. These authors attributed the effects to the presence of nitrogen and noted the similarity to electrolyte shifts observed with various anesthetic agents. Schaefer, Bond, Mazzone, Carey, and Dougherty (1968) noted transitory increases in urine sodium, potassium, and chloride during a 12-day HeO_2 dive at 7 ATA. Albano (1970) also saw increased urinary output of sodium and, more particularly, of potassium during an exposure to high pressure (9 ATA). Bennett and Hayward (1967) found significant decreases in the sodium levels of cerebral spinal fluid of cats exposed to 10 ATA of nitrogen-oxygen or argon-oxygen but not helium-oxygen. Bennett (1968) hypothesized that nitrogen at high pressure might interfere with the membrane sodium pump mechanism leading to the intracellular accumulation of sodium. It is of interest to note that chlorpromazine, one of the first drugs reported to offer protection against experimental decompression sickness in animals, is known to have a membrane-stabilizing effect and thus to protect red cells from hypotonic hemolysis (Seeman 1966; Seeman and Weinstein 1966; Seeman, Sha'afi, Galey, and Solomon 1970).

BLOOD CHEMISTRY

ENZYMES

The knowledge that numerous pathological states induce cell damage and the release of intracellular isoenzymes into the blood prompted the study of these enzymes in hyperbaric experiments to determine whether hyperoxia and/or decompression induced sufficient cell damage to yield detectable increases in blood enzyme levels. As with many of the parameters discussed thus far, the results to date have been somewhat equivocal.

Barthélémy (1963) did not find any significant changes in plasma or corpuscular cholinesterases following short exposures to either 30 or 60 msw (3.9-6.8 ATA) when divers breathed air. Philp, Inwood, Ackles, and Radomski (1974) reported that serum cholinesterase activity was depressed upon decompression, and for 3 days after a 10-min chamber dive (air) to 10 ATA. Creatinine phosphokinase (CPK) levels tended to be depressed postdive and lactic acid dehydrogenase (LDH) and glutamic oxaloacetic transaminase (GOT) levels were significantly depressed 24-72 hr later. These changes were largely prevented by the antiplatelet drug VK744, and the authors speculated that the decline, especially in LDH and GOT, might be related to the observed loss of platelets since these enzymes occur in platelets (Zucker and Borelli 1958). Previously Martin, Gray, and Nichols (1973), using a 1-hr exposure to 4 ATA air, reported that newly trained divers demonstrated significant increases in alkaline phosphatase (AlPh) and aspartate aminotransferase (AsAm) during the dive whereas untrained subjects did not. Some subjects in both groups, however, showed elevated CPK levels up to 3 days postdive but the trained subjects also showed elevated predive levels.

Kindwall (1972) did not observe any significant difference in CPK levels between tunnelers working in free air as opposed to those working at pressure of 35-38 psi (3.6 ATA).

Studies of air saturation dives have also revealed minor changes in blood enzyme levels. Schaefer, Jacey, Carey, and Mazzone (1968) found that a 36-hr air saturation dive at 2 ATA with excursions to 6.0 ATA did not produce any significant changes in serum GOT or glutamic-pyruvic transaminase (GPT) either during the dive or within 3 hours of surfacing. LDH, however, rose during and after the excursions to 6 ATA. The authors felt that this response was to some extent related to circadian rhythms of LDH activity since it occurred only when the excursion took place at 1200 hr. In a subsequent publication (Jacey and Schaefer 1968) these authors demonstrated a circadian cycle for LDH with peak activity in plasma occurring between 1200 and 2400 hr. High-pressure stress (no-decompression dive to 5 ATA) elicited increased plasma LDH activity only when applied during the descending phase of the normal circadian cycle.

Studies of the TEKTITE II missions (Beckman and Smith 1972) revealed significant postdive increases in LDH and GOT, which the authors felt were due to cell destruction. Conversely, in HYDRO-LAB air saturation dives, slight, but statistically significant postdive decreases in AlPh, CPK, and LDH were observed which may have been due to hemodilution or to platelet loss (Philp, Freeman, Francey, and Ackles 1974).

Helium-oxygen saturation diving has been the subject of much research relating to blood isoenzyme patterns. Bennett and Gray (1971) found that no significant changes occurred in levels of several enzymes (LDH, AsAm, AlPh, alpha hydroxybutyrate dehydrogenase [HBD] and LDH-HBD ratios) following a HeO_2 dive to 1500 fsw (46.5 ATA). Waldvogel and Bühlmann (1968) reported a slight increase in CPK in subjects exposed to 22 ATA of HeO_2 for 60+ hr. SEALAB II data revealed significant increases in GOT and LDH during the dive (MacInnis and Bond 1969). Commenting on a series of HeO_2 saturation dives at a variety of pressures, Linaweaver (1969) noted no significant changes in AlPh, GOT, GPT, or LDH levels in serum. In one 600-fsw dive (19.2 ATA) there was an increase in the proportion of heart LDH isoenzyme but GOT was normal, indicating that tissue damage had not occurred. Bühlmann et al. (1970) measured a variety of isoenzymes before and after an 81-hr saturation dive at 31 ATA with excursions to 36 ATA. In comparing the results before and after the trial, they found no significant change in AlPh, slight increases in LDH and HBD with varying ratios in each subject, and a decrease in AsAm.

Existing evidence suggests that neither the degree of hyperoxia commonly encountered in saturation diving nor the effects of *safe* decompression induces enough tissue damage to cause significant increases in blood isoenzyme levels. Enzyme levels could, of course, be elevated by the physical exertion of diving since this effect of exercise is well-documented (Schlang and Kirkpatrick 1961; Halonen and Koltinen 1962; Nuttall and Jones 1968; Refsum, Schomm, and Tveit, 1972). Martin and Nichols (1974) noted elevated CPK levels in the early stages of diver training with a return toward normal after 6 weeks. The effect was more pronounced in winter than in summer, suggesting to them that cold stress exaggerates the response. These authors felt that the CPK response might be a useful indicator of an individual's degree of adaptation to the hyperbaric environment, but others (Nuttall and Jones 1968) pointed out that physical conditioning influences the degree of elevation of this and other isoenzymes in serum. As indicated above, the existence of several of these enzymes in blood platelets could also influence serum measurements if the platelet count should change significantly during an experiment.

Information about blood enzyme changes in overt DS is scanty. Stegal and Smith (1972) noted marked increases in CPK levels after both fast and slow decompression of miniature

swine whereas LDH levels fell in the same samples. These authors also found laboratory evidence of disseminated intravascular coagulation. Using the treadmill test devised by Philp and Gowdey (1962), Powell (1973) decompressed rats, rabbits, and guinea pigs and correlated elevations in serum isoenzymes with the severity of DS. In the absence of overt signs of DS, no elevation of enzymes was observed. LDH and CPK levels tended to rise in less severely affected animals and severe DS was accompanied by rises in GOT and GPT. The authors felt the pattern was indicative of myocardial damage. Using a similar approach Freeman and Philp (1974) found increases in LDH and GOT levels in moderately affected rats 24 hr after decompression and severely affected animals showed even greater levels of these enzymes. The results of assays performed immediately after decompression were equivocal, suggesting that blood isoenzyme assays may be of greatest clinical use in cases of DS where the onset of symptoms is delayed.

This delay in the rise of blood isoenzyme levels has been observed in other pathological states. Coodley (1966) pointed out that GOT levels in serum do not peak for 24-48 hr after myocardial infarction, with increases in LDH being delayed even more. In his opinion, the HBD isoenzyme form of LDH is more specific for infarction and HBD-LDH levels more useful than total LDH activity. He also found that increased CPK levels were highly specific for myocardial infarction 12-72 hr after the event, provided that the patient was euthyroid and that no brain damage or skeletal muscle disease was present. Authorities in this field generally agree that the absolute increases in blood isoenzyme levels correlate well with the extent of tissue damage, that the temporal factor is important and varies from one enzyme to another, and that the pattern of enzyme changes is dependent upon the organ incurring the injury (Wroblewski 1958; Kibe and Nilsson 1967; Ramsey, Yap, and Spector 1968; Nerenberg and Pogojeff 1969). The infusion of norepinephrine into anesthetized dogs has been shown to increase circulating levels of GOT and this response can be blocked by adrenergic blocking drugs (Loegering and Critz 1968). Nonspecific stress responses undoubtedly affect isoenzyme levels in divers and complicate the interpretation of data.

CATECHOLAMINES AND CORTICOSTEROIDS

Evidence from human diving and decompression experiments suggests that a stress response is not uncommon. Elevations in blood and urine levels of catecholamines and corticosteroids and their metabolites during compression and during or after decompression have been demonstrated by several authors (Schaefer, Bond, Mazzone, Carey, and Dougherty 1968; Chouteau 1969; MacInnis and Bond 1969; Bühlmann et al. 1970; Waldvogel and Bühlmann 1968; Bennett and Gray 1971). Decreases in blood cortisol levels have also been reported during compression (Chouteau 1969) and following decompression (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972; Beckman and Smith 1972; Martin et al. 1973). These reductions have been attributed variously to increased utilization as an extension of the stress reaction or to decreased output because of blockage of the capillary microcirculation of the adrenals by bubbles. Gersh and Catchpole (1946) demonstrated bubble formation in the adrenal cortex of decompressed rabbits.

Lambertsen (1968) pointed out that DS constitutes a form of stress resulting in the increased output of catecholamines from the adrenal medulla and he elaborated on the hemodynamic consequences and their significance in DS. Existing evidence indicates that diving and/or compression-decompression may cause increased catecholamine output in the absence of DS. This may initiate a complex sequence of events. In addition to elevating free fatty acid (FFA) levels, (see following section) catecholamines may increase Factor VIII

activity (Nour–Eldin 1967), increase clotting activity, shorten platelet half-life (Ozge, Mustard, Hegardt, Rowsell, and Downie 1963) and perhaps predispose to thrombus formation (Ozge et al. 1963; Rowsell, Hegardt, Downie, and Mustard 1966). Catecholamines have been shown to aggregate platelets in vitro (Clayton and Cross 1963; Mills and Roberts 1967b). As discussed previously, catecholamines may also elevate blood isoenzyme levels. Most of these effects may also be triggered by elevated plasma lipid levels, and a complex interaction between these two factors undoubtedly exists.

PLASMA LIPIDS

Ever since Vernon (1907) observed that gaseous nitrogen was 5.3 times more soluble in fats than in water, considerable attention has been given to the possible influence of body lipids in the etiology of decompression sickness. Most of the early work centered on the role of storage fat depots as nitrogen reservoirs. It was not until 1945 that Berg, Harris, Whittaker, and Twitty recognized the possible significance of plasma lipids. Because their experiments in vitro showed that hydrophobic surfaces such as lanolin and paraffin retained minute air films which acted as nuclei for bubble growth, they suspected that a similar phenomenon might occur in vivo. Studies with hyperlipemic animals, however, failed to yield supporting evidence for this hypothesis.

Interest in plasma lipids was renewed when it was found that fat embolism was a not-uncommon post-mortem finding in human fatalities from DS, particularly following decompression to high altitudes (Haymaker and Davison 1950; Haymaker and Johnston 1955). Haymaker, Johnston, and Downey (1956) reported two fatalities after high-altitude flying. Both victims had histopathological evidence of extensive fat embolism and both had a patent *foramen ovale*. The authors also noted "intense generalized lipemia" and pointed out that the patent *foramen ovale* would permit the entry of venous gas bubbles, which otherwise would be filtered out by the lungs, into the left side of the heart, and hence reach the brain and other vital organs. The same would, of course, be true for lipid emboli. Subsequently, laboratory experiments confirmed the presence of fat emboli in various organs and tissues in animals with severe DS (Clay 1963; Cockett et al. 1965).

Barthélémy (1963), in commenting on the ameliorative action of heparin in both experimental and clinical DS, speculated that some of this benefit might derive from the known lipemia-clearing action of the drug. Our laboratory (Philp 1964) found that anticoagulation with coumarins did not afford significant protection against DS in rats whereas an experimental antilipemic agent did so, thus providing supporting evidence for Barthélémy's suggestion. Further studies in our laboratory, using the rat-treadmill decompression test, demonstrated that susceptibility to DS was increased following alimentary lipemia. Severity was related to plasma lipid levels, with the paradoxical exception of severely afflicted animals, in which there was a marked reduction in circulation lipids (Philp et al. 1967). We postulated that intravascular bubbles triggered the aggregation of platelets and that coalesced plasma lipids became incorporated into such aggregates. The involvement of lipids in clinical thrombi has been noted (Mustard, Murphy, Rowsell, and Downie 1964.) The absence of a significant shift in the gas chromatography spectrum of neutral lipids or phospholipids following DS supported our hypothesis that the reduction in total plasma lipids was a physical, rather than biochemical, phenomenon (Clark, Philp, and Gowdey 1969a). Previously, lipid emboli associated with clinical or experimental DS had been thought to derive from bone marrow fat or lipid depots. Kalberer (1969) demonstrated no difference in the extent of lipid emboli in the lungs of thin mice with DS as compared to obese litter-mates, nor were they able to correlate the severity of DS with the degree of lipid embolization. Earlier Reidbord (1967) found no difference in the incidence of pulmonary

fat emboli between rabbits fed a normal diet, those fed a high cholesterol diet, and those with fatty livers induced by treatment with ethionine. Hartveit, Lystad, and Minken (1968) saw fat emboli in the right ventricle, coronary arteries, and kidneys of rabbits and mice following the rapid intravenous injection of air, further indicating that the source of such emboli is unlikely to be tissue fat. Pauley and Cockett (1970) felt that the coalescence of plasma lipids was the most likely source of fat emboli. Our laboratory recently obtained electron microscopic evidence that lipid particles become incorporated at the gas-liquid interface of intravascular bubbles produced in rats by rapid decompression (Philp, Inwood, and Warren 1972; Warren, Philp, and Inwood 1973). The trapping of such thrombi, composed of bubbles, platelets, and lipids, would explain the disappearance of plasma lipids from the circulating blood which we observed previously in rats severely affected with DS.

Changes in plasma lipid levels in man have been observed both in chamber dives and in open-water dives. Radomski and Bennett (1970) recorded moderate but statistically significant decreases in FFA and cholesterol levels during a 30-min HeO_2 chamber dive to 200 fsw (7.1 ATA), whereas Waldvogel and Bühlmann (1968) did not see any clear-cut changes in cholesterol levels of two subjects following a HeO_2 saturation dive at 21-22 ATA. Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski (1972) showed slight but statistically significant increases in serum FFA levels in subjects after a 10-min exposure to 10.1 ATA (air). The TEKTITE II missions (Beckman and Smith 1972) did not appear to elicit any significant postdive changes of cholesterol levels in the divers. Philp, Inwood, Ackles, and Radomski (1974) obtained evidence of postdive elevations in FFA after a 1-hr chamber air dive to 4 ATA. Martin et al. (1973) reported similar postdive increases in FFA levels using the same dive profile. Triglyceride and cholesterol levels remained unchanged. Air saturation dives (2.5 ATA) in the HYDRO-LAB habitat showed a slight but progressive reduction in FFA and cholesterol values for 2-3 days postdive (Philp, Freeman, Francey, and Ackles 1974). Changes in FFA levels appear to have been encountered more commonly in divers than changes in cholesterol or triglycerides. Since catecholamines have been shown to elicit a lipolytic effect with elevation in serum FFA's (Gordon and Cherkes 1956; White and Engel 1958; Mayer, Moran, and Fain 1961; Burns and Colville 1962), such postdive increases probably represent a generalized stress response.

Elevated plasma lipids have been shown experimentally to accelerate blood clotting (MacFarlane, Trevan, and Attwood 1941; Fullerton, Davie, and Anastasopoulos 1953; Poole 1955; O'Brien 1957; McDonald and Edgill 1958; Margolis 1962), favor experimental thrombogenesis (Thomas and Hartroft 1959; Gresham and Howard 1960; Connor and Poole 1961; Mustard, Murphy, Rowsell, and Downie 1962; Connor, Hoak, and Warner 1963; Hoak 1964; Born and Philp 1965; Warner, Hoak, and Connor 1967), increase platelet adhesiveness (Cullen and Swank 1954; McDonald and Edgill 1958; Hellem 1960; Kerr, Pirrie, MacAulay, and Bronte-Stewart 1965; Philp and Wright 1965), precipitate red cell and platelet aggregation in vivo (Thompson, Williams, and Walters 1969), reduce the circulating platelet count (Loughry and Cole 1954; Meng, Cress, and Youmans 1958; Philp and Wright 1965), and aggregate platelets in vitro (Haslam 1964; Kerr et al. 1965; Farbiszewski, Skrzydlewski, and Worowski 1969). In the light of these observations it is small wonder that elevated lipid levels increase the incidence and severity of experimental DS and it would seem reasonable to assume that plasma lipids play a significant role in the etiology of clinical DS.

PLASMA PROTEINS

Although changes in plasma proteins have been reported in association with compression-decompression, the results have been equivocal and difficult to interpret. Radomski and Bennett (1970) found significant decreases in albumin and total protein levels following

decompression from 10 ATA HeO_2 and felt this to be due to increased capillary permeability and fluid shifts. Conversely, Beckman and Smith (1972) found slight but statistically significant increases in total plasma protein in two groups of TEKTITE II divers, which probably reflected the state of hydration at the time. These authors also found increases in angiotensin I and unexplained increases in immunoreactive proteins. Other investigators (Waldvogel and Bühlmann 1968; Bühlmann et al. 1970; Philp, Inwood, Ackles, and Radomski 1974) were unable to find significant shifts in albumin or total proteins following a variety of compression-decompression profiles. Earlier, Smith and Brown (1951) reported significant increases in the total plasma proteins of cats decompressed to simulated high altitude. Because PCV decreased, they did not believe this to reflect hemoconcentration but rather felt that it might be due to the release of stored protein. It is most likely, however, that changes observed in man are secondary to fluid shifts. It is of interest to note that Bove, Hallenbeck, and Elliott (1974) found that Cr^{51}-labeled red cells proved a more reliable indicator of fluid shifts in dogs with bends than did I^{125}-labeled albumin. These authors found that limb bends were not associated with hemoconcentration whereas paralyzed dogs showed loss of plasma.

DRUGS AND DECOMPRESSION SICKNESS

Early investigations on the effects of drugs on DS were aimed at the alleviation or prevention of joint pain in high-altitude aviators. A number of WW II military reports on this subject were reviewed by Adler (1964). A variety of narcotic and nonnarcotic drugs, including aspirin, were tried without notable success. In one report, dextroamphetamine significantly reduced the incidence of incapacitating bends, but other workers were unable to confirm this observation. Aminophylline was claimed to reduce the incidence and severity of bends at altitude. Subsequently other workers (Campbell and Spencer 1969) showed that theophylline administered to guinea pigs by means of a nebulizer offered protection against DS. Williams, Lyons, Bridge, and Cook (1946), however, did not find that aminophylline provided any significant protection against DS for subjects decompressed to simulated high altitude, nor did analgesics, including aspirin, but other authors (Smith 1946; Wünsche 1958) reported that narcotics and sedatives did reduce the severity of DS somewhat. Lyle and Dahl (1961) reported that protection against DS was afforded to experimental animals by various local and general anesthetics and autonomic depressants. Bennett (1972) reviewed much of the current work relating to the use of pharmacological agents in diving.

The pioneer work of the French regarding the protective action of chlorpromazine and heparin has already been discussed. Our laboratory (Philp 1964) later confirmed that heparin reduced the incidence and severity of DS in rats and showed that an experimental antilipemic agent (partially depolymerized hyaluronic acid) had similar properties whereas coumarin anticoagulants did not. Hartveit et al. (1968) found that prior heparinization improved the survival of rapidly decompressed mice. Campbell and Ward (1968) reported that heparin and papaverine, administered to guinea pigs by nebulizer, afforded protection against DS whereas Reeves and Workman (1971) were unable to find any prophylactic or therapeutic benefit of heparin against DS in dogs. More recently McCormick, Philbrick, Holland, and Harrill (1973) measured cochlear potential function in guinea pigs and found a reduction associated with DS. This loss of function was prevented by heparin. These authors felt that the loss of function, and possibly the sudden onset of deafness sometimes seen in divers following decompression, might be related to a microthrombotic syndrome.

More recent work in our laboratory (Inwood and Philp 1973), using the rat decompression model, found that both heparin and dicumarol provided apparent but not

statistically significant protection against DS. Highly significant reductions in morbidity and mortality were obtained with an experimental antiplatelet agent (VK774, Pharma Research Canada Ltd.), an experimental drug which has antiplatelet and anti-blood sludging properties (polyoxalkol, Cutter Laboratories), and the drug Arvin (Twyford Laboratories) which converts fibrinogen to an unclottable derivative. Drugs which inhibit the fibrinolytic process (epsilon aminocaproic acid, Amicar, Lederle; Trasylol, Bayer) caused statistically significant increases in morbidity and mortality and the analgesics apsirin and indomethacin had no effect. Bennett and Brock (1969) also failed to detect any beneficial effect of aspirin in experimental DS. Ehm et al. (1971) and Schimpf, Piechotta, Ehm, and Fritsch (1971) reported that both Trasylol and heparin afforded protection against DS to decompressed rabbits and dogs. This observation is difficult to reconcile with the effect of Trasylol on the clotting system. Nevertheless Fasciani (1970) used Trasylol both systemically and by intra-articular injection in divers with Type I and Type II bends and reported that it accelerated recovery when used in conjunction with recompression and oxygen therapy. He appeared to attribute these beneficial actions to a general proteolytic activity of the drug.

Many drugs have been shown experimentally to increase the incidence and severity of bends. These include carbachol, doriden (glutethimide), phenacetin (acetophenetidin), epinephrine, leptazol (pentylenetetrazol), megimide (bemegride) and hyoscine (Bennett and Brock 1969), serotonin (Clark, Philp, and Gowdey 1969b) and bradykinin (Chryssanthou, Kalberer, Kooperstein, and Antapol 1964). These last authors also reported that bradykinin antagonists reduced the incidence of DS in mice. Further, they have identified a humoral substance which they have named Smooth-Muscle Activating Factor (SMAF) (Chryssanthou, Teichner, Golstein, Kalberer, and Antapol 1970) which, when injected into mice, will increase their susceptibility to DS and which can be antagonized by certain bradykinin antagonists (Chryssanthou, Kalberer, Kooperstein, and Anatapol 1971). The possible involvement of bradykinin in the pathophysiology of DS might provide an explanation for the apparently controversial results which have been obtained with the drug Trasylol. It has been shown that Trasylol is capable of inhibiting a variety of protease enzymes including kallikrein, which liberates kinins from precursors, and some enzymes involved in the early stages of the coagulation process (Haberland 1970). Thus, whether Trasylol demonstrates beneficial or detrimental effects might well depend upon the extent of involvement of the clotting system in a given situation. If fibrin formation is proceeding actively, Trasylol could have adverse effects by inhibiting fibrinolysis. At an earlier stage, the antibradykinin activity might be beneficial provided that the rate of fibrin production is minimal. Trasylol has been shown to relieve morphine-resistant myocardial pain and this effect is thought to be due to its inhibitory action on kallikrein (Sicuteri, Del Bianco, and Faniciullaia 1970).

Malette, Fitzgerald, and Eiseman (1960), reporting on the protective effects of the surfactant methylsiloxone (Antifoam A, Dow-Corning) against DS in rapidly decompressed rats, were the first to draw attention to the formation of a coagulavelum, or envelope around intravascular bubbles, and thought that the beneficial effects of methylsiloxone were in some way related to this coagulavelum. Subsequently, work in our laboratory indicated that this envelope consists of plasma proteins, lipids, and aggregated platelets (Philp, Inwood, and Warren 1972; Warren et al. 1973). Experiments in our laboratory with antiplatelet drugs related to the coronary vasodilator agent dipyridamole (Persantine, Ciba-Geigy) indicated that such agents were capable of affording protection against DS in rats and, moreover, there was a direct relationship between their potency as inhibitors of aggregation and their effectiveness in protecting against bends (Inwood and Philp 1973). Dipyridamole itself is a very weak inhibitor of aggregation (Philp, Francey, and McElroy 1973) and afforded no

protection against DS in rats (Clark et al. 1969b), whereas more potent derivatives (RA255, VK774, VK744) afforded significant protection (Inwood and Philp 1973). Recently (Philp, Inwood, Ackles, and Radomski 1974) we reported that two of these agents (RA255 and VK744), when administered to volunteers before and after a simulated dive, significantly reduced the postdive loss of circulating platelets which occurred in placebo-treated control subjects. Inhibition of platelet function tests was also observed in the drug-treated groups.

The replacement of fluids in severe DS by plasma expanders such as dextran-40, as originally advocated by Cockett and Nakamura (1964a,b) would now appear to be a well-established practice. Saumarez et al. (1973) claimed to have successfully treated a case of Type II bends, without recompression, using dextran-40, heparin, and aminophylline. Hemoconcentration and some depression of platelets were evident. It is conceivable that some of the benefits of dextran-40 might derive from the fact that it also inhibits platelet adhesion and aggregation (Bygdeman and Eliasson 1967). Most drugs which have been shown to have a beneficial effect in experimental DS have, in fact, some antiplatelet activity as well. In addition to the dipyridamole derivatives and dextran-40 these include chlorpromazine (Mills and Roberts 1967a; Bounameaux 1971; Mason, Read, Saba, and Shermer 1972; Brinson 1973), heparin (Besterman and Gillett 1972), local anesthetics (Aledort and Niemetz 1968; Deutsch, Lechner, Moser, and Stockinger 1971; Mason et al. 1972), aminophylline (Brinson 1972) and theophylline (Ball, Brereton, Fulwood, Ireland, and Yates 1970; Cole, Robison, and Hartmann 1970; Bounameaux 1971; Mason et al. 1972). While it would be naive to suggest that these all worked via the inhibition of platelet aggregation, it may well be that some common property is involved. The notable failure of aspirin, a well-documented inhibitor of platelet function, to alleviate experimental or clinical DS, may be related to the fact that aspirin, although it inhibits the release reaction of platelet constituents, is not an inhibitor of primary platelet aggregation.

General supportive therapy will not be discussed in detail, but some mention should be made of the possible application of high doses of corticosteroids in cases of DS involving severe circulatory shock. The benefits of this therapeutic approach have been demonstrated in the treatment of clinical shock and probably relate to the dilating action of corticosteroids on post-capillary sphincters with improved venous return as the consequence (Lillehei, Longerbeam, Block, and Manax 1964; Lefer and Verrier 1970; Moran 1970).

SUMMARY

Diving, especially saturation diving, entails manifold stress factors which can influence the formed and chemical elements of the blood. These may include physical stress, psychological stress, weightlessness, dehydration, hypothermia, hyperoxia, inert gas effects, and the production of bubbles during decompression. The changes wrought by these factors do not necessarily operate in the same direction, thus it is not surprising that the interpretation of physiological data collected in diving experiments is fraught with difficulties, particularly in view of their often subtle nature. Nevertheless, an assessment of available information permits some tentative conclusions to be drawn.

The generalized stress response probably accounts for many of the observed changes including elevations of blood catecholamines, FFAs, isoenzymes, leucocytes, and cortisol. In this author's opinion, the partial pressures of oxygen which have been utilized in saturation diving do not appear to be correlated with the elevated isoenzyme levels, suggesting that there is not associated tissue damage. Similarly, the reduction in red-cell count which has been observed frequently in connection with saturation diving appears to correlate better with the occurrence of swimming activity than with oxygen tension and may be related to

intermittent weightlessness and fluid shifts or to some unidentified effect, rather than to suppression of erythropoiesis by hyperoxia.

There appears to be a more substantial relationship between decompression, particularly hazardous decompression, and the observations of thrombocytopenia, increased fibrin formation, and hemoconcentration. It now appears highly likely that most decompressions from any significant depth are accompanied by some degree of bubble formation and the occurrence of DS is probably dependent upon the size, frequency, and location of the bubbles. Evidence from animal experiments strongly indicates that the blood reacts to the intravascular bubble in the same fashion as it would to any other foreign surface. A layer of protein, probably fibrinogen in the main, is deposited at the blood-bubble interface as are coalesced plasma lipids. The protein molecules, oriented with their hydrophilic moieties toward the plasma, present a thrombogenic surface which attracts platelets. This leads, in extreme situations, to platelet aggregation and the release of clotting agents such as platelet phospholipid. This bubble membrane may be stripped off to serve as a locus for additional platelet aggregation. These effects, together with stasis of the blood in occluded vessels, may activate the fibrin clotting system. Experiments with human subjects suggest that the process is occurring, at a much reduced level, even after decompressions which induce no clinical signs of DS. The hemoconcentration which has been observed frequently in association with severe DS is thus likely due to the extravasation of fluid as is commonly encountered in stagnant shock, particularly when disseminated intravascular coagulation is a complication. The incorporation of plasma lipids into microthrombi has been noted and would account for the reduction of plasma lipid levels which has been observed in experimental DS and, to a lesser extent, following decompression of human subjects. The occurrence of lipid emboli in severe DS is well documented and also could be related to the coalescence of plasma lipids. A complex interrelationship also exists between plasma lipids, platelet adhesiveness, and the blood clotting system.

The extent to which these reactions occur would be dependent upon the total surface area of gas which is in contact with blood. Bubble size may be an important factor in determining whether or not changes in platelets and clotting factors will be detected. For example, 10 cc of a gas, if present as bubbles of 100μ diameter, would present a total surface area of approximately 0.6m^2. The same volume of gas, existing as bubbles of only 10μ diameter, would have a total surface area of 6.0m^2. Thus, multiple small bubbles may involve a greater risk of activation of the clotting system than a few, large gas emboli. Some preliminary evidence suggests that the state of an individual's platelet population may have a bearing on the degree of platelet loss, a high percentage of extremely reactive platelets leading to increased loss, and a mild platelet defect having the opposite effect. There is evidence that the most active platelets are removed preferentially from the circulation. Adjunctive therapy for severe DS, when indicated, should thus be directed toward expansion of plasma volume and the inhibition of platelet adhesion and aggregation by platelet-inhibiting drugs. Since dextran-40 possesses both of these attributes, it is currently the agent of choice. Antithrombotic drugs of the future may prove useful prophylactically, especially if the problem of hyperbaric osteonecrosis is proven to have a microthrombotic basis.

Far too little information is available concerning changes in blood isoenzymes, electrolytes, catecholamines, cortisol, etc. in clinical DS. This information must be accumulated in order to evaluate the prognostic and diagnostic usefulness of these tests. Existing information indicates, however, that even a moderately elevated PCV or a slightly depressed platelet count ought to be viewed as an indication for adjunctive therapy.

During the preparation of this manuscript the Government of Canada announced, in the Speech from the Throne opening the spring session of Parliament, that, as part of a reorganization of research granting in this country, the Defence Research Board of Canada would cease to exist as a granting body. This agency has provided continuous research funding to our laboratory since 1962. It is the author's hope that this review will be regarded as a modest, farewell tribute to the agency which has served the field of hyperbaric physiology so well for so many years.

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