Hematology Observations in

Space Flight and Simulated Space Flight

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There is evidence astronauts have decreased red cell mass during space flight. The loss may result from decreased rates of cell production, increased rates of loss or a combination of the two processes. The causes for the red cell depletion have not been defined, and the possibilities are multiple. Previous observations of erythropoeisis in humans and animals, in space flight and in experiments of altered oxygen tensions provide evidence as to causes and mechanisms of the anemia.

Changes which astronauts are subjected to, or which are potential exposures in the event of an environmental control system failure include vibrations, thermal insult, closed ecologic environment, restricted physical activity and hyperoxia. Some of the effects of these alterations of environment on red cell mass are partially described in the following cited experiments.

WEIGHTLESSNESS cannot be simulated at ground level comparable in time and extent to that of space flight. Recently completed studies ( ) in four normal male medical students placed at bed rest for 10 days included quantitation of red cell mass and rates of red cell destruction. The hematocrits, reticulocytes, red cell masses and rates of hemolysis were all normal. Prolongation of similar experiments may be of value but the inability to simulate weightlessness at ground level makes necessary the observations during space flight.

Studies of the effects of VIBRATION on red cell production and in vivo destruction are not available, but it is conceivable that vibration or sound waves may at certain frequencies induce physical destruction of the cell. Examples of physical or mechanical hemolysis include march hemoglobinuria ( ) and the anemia associated with heart valve prosthesis or jet stream

effects in stenotic or in regurgitant valvular heart disease ( ). It has been suggested that ultrasonic vibrations, produced by plastic valve impingement on the metallic prongs of the Starr-Edwards type of valve prosthesis may cause disruption of red cells (Wm. J. Williams). The effect of increased force on red cells such as occurs during lift off have been studied by a group at the Aerospace Medical Center at Dayton (Neil Abramson). Forces of 3 times gravity for a period of 90 minutes in the human do not cause hematocrit changes, but there are increased numbers of macrocytes an increase in mean corpuscular volume, an increase in osmotic fragility of red cells and fragmentation of cells.

THERMAL INJURY to red cells by excessive heating or cooling under in vivo or in vitro conditions are known to occur. Temperatures of less than 4° C cause red cell damage by the formation of crystals of water within the red cells, which leads to membrane damage and hemolysis under in vitro or in vivo conditions unless special suspending media and freezing methods are used. The heating of blood in vitro from 47 to 60° C causes morphologic changes with the formation of microspherocytes and red cell fragments. This technique has been used to "heat-crack" red cells which are then labelled with radiochromate and the very rapid rate of the damaged cells by the spleen used to provide scintillation scans of the spleen.

Burns take place at skin temperatures of 45 to 50°C. At temperatures of approximately 40°C there is no change in red cell morphology, but the cells have increased osmotic fragility and red cell survival studies have not been performed. It seems entirely possible that the total body or a portion of the body may be exposed to ambient temperatures which might decrease red survival, but fail to produce skin burns. This would require an exposure in the order of 70° C (160° F) or more and water vapor and air flow over skin would be

important variables. Measurements of rates of red cell in vivo destruction should be done at different skin temperatures from normal to approximately 40° C. Additionally, it may be suggested that certain individuals, may have increased sensitivity to heat. An animal model exists, the species of mice (Peromyscus) have a form of hereditary spherocytosis and are very sensitive to increased ambient temperature. Elevations of the surrounding temperature to 80-85° F causes massive hemolysis and death in these animals. Whether or not persons with spherocytosis have similar heat susceptibility is unknown.

HYPOXIA in humans and animals has been extensively studied and the relations between chronic and acute hypoxia of varied degree and erythropoeisis well documented. These many studies provide several important general conclusions.

Tissues are apparently the site of important sensors, which respond to variations in tissue oxygen tension and react with an elaboration of erythropoeitin, a substance which acts as a regulator of erythropoeisis. Precise definition of the organs, cells or cell organelles which elaborate erythropoeitin is not available, but there is evidence that the kidneys are sites of erythropoeitin production. The hypoxic stimulus may be anemia, ambient hypoxia, or altered oxygen transport proteins (such as methemoglobin). There is a prompt response to hypoxia, elaboration of erythropoeitin takes place which causes an increased division of stem cells into the red cell pool and thus increased rates of formation of red cells. Since the red cells in ambient hypoxia have normal life span and total blood volume is not altered, there is a concommitant increase in hematocrit. The entire mechanism is responsive and changes in rates of red cell production have been demonstrated to occur within hours of the ambient or anemic hypoxia.

Studies of the effects of hyperoxia on erythropoeisis are fewer than of hypoxia. Transfusional hyperoxia or exposure to relative ambient hyperoxia causes an abrupt decrease in the rate of red cell production and a downward adjustment of red cell mass.

When animals or man ~~are~~ is exposed to hyperoxia, ~~the factors of importance are~~ the duration and degree (partial pressure) of oxygen exposure of the cell or tissue are of prime importance. Untoward effects on respiratory tract, renal function reticuloendothelial system, etc., ~~should be assessed since such dysfunction~~ may modify the manner or rate in which red cells are synthesized and destroyed. For example, the production of pulmonary disease by hyperoxia might result in improper ventilation/perfusion of the lungs and consequently hypoxia rather than hyperoxia.

The studies of hyperoxia in man prior to 1945 are summarized by Bean. ( ) The observations were done with imprecise ~~are subject to less precise~~ methods for ~~of~~ measurement of concentrations of cells, and measurements ~~of~~ red cell production and destruction were ~~not available~~. Fall and von Friedrich in 1923 and Izumijama (1928) found that breathing O_2 at pressures of +8 to 10 cm. H_2O by mask caused a decreased hemoglobin concentration. Anthony and Bechthold (1939) found that O_2 breathing caused temporary fall in Hb within a few minutes. Hitzenberg and Molenar (1934) reported the breathing of oxygen for 20 minutes caused decreased cell diameter, cell volume, and an increased plasma volume. Ten persons studied by Anthony and Bechthold had decreased cell diameter after breathing oxygen. In 1944, Reinhardt showed that exposure to 1 atmosphere of 100 per cent oxygen concentration for 6-8 days caused decreased rates of erythropoeisis in patients with sickle disease. The work done prior to 1945 gave little quantitative data of the effects of hyperoxia on red cell formation and destruction.

From 1945 to 1960 little data was accumulated regarding hyperoxia, but the use of ~~therapeuti~~ hyperbaric oxygen ~~as a therapeutic measure~~ in therapy, and as an investigational technique, and the underwater and space explorations stimulated ~~a resurgent~~ interest in the effects of hyperoxia.

Hendler (1963, Fed. Proc., Aug., 1963) reported the results of a simulated flight in three persons, in which a modest fall in hematocrit concentration was ascribed to phlebotomies incurred during the study period. Conroe (1945), Hall (1960,1962), Gallagher (1965), and Nobrega (1965), and Dubois (1966) reported studies in humans in which no erythrocytic changes were noted with various degrees and times of hyperoxia. Others (Morgan, 1961; Melch, 1961; Helvey, 1962; Mamman,1963; Morgan, 1963; Critz, 1964; Herlocher, 1964; Robertson, 1964; Zalusky, 1964; and Fischer, 1966) have reported a variety of hematologic changes with hyperoxia.

These apparently contradictory results are impressive and not easily resolved on the basis of the times and degrees of exposure to hyperoxia. The various studies were often done with different methods of measurement (hematocrit or Hb concentrations, reticulocyte determination, red cell mass measurements, erythrokinetics, etc.), which adds to the difficulty of evaluation of the effects of hyperoxia on red cell formation and destruction.

~~Of these~~ The reports, ~~that~~ of Zalusky et al, is worthy of particular attention because of the detailed studies, done with precise methods of measurement of rate of red cell production and destruction. Four subjects were exposed to oxygen at 700 mm Hg pO_2, and another four to 258 mm Hg pO_2 for periods of 30 days. There were reductions of hematocrit of 6.7 and 9.1 per cent respectively in the two groups, but no reticulocytosis, nor shortening of RBC Cr^{51} survival. Serial or repeated cell mass determinations were not performed during the exposure period and rate of red cell formation was done after two weeks of exposure. The data allow the impression that accelerated hemolysis, if present, was mild and that if suppression of red cell production occurred,

it was minimal. There was a post-oxygen exposure reticulocytosis which suggests that the hyperoxia had caused erythropoeitic suppression.

The observations of Fischer on three normal men exposed for 8 days to 230 mm Hg pO_2 gave no evidence of hemolysis. The astronauts of Gemini IV, V, and VII, had decreased red cell masses (Berry, et al). There was no apparent relation between decrement of red cell mass and the time of space flight. Astronauts McDivit and White had 18 and 12 per cent decreases during a four day flight whereas Lovell and Borman had similar decreases of 20 and 5 per cent during flight of fourteen days. Fischer reported that three of four astronauts in Gemini IV and VII had decreased red cell life spans but the data are less than ideal to make this conclusion. ~~obtained do not allow great confidence.~~

A facet not fully considered in astronaut environment hyperoxia ~~was~~ is the oxygen exposure incurred during the pre-flight period. Data provided by Dr. Lawrence Dietlein on exposures of Captain Lovell and Colonel Borman on GT-7 showed that Captain Lovell had an exposure of 1 hour at 198 mm Hg pO_2 9 1/4 hours at 760 mm Hg pO_2, and 26 minutes at 950 mm Hg pO_2 during the one month period prior to flight. Of this exposure, ~~only~~ 2 hours and 35 minutes occurred after the initial measurement of ~~the~~ red cell mass and prior to space flight. Colonel Borman had ~~a similar~~ an exposure of 2 hours and 5 minutes at 198 mm Hg pO_2, 9 hours and 30 minutes at 760 mm Hg pO_2 and 16 minutes at 950 mm Hg pO_2. Three hours and 35 minutes occurred after the red cell mass determination and prior to space flight. These data do not include exposure to hyperoxia during the immediate pre-flight period. ~~but the exposures seem insufficient to cause suppression of red cell formation or hemolysis.~~

Studies of various animals subjected to hyperoxia give different results, only part of which are explained on time and degree of hyperoxia. The most systematic studies available are those of Mengel, designed to obtain information in the normal and in the vitamin E deficient mouse and rat.

Severe, sometimes lethal hemolysis of the mouse occurs on exposures to hyperbaric oxygen. In the vitamin E deficient animal, lesser ~~degrees of times of~~ hyperbaric oxygen exposure causes hemolysis. Normal mice exposed 70 hours at one atmosphere to 100 per cent oxygen show accelerated hemolysis. Experiments with the use of lesser degrees of hyperoxia are currently being done.

Measurement of rates of red cell formation and of rates of destruction at various exposures of hyperoxia have not been done in a systematic fashion. Such studies are needed in both animals and in man with a wide dosage range, with particular attention to low level hyperoxia for prolonged periods. The peroxidation changes in red cell membranes which occur at greater degrees of hyperoxia and particularly in antioxidant depleted (alpha tocopherol) animals make clear the possibility of similar, more subtle changes at lesser oxygen pressures. Whether the red cell is unique in this regard is not known, but seems unlikely, in view of the changes already described in other lipid membrane structures such as pulmonary alveolar cells, hepatic cells and, of great interest, mitochondria. Thus it seems ~~possible~~ that the peculiar ability to study the red cell (because of availability and applicable techniques) may have ~~fortuitously~~ provided a cell system or model, which may be used as an indicator of damage in many other types of cells. Whether other cells have greater, lesser, or similar susceptibility to damage by hyperoxia must be determined as well as whether such damage causes immediate, or more remote illness.

A recurrent theme in thought in the biomedical aspects of space flight is the factor of weightlessness. There is no apparent reason that the space environment except for weightlessness and possibly certain types of radiation exposure cannot be simulated. Despite the large cost of studies in such an environment, it seems necessary that these be obtained. This information is necessary if reasonable predictions of safety in space flight

To obtain the needed data, a systematic study of the dose response relations of the various possible causative agents in sub-human species of animals and humans (when possible) should be done. These should emphasize studies of low dose hyperoxia over protracted periods (i.e., weeks to months). Precise methods must be used and multiple methods would be advisable. Red cell lifespan should be measured by DFP^{32} or glycine C^{14} methods, rather than the radiochromate methods and determination of rates of endogenous production of carbone monoxide should be made. Wherever possible, precise morphologic studies of reticulocytes and bone marrow must be obtained. These are to be studied for subcellular abnormalities as well as cell membrane and hemoglobin characteristics. At the same time, and on the same animals, rates of erythrocyte production must be obtained. Additional challenges should be incorporated into some experiments such as phlebotomy, to ~~further~~ detect possible abnormalities in ability to regenerate cells.

LEUKOCYTES

Currently there is little, or no reason to expect that the space cabin, or other projected space environment control systems will impose unusual alterations of mans ability to effectively control infection. A possible exception to this would be the ~~relatively unlikely~~ occurrence of excessive exposure to ionizing radiation. Infection as herein discussed is caused by bacteria, fungi, viruses, and less commonly by various parasites. The infection defense mechanisms include the following cells and cell products: Skin and/or mucous membranes, polymorphonuclear leukocytes, mononuclear phagocytes, lymphocytes and plasma cells, fibroblasts and immune-globulins.

Response to infection may be evaluated with a multifaceted approach. These may be done by induction in animals and humans of the cellular inflammatory cycle (Rebuck or Rinch, skin window methods), phagocytosis, quantitations of

of various types of immunoglobulins, in vivo clearance of particles by phagocytosis and determination of cutaneous reactivity (cellular antibody). These observations should be done at ground level and in space. The effects of weightlessness on resistance to infection will require that measurements be done during space flight. The simplest of these which would provide the most information would be those of the inflammatory cycle studies, by techniques described by Rebuck. Quantitation of granulocytes, measurement of their ability for chemotaxis, phagocytosis and respiration should be done prior to and following space travel.

Lymphocytic numbers, morphology, and function are possible only by the use of relatively complex, sophisticated methods which would not be possible during space flight. In vitro lymphocyte cultures with effects of transforming agents and examination of ability to synthesize immunoglobulins may be performed before and after space flight. Similarly, the reticuloendothelial system may be studied before and after flight by measurement of disappearance rates of colloid particles from the blood.

The ~~suggested~~ studies should be done on ground, ~~but the factor of weightlessness would require studies~~ before and after flight. ~~or much less feasibly, during flight~~.

HEMOSTASIS:

Hemostasis has not been studied under space flight simulated conditions. It seems ~~most~~ likely that abnormalities of coagulation proteins will not be found and if abnormal hemostasis occurs, it would be related to weightlessness or acceleration and deceleration. Because of the seriousness of disability which would be imposed by hemostatic defects, it is necessary to obtain at least minimal observations of hemostasis. These would entail a series of ~~quite~~ detailed analyses of coagulation proteins, platelet function and vascular integrity prior to and after space flight.