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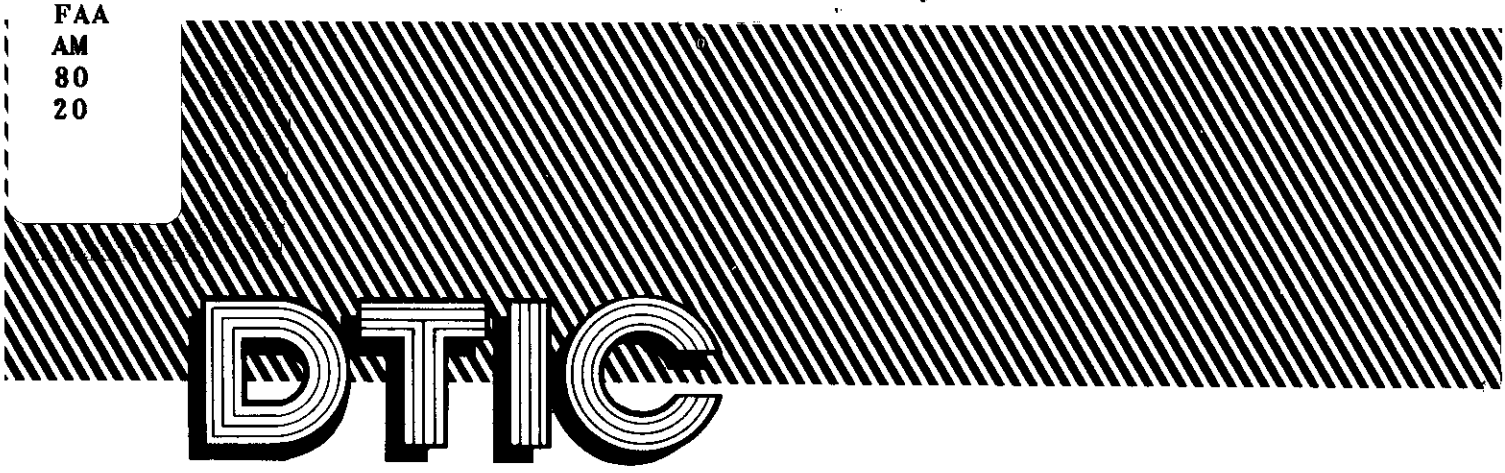

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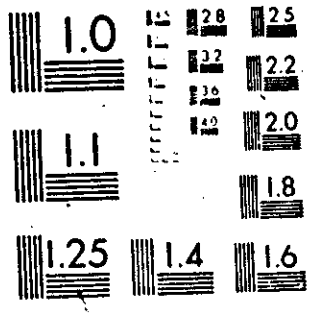

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VOCATIONAL OPTIONS FOR THOSE WITH SICKLE CELL TRAIT: QUESTIONS ABOUT HYPOXEMIA AND THE INDUSTRIAL ENVIRONMENT

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November 1980

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16. Abstract

This report is based on an oral presentation to physicians interested in the treatment of patients with sickle cell disease. Many patients have parents and siblings who possess the sickle cell trait (SCT), and who often require not only genetic counseling, but also information about their own health. Some have been informed that they cannot pursue careers in aviation. Some have been told that they are at special risk from the hypoxemic effects of heavy exertion, especially the exertion associated with some sports. A few believe that certain elements of the industrial environment are unusually hazardous to them. An examination of the literature reveals little evidence in support of any of these beliefs. Most, if not all, unfavorable reports are clouded by faults of various kinds. All of them are of anecdotal type, based on small numbers of cases; the evidence offered is circumstantial. On the other hand, experiments designed to test the susceptibility of those with SCT have yielded favorable results. Studies of large populations indicate that those with the trait have normal health and normal life expectancy. Also, there are almost as many favorable anecdotal reports as there are negative ones. We must conclude that people with SCT are just as tolerant to aviation and industrial environments as those who are homozygous for hemoglobin A. Also, there are strong indications that those with SCT are not endangered by heavy physical exertion, including the exertion of athletic competition.

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VOCATIONAL OPTIONS FOR THOSE WITH SICKLE CELL TRAIT: QUESTIONS ABOUT HYPOXEMIA AND THE INDUSTRIAL ENVIRONMENT*

INTRODUCTION

It may be characteristic of panel discussions that they seldom follow the planned form. This is certainly true for the discussion we report here. Because of the many questions and comments from the floor and from other panel members, the written form and the title have been changed somewhat to best represent the tone of our discussion. I hope that those who attended the actual session will approve.

This section will present some vocational considerations for those who possess the sickle cell trait (SCT). Dr. Adams will present separately a discussion of the profession, and avocation, of diving; here we will consider other vocations, especially those that may involve exposure to moderate hypoxia and to industrial chemicals.

In our earliest courses in physiology we learned that hypoxemia can be caused through a number of mechanisms. Two of these mechanisms are important to the present discussion: (i) oxygen tensions can be reduced on the arterial side through a reduction of ambient barometric pressure, which lowers the partial pressure of oxygen in the alveoli; and (ii) venous and capillary oxygen tensions can be reduced when tissue oxygen consumption is sufficiently augmented; during certain kinds of physical exertion (e.g., the hundred-yard dash), this mechanism is compounded in effect by breathholding.

When the blood pO_2 is lowered sufficiently, erythrocytes containing hemoglobin S (HbS) will become sickled and so inelastic that they cannot pass through the smallest vessels. If these vessels are blocked, tissue oxygen consumption will continue, pO_2 will be further reduced, more red cells will sickle, and the vicious cycle of a local or general sickling crisis will ensue.

In this paper we will evaluate the importance of these hypoxia-induced effects and of some industrial chemicals to individuals with SCT.

AEROMEDICAL IMPLICATIONS OF SICKLE CELL TRAIT

Although it is now established that most people with SCT are as healthy and as long lived as those without HbS in their erythrocytes, we still see occasional reports that associate the trait with a variety of pathological conditions. For the most part it is unclear whether the authors of these reports consider SCT to be a cause of these conditions, or merely contributory to the morbid consequences of the primary cause. In reports dealing with the effects of high altitude, however, the claim is clearly made: type AS red cells will sickle under hypoxic conditions; collapse at altitude, especially when there are signs and symptoms of splenic or bowel infarction, is directly attributable to a sickling crisis.

*A portion of the workshop: "Is Sickle Cell Trait a Health Hazard?", held during the postgraduate course, SICKLE CELL DISEASE: CHALLENGE OF THE EIGHTIES, sponsored by Howard University Center for Sickle Cell Disease, in cooperation with the Office of Continuing Medical Education, Howard University College of Medicine.

There have been quite a few of these reports. Rather than consider them individually, let me summarize them in a single hypothetical case:

> A civilian pilot, flying under instrument flight rules, is within 2 h of his destination when he is called by Air Route Traffic Control Center and informed of severe weather ahead. The Center directs him to a new heading to avoid the storm, and instructs him to ascend from his present altitude of 9,000 ft to an altitude of 11,000 ft. Although he does not have oxygen equipment aboard, this higher altitude is of no concern because the Federal Aviation Regulations (Part 91.32) do not require him to use oxygen until he flies above an altitude of 12,500 ft (and below 14,000 ft) for over 30 min.
>
> Later, the pilot calls Center to inform them that he is on the new course and at the higher altitude. However, he has encountered severe weather and turbulence is extreme. His transmission is interrupted and radio contact is permanently lost. Next morning the crash site is located and the pilot's body found in the wreckage. Autopsy protocol reveals severe impact trauma; in fact, not all of the tissues can be found. Samples of blood and tissues are sent to the FAA's Aviation Toxicology Laboratory in Oklahoma City; tests for drugs, alcohol, and carbon monoxide are negative. Later histological examination, however, reveals sickle-shaped red cells in some organs, and paper electrophoresis results indicate the presence of both HbS and HbA.

The important fact to recognize from this case is that if HbS had not been detected, we might have concluded that the most probable cause of this accident was the weather; the pilot had, after all, reported extreme turbulence just before contact was lost. How much weight should we give to the finding of sickled cells in the tissues? Because of them, should we ignore the weather and rule instead that the pilot had become incapacitated by a sickling crisis at 11,000 ft? We might, if we forgot a well-known fact: there is little oxygen left in a cadaver several hours after death. This fact, and the tendency of some people to ignore it, are important elements in numerous reports naming SCT as a cause of death in otherwise unexplained cases that also involved other possible causes, including alcohol abuse, drugs, and trauma. Rosenheim (1) has warned us that approximately 8 percent of all black people will exhibit sickled red cells at necropsy, and that this finding has no value in establishing the cause of death.

How should we interpret the electrophoretic findings in our hypothetical case? It should be enough to say, after considering the literature on the subject, that electrophoresis can fool us sometimes, especially paper electrophoresis. This is particularly true if we are a bit naive concerning technique. For example, our pilot might have possessed, instead of a pure sickle cell trait, some other, electrophoretically "silent" double mutation, such as Hb-Travis, reported by Moo-Penn et al. (2), in the red cells of an airman who collapsed during a transoceanic flight. This hemoglobin contains two beta substitutions, the B6 substitution of HbS and

another, B142 ALA → VAL. The resulting hemoglobin, besides being susceptible to sickling, is quite unstable. Moo-Penn and his collaborators were able to detect it by cellulose acetate electrophoresis, but it seems likely that non-experts would have difficulty distinguishing it from ordinary HbS. Certainly, paper electrophoresis would not be a satisfactory method for detecting this variant.

The hypothetical case we have just reviewed represents the type of anecdotal evidence upon which former FAA policies were based. Such reports offer poor evidence in support of a ruling that can affect careers. As you know, present FAA policy does not discriminate against the AS phenotype.

As do cells containing only HbS, those containing mixtures of it with HbA and other hemoglobins can also become sickled when the oxygen tension is low enough, but this statement tells us nothing about the threshold altitude for the sickling of SCT cells. Figure 1, taken from the data of Griggs and Harris (3) is more informative. This chart shows, superimposed on a normal oxygen-hemoglobin dissociation curve, the oxygen tensions at which various types of red cells begin to sickle. We can see that there is an impressive difference between the sickling thresholds of SS and of AS cells, which seem refractory to sickling above about 10 Torr. Recently, Benesch et al. (4) have helped to explain this difference by demonstrating that HbF and HbA are incorporated into the HbS polymer that forms under hypoxic conditions, and that the presence of these other hemoglobins enhances the solubility of the polymer.

Using a sort of physiological Dalton's law, we can recalculate the data of Figure 1 to find the altitudes equivalent to these threshold oxygen tensions. Assuming normal values for pH_2O and pCO_2, 47 and 40 Torr:

$$P_B = ((pO_2 + pCO_2) / 0.21) + pH_2O = 285.1 \text{ Torr}$$

when P_B is the total atmospheric pressure, the lower case p denotes partial pressures, and 0.21 is, of course, the fractional concentration of oxygen in air. Using this equation we can calculate that an alveolar pO_2 of 10 Torr should result from exposure to an altitude of about 25,000 ft. This is only an approximation, however, and maybe we have assumed too much in our calculation. We have not taken into account, for example, possible reductions in alveolar pCO_2 that may occur at high altitudes. A more satisfying number would be one obtained from physiological measurements, not of alveolar tensions but of those in the capillaries where sickling, if it occurred, would have its earliest effects. Fortunately, the literature provides us with a fairly useful number; mean capillary oxygen tensions a little above 20 Torr have been measured in human subjects while they breathed air at 22,000 ft (5). Because 20 Torr is twice the tension required to initiate sickling of AS red cells, 22,000 ft seems a reasonable altitude to set as a limit for long-term exposure of individuals with SCT. At this altitude, by the way, most individuals will lose consciousness within about 110 s.

The Federal Aviation Regulations (FAR 91.32a) state:

> No person may operate a civil aircraft . . . . . at cabin pressure altitudes above 14,000 ft (MSL) unless the required minimum flight crew is provided with and

> uses supplemental oxygen during the entire flight at those altitudes . . . . . (nor) . . . . . at cabin pressure altitudes above 15,000 ft (MSL), unless each occupant of the aircraft is provided with supplemental oxygen. (Note: The phrase, "cabin pressure altitudes" is needed here to provide for differences between inside and outside pressures in the case of pressurized, or partially pressurized, aircraft.)

If it appears from the above quotation that passengers of commercial transport aircraft are required to tolerate an altitude of, say, 13,000 ft, this is not the case at all. As I am sure you have guessed, there are other Federal Aviation Regulations (e.g., Part 121)* to be considered. Most passenger aircraft are pressurized to at least 8,000 ft. If a decompression were to occur, oxygen masks would be deployed. Even after a sudden decompression to very high altitudes, everyone, even those with SCT, would have at least 10 s of useful consciousness, time enough to don a mask. Please note such severe decompressions are extremely rare. Most decompressions recorded by the FAA are caused by a malfunction of the outflow valve, a component of the cabin pressurizing system. Such decompressions are very slow, and rarely do cabin pressure altitudes approach 18,000 ft.

The pilot with SCT has the same minimum time, about 10 s, to don an oxygen mask. Beyond this time there is a risk of losing consciousness and control of the aircraft; so the question of sickling is pretty academic. Regardless of hemoglobin phenotype, the pilot must remain conscious. Remember, however, that airline pilots receive some training in mask donning, and that yet other regulations (FAR 121.333c) have been issued to assure that there is at least one conscious pilot at the controls in the event of a decompression.

In our first report on this subject (6) we concluded that, although SCT seems no threat to the airman, those with the trait should avoid the hypoxic experience portion of physiological (altitude chamber) training. Frankly, this conclusion was based on my own personal biases; I am not sure that the value of this portion of physiological training outweighs the risks from periodic hypoxic exposures throughout a pilot's career, regardless of hemoglobin type. Perhaps this is an overly conservative opinion. In any case, since the publication of that report I have been made aware of a number of people with SCT who have undergone the hypoxic experience to the point of definite signs and symptoms of hypoxia, with no unusual consequences whatsoever. We have documented a number of these cases and expect to collect more of them. Some of these people, of both sexes, have "flown" in our own altitude chamber in Oklahoma City. Some, before their trait was detected, underwent these experiences in military chambers. Some of the latter group were members of Dr. Marchbanks'** own 332d Fighter Group, who flew combat missions during

*FAR 121.327c deals with a variety of cabin pressure altitudes and permissible exposure times. Physicians concerned for susceptible patients who are planning air travel may wish to consult with the nearest FAA regional flight surgeon or with a local FAA-designated aviation medical examiner.

**Vance H. Marchbanks, Jr., M.D., Hartford, Connecticut, was one of the first black flight surgeons. He entered the U.S. Army Medical Corps in 1941, became rated as a flight surgeon in 1944, and was assigned to the all-black 332d Fighter Group. Dr. Marchbanks was a member of the panel whose discussion is reported here.

World War II; 7 to 8 percent of these men had red cells that would sickle under hypoxic conditions. Henderson and Thornell (7) reported that four cadets with SCT tolerated an exposure to 16,000 ft. Some of the group continued their military flying careers after the war and thus went on to periodic training exposures at approximately 26,000 ft. Table I presents data on two of our experimental subjects who were applicants for military flying waivers.

In summary, it is fair to say that sickle cell trait is not a risk factor in the majority of pilots and passengers who possess it. Reports associating SCT with collapse during or after flight are clouded with incomplete diagnosis of hemoglobin phenotype, failure to consider other factors that may have been involved, poor logic (post hoc ergo propter hoc (6)) and other faults (8,9). There may be factors that can contribute to a sickling crisis at altitude, but these factors obviously do not occur in the majority of people with SCT. Anecdotal reports are a poor basis for policies that deny careers in aviation, and the social and economic benefits of those careers, to 8 percent or more of the world's black people. It is the responsibility of aviation medical examiners and policymakers to insure that denial of certification is based on real dangers. An airline pilot, speaking to another medical group about another medical problem, stated:

> The easy way out is to say no, quote the rule book, ground the pilot, and escape any possible criticism for the decision. The difficult decision is that of the doctor who says he believes, on the basis of his training and background, that a specific condition is not related to safety, and that, given proper medical surveillance and control, the pilot can fly. It is usually one of the leaders of your profession who makes that determination . . . . . (10).

ATHLETICS AND OTHER FORMS OF PHYSICAL EXERTION

In the 1970's there appeared in the literature three reports linking the trait with pathological consequences of heavy exercise. Jones et al. (11) reported four cases of sudden death in army recruits during basic training at an altitude of 4,060 ft. In each case an initial collapse was followed by loss of consciousness and death. Two recruits died within 8 h. In the other two, who died at 24 and 25 h, there were signs of disseminated intravascular coagulation (DIC). "Electrophoresis" revealed both HbS and HbA, and sickled red cells were seen at necropsy.

Although Jones et al. reported no muscle involvement in their patients, Zimmerman and Mummert (12) and Koppes et al. (13) found rhabdomyolysis (RML) following severe exertion in a total of five young recruits with SCT. All four of the patients studied by Koppes et al. exhibited signs of DIC; two of them died after admission to the hospital. Interestingly, the two survivors collapsed after exercising at an altitude of 7,200 ft. Both were athletes in excellent condition before their problems occurred and, presumably, had not experienced similar problems in the past at this same altitude. No deficiencies in muscle phosphorylase or phosphofructokinase were found in the two survivors, but carnitine palmityl transferase (CPT) was not measured; deficiencies in CPT are reportedly associated with familial exertional RML. Many other factors have also been incriminated (see Table II).

Koppes et al. make a point of the occurrence of DIC in their patients, stating that, "a clinically significant bleeding diathesis . . . has not been described in patients with exertional-induced rhabdomyolysis," but Schreir et al. (31) reported DIC and muscle involvement in a white patient after he had exercised in a hot environment. Dudding et al. (25) found consumption coagulopathies in three U.S. Army recruits who died from an adenovirus Type 7 pneumonia. Adenoviruses have been reported to induce RML (24). Two of the patients studied by Dudding et al. exhibited signs of muscle involvement; in one, "occasional muscle fibers had lost cross-striation and were acidophilic." Signs of renal involvement were also present. A mountain climber studied by Niwa et al. (15) exhibited both DIC and RML; this patient possessed the beta-thalassemia trait.

There is more to be found in the literature on this question than we have space to cover, but this quick look should satisfy us that the case against SCT as a cause for rhabdomyolysis, or as a reason for avoiding sports and other forms of exertion, is tenuous at best. Other facts support this conclusion. SCT certainly has not been a factor in the selection, for health or ability, of black players in the National Football League. League players with SCT number about 8 percent of black athletes, including those who play most of their games at altitudes greater than 5,000 ft (32). Several athletes with documented SCT participated in the 1968 Olympiad in Mexico City, where they exerted themselves maximally and suffered no untoward consequences (6). Robinson et al. (33) found no significant differences between the exercise capacities of 16 male subjects with SCT and 16 matched control subjects. I hope that you will conclude with me that those cases seen by Zimmerman and Mummert and by Koppes et al. might just as likely have been associated with some infectious agent. Organisms capable of causing DIC and RML are known to be endemic or epidemic in military populations (e.g., 34).

HAZARDS OF THE INDUSTRIAL ENVIRONMENT

It seems appropriate to consider also another, more recent, threat to a free career choice for those with SCT. Beginning early in 1980, there have appeared a number of newspaper articles referring to "discriminant" policies of industry toward women, those with inherited enzyme deficiencies and, of course, toward people with SCT (see, for example, references 35-38). With such policies have come screening programs, designed to detect various genetic differences. Those who defend the programs say that they are intended to protect the worker who may be especially susceptible to working conditions that are not "normally" hazardous. Those who object to screening point out that: (i) there may be many susceptible conditions that are not screened for; and (ii) it is yet to be proven that SCT, for example, can increase the hazards of industrial conditions that are safe for those without it. It is not difficult to agree with both these latter points. Although Asakura et al. (39) showed that HbS in solution may become insoluble when shaken and then diluted with a 17 percent isopropanol buffer, this finding does not prove that industrial solvents present a special danger to those with SCT. I have found no reports in the literature that HbS-containing red cells become destabilized by otherwise tolerable levels of any chemical used in industry. On the other hand, it is known that Hb-Zürich, a notoriously unstable protein, has a very high affinity for carbon monoxide (40), and Beutler (41) points out that Hb-Zürich-containing red cells are susceptible to a number of drugs and chemicals. Beutler's list of unstable hemoglobins does not include HbS, but HbS is easily detected. Hemoglobin

Zürich is not easily detected, and as far as I know, no screening programs for it have been instituted.

CONCLUSIONS

Sickle cell trait has been associated in the medical literature with a variety of pathological conditions.* With the possible exception of malaria, the trait has not been proven to protect against any disease; therefore, it is not surprising that people with the trait have in the past, and will in the future, become ill or injured. The most convincing evidence, based on studies of large populations and on controlled experiments, indicates that people with the trait are not unusually susceptible to the moderate hypoxemia of altitude or of competitive sports. There are hemoglobin phenotypes that may confer abnormal susceptibility to certain industrial pollutants, but HbS has not been proven to be one of these hemoglobins.

*For other references dealing with SCT and health see the review by Sears (42).

TABLE I. Data for Two Experimental Subjects With Sickle Cell Trait.

SUBJECT	AGE	HISTORY OF SICKLING	HISTORY OF HYPOXIA	HEMOGRAM/ ELECTROPHORESIS	O_2-Hb DISSOC	HYPOSTHENURIA	IN VITRO* SICKLING
1	25	None	Competitive swimming; Underwater 106 s/75m. Physiological Training Military, 1978	Normal/40% HbS, 60% HbA	Normal	Negative	10%
2	27	None	Water Safety Inst. Qual. Comp. swimming/Track Alt. Tolerance Test (25,000 ft) Military, 1980	Normal/30% HbS, 70% HbA	Normal	Negative	95%

Dr. Wayne March of the Dean A. McGee Eye Institute, Oklahoma City, examined both subjects. Fundus photography and fluorescein angiography revealed no abnormalities, including those that have been reported in SCT.

*Sealed cover slip

NOTE: I am grateful to Dr. Frank Brunstetter of the Air Rescue Service, USAF, for assistance, and to Dr. Donald Waugh of the Flight Surgeon's Office, Mather Air Force Base, California, for information on the altitude tolerance test performed on Subject #2. Dr. Rose Schneider, Department of Pediatrics, The University of Texas Medical Branch, Galveston, Texas, performed the electrophoretic tests.

TABLE II. Reported Causal Factors in Rhabdomyolysis. Some examples.

FACTOR	COMMENT	REFERENCE*
Carnitine Palmityl Transferase Defic.		14
Sickle Cell Trait		12,13
B-Thalassemia Trait		15
Hyperuricemia		16
Trauma/Ischemia		(Many)
Phosphorylase Defic.	McArdle's Synd.	17
Phosphofructokinase Defic.	Tarui's Synd.	18
Alcohol Abuse/ Sensitivity		19
Bacteremia	e.g., E. coli	20
Hypokalemia		21
Hyponatremia		22
Cold Exposure		23
Adenovirus Infection	Several Types	24
Toxic Shock Synd.		26
Legionnaires' Dis.		27
Epsilon Amino Caproic Acid Ther.	For hemmorrhage	28
Herpesvirus Inf.		29
Epstein-Barr Virus		30

*Citations are given as examples only and are not intended to indicate priority of publication.

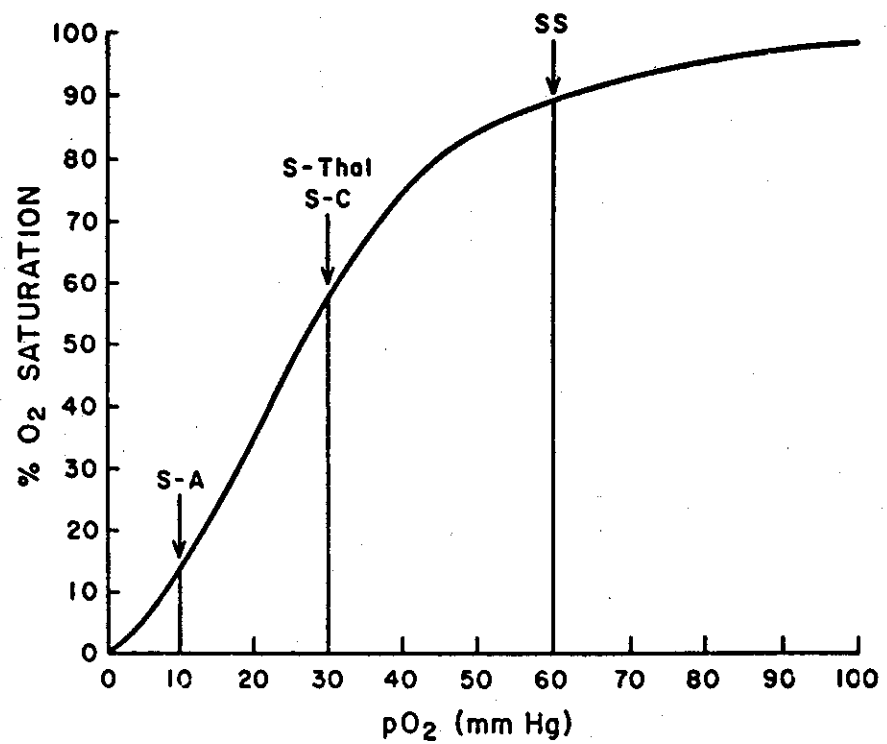

Figure 1. Normal oxygen-hemoglobin dissociation curve. Sickling thresholds for some combinations of HbS with normal and other hemoglobins are superimposed on the curve. From the data of Griggs and Harris (3). Figure reproduced from reference 6.

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