A CLOSER LOOK

Concocting Blood: Artificial Blood Substitutes

The term "blood substitute" is somewhat misleading. Blood has many components and plays such a wide variety of roles—from fighting infection to transporting oxygen—that no single artificial substitute yet engineered can fulfill all those functions. However, substitute liquids are available that can transport oxygen from the lungs through the body and can "stretch" a limited blood supply, while sidestepping transfusion reactions. An important benefit of these blood substitutes is that the recipient is not at risk for transmission of bloodborne disease factors.

Modified Hemoglobin

Let's pretend to be biomedical engineers for a moment. If you wanted a substance to transport oxygen in the blood, what would you use? Like many researchers, you'd probably start with hemoglobin, the blood's own oxygen carrier. You could obtain hemoglobin from human red blood cells too old for transfusion, from readily available cow blood, or by genetic engineering. Unfortunately, hemoglobin by itself is unusable—it spontaneously splits in half in the plasma, and is rapidly cleared by the kidneys (which can lead to renal shutdown). Chemically linking hemoglobin subunits together so that they don't come apart or tying hemoglobin molecules together into long chains reduces clearance by the kidneys. Some types of these hemoglobin chains can stay in the blood for as long as 24 hours.

Another problem with free human hemoglobin is that it binds oxygen much more tightly (has a higher affinity) than hemoglobin contained inside a red blood cell, only reluctantly giving up oxygen to needy tissues. Cow hemoglobin, on the other hand, naturally binds oxygen less tightly. This solution has its own problems: the possible transmission of mad cow disease and the risk of immune reactions. Nevertheless, a cow-based product is licensed for use in South Africa where the high prevalence of HIV has made collecting uninfected blood extremely difficult. It's also possible to modify the hemoglobin with chemicals (such as pyridoxal phosphate) which mimic chemicals that lower oxygen affinity in the normal red blood cell. Hemoglobin's affinity for oxygen can also be lowered by genetically engineering its oxygen binding pocket. Each of these modified hemoglobins has undergone clinical trials with varying degrees of success.

A common problem in these trials is an increase in blood pressure when the hemoglobin compound is infused into the patient's blood. Blood vessels are normally held in a relaxed state by the action of the chemical messenger nitric oxide. Hemoglobin mops up nitric oxide, causing blood vessels to constrict and blood pressure to rise. Normally, hemoglobin in red blood cells is too far away from the source of nitric oxide to mop up much of it. The small free hemoglobin chains, however, slip close to the walls of the blood vessel where the concentration of nitric oxide is very high, and so absorb it in large quantities.

A miniature artificial cell (called a liposome) enclosing our modified hemoglobin would keep it away from blood vessel walls. Unfortunately, liposomes are cleared very rapidly by macrophages of the immune system.

examinations and before hospital admissions. SMAC is a blood *chemistry* profile. The CBC includes counts of the different types of formed elements, a hematocrit, measurements of hemoglobin content, and size of RBCs. Together these tests provide a comprehensive picture of one's general health status in relation to normal blood values.

A listing of the normal values for selected blood

inactive yellow bone marrow regions (essentially fatty tissue) may reconvert to active red marrow.

Blood cells develop from collections of mesenchymal cells, called *blood islands*, derived from the mesoderm germ layer. The fetus forms a unique hemoglobin, **hemoglobin F**, that has a higher affinity for oxygen than does adult hemoglobin (hemoglobin A). It contains two alpha and two gamma (γ)