carrying agents have, to date, not been proven. Thus, this author is convinced that any form of oxygen carrier within the blood circulation should meet the following basic requirements:

1. Remain in the plasma for approximately 2 days
2. Decompose by the body's natural metabolic system
3. Does not interfere with capillary circulation
4. The molecular weight of the agent should be between 70,000–120,000 daltons
5. Does not cause foreign body reaction
   i. Should be immunologically inert
   ii. Should not stimulate coagulation cascade
   iii. Should not stimulate complement system
   iv. Should not stimulate other defense systems inside the body

Any artificial oxygen-carrier that satisfies the above requirements is called an "oxygen-carrying macromolecule."

Classification of "Red Cell Substitute"

Traditionally, a man-made intravascular oxygen-carrier has been called a "blood substitute" or "artificial blood." However, these terms are not proper expressions of the currently developing red cell substitutes, they related to agents that can only deliver oxygen to the hypoxic tissues and retrieve carbon dioxide from tissues. Thus, in 1992, this author, together with Dr. N. Minato, proposed classifying the oxygen-carrying agents into the following three groups:[5]

oxygen-carrying microcapsules	larger than 1 μm in diameter
oxygen-carrying microparticles	larger than 0.1 μm in diameter
oxygen-carrying macromolecules	less than 0.1 μm in diameter

However, it is difficult to classify them only according to the size of the oxygen-carrying agents. Thus, further classification of the term "oxygen-carrying macromolecules" was made in the previous section. Further explanation stressing only the oxygen-carrying properties for these agents is made in the following section.

O_2 and CO_2 Kinetics Inside the Body

In order to recognize clearly the differences in the blood gases carried inside the red cells and inside the plasma, it is necessary to review the basic physiology of O_2 and CO_2 kinetics within the body.[6] The oxygen gas inside the alveolar air (Fig. 1) is transferred to the hemoglobin inside the red cells through three layers consisting of the alveolar wall, plasma and the red cell wall (Fig. 2). This process generally takes 0.4 to 0.5 seconds (Fig. 3). Contrary to O_2, CO_2 is dispersed from the blood to the alveolar air in 0.1 seconds, in spite of the low pressure gradient of the CO_2 content between the venous blood and the alveolar air due to its high diffusion coefficient. Thus, O_2 and CO_2 exist in the arterial and the venous blood, as shown in Fig. 4. It is very important to recognize that inside the arterial blood, 19 ml of oxygen in 100 ml of blood exists inside the red cells while only 0.3 ml of oxygen exists in the plasma. In the venous blood, 14 ml of oxygen in 100 ml of blood still exists inside the red cells, while only 0.13 ml of oxygen remains in the plasma. This very important basic fact is very often forgotten. Thus, even conservatively calculated, only less than 5 ml of oxygen remains in the plasma of the whole body, while 750 ml of oxygen is kept inside the red cells (Table 1). Contrary to oxygen, the majority of CO_2 in the body is kept in the plasma (Table 2).

Thus, for the expectancy of therapeutic effects of oxygen supply to patients, it is extremely important to increase the oxygen content in the plasma but not that

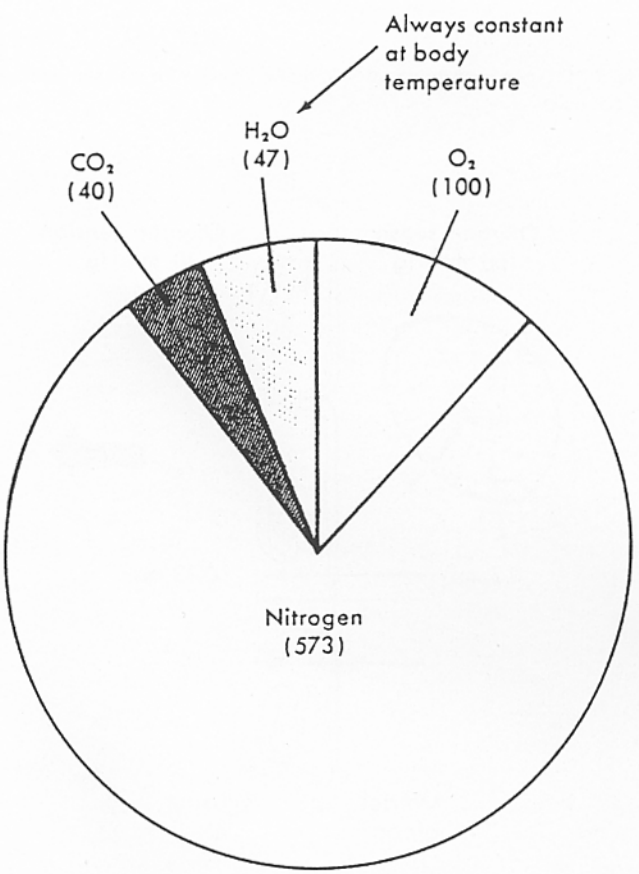

Fig. 1 Gas contents (mmHg) of the alveolar air.