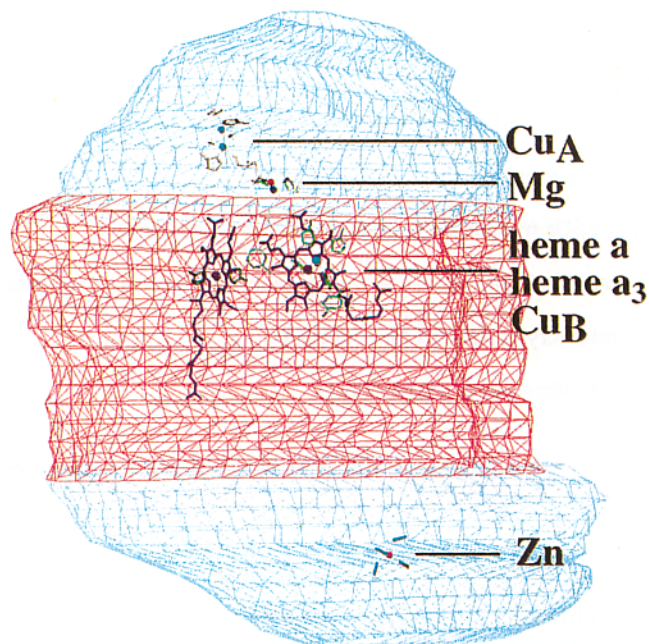


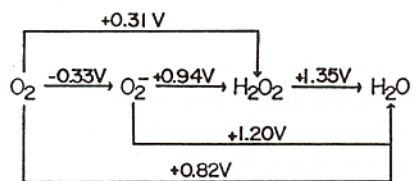
**Fig. 2** Ca back bone traces of bovine heart cytochrome *c* oxidase at 2.8 Å resolution. A) a side view, B) a top view from the outside of mitochondrial inner membrane.

process.

Hypotheses about where oxygen binds to cytochrome oxidase were already being advanced thirty-some years ago, long before the X-ray structure of cytochrome oxidase became known. At that time, it was known that the oxygen formed a bond with iron and that a copper ion existed very near this oxygen-binding site. It was Professor Winslow Caughey, whom I introduced earlier, who first recognized the importance of the proximity of this copper ion to the oxygen-binding site. That is, the location of this copper ion makes two-electron reduction possible. Two electrons can be transferred simultaneously, one from the iron and another



**Fig. 3** Locations and structures of metal sites in cytochrome *c* oxidase. Balls denote positions of metal ions. Molecular surface defined with the electron density map at 5 Å resolution is shown by the cage.



**Fig. 4** Standard oxidation-reduction potentials for the steps involved in the conversion of dioxygen to water at 25 °C and pH 7.

from the copper, to produce a  $\mu$ -peroxy intermediate, as shown in Fig. 5. Specifically, Dr. Caughey noted the importance of the proximity of  $\text{Cu}_B$  and nearly thirty years ago proposed the bridging peroxide mechanism, stating that oxygen is reduced by way of a  $\mu$ -peroxy intermediate.<sup>6</sup>

Because this bridging peroxide mechanism is extremely clear, it was readily accepted by many people working in the field of cytochrome oxidase. Although most people recognized the formation of the  $\mu$ -peroxy intermediate, they failed to notice an important point. That is, assuming that this mechanism is correct, the reaction that would produce the  $\mu$ -peroxy intermediate should be extremely rapid. The distance between the oxygen and copper is approximately 2 Å. The rate of