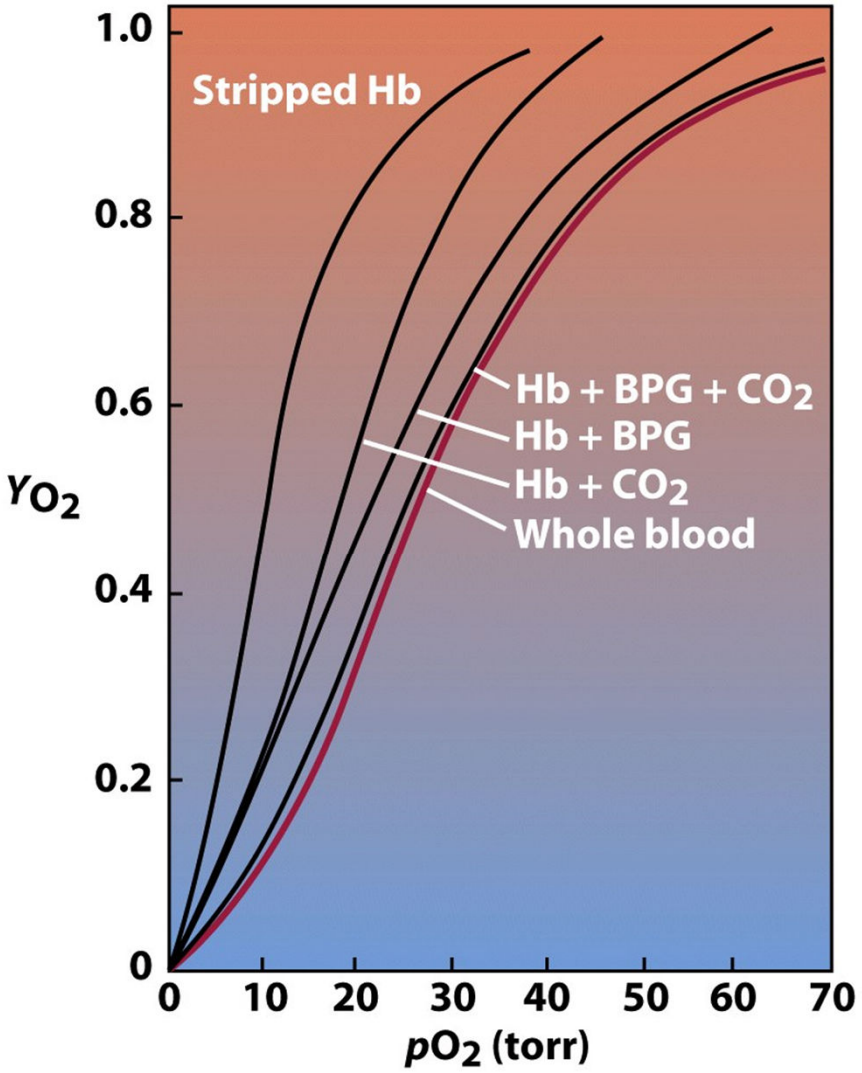
Modulators (effectors) influence oxygen binding to hemoglobin:

- Positive effectors stabilize the ‘R’ state:
  - Oxygen
  - (Carbon monoxide – CO)
  - (Nitric oxide – NO)
  - (Hydrogen sulfide – H_2S)
- Negative effectors stabilize the ‘T’ state:
  - D-2,3-Bisphosphoglycerate (BPG)
  - H^+ (low pH) – ‘Bohr effect’
  - Carbon dioxide (CO_2)
  - Chloride ion (Cl^-)

Negative effectors in the blood enhance Hb's ability to release oxygen



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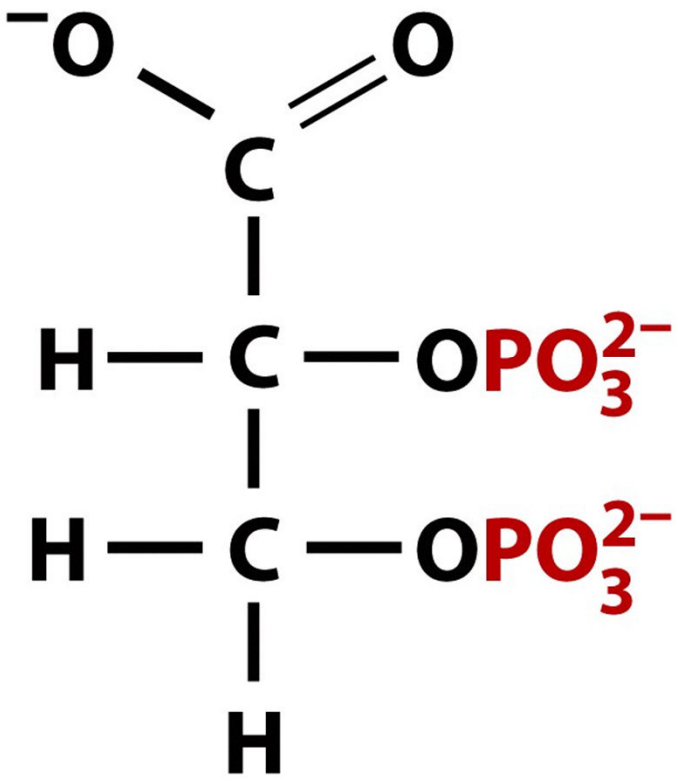

D-2,3-Bisphosphoglycerate (BPG)

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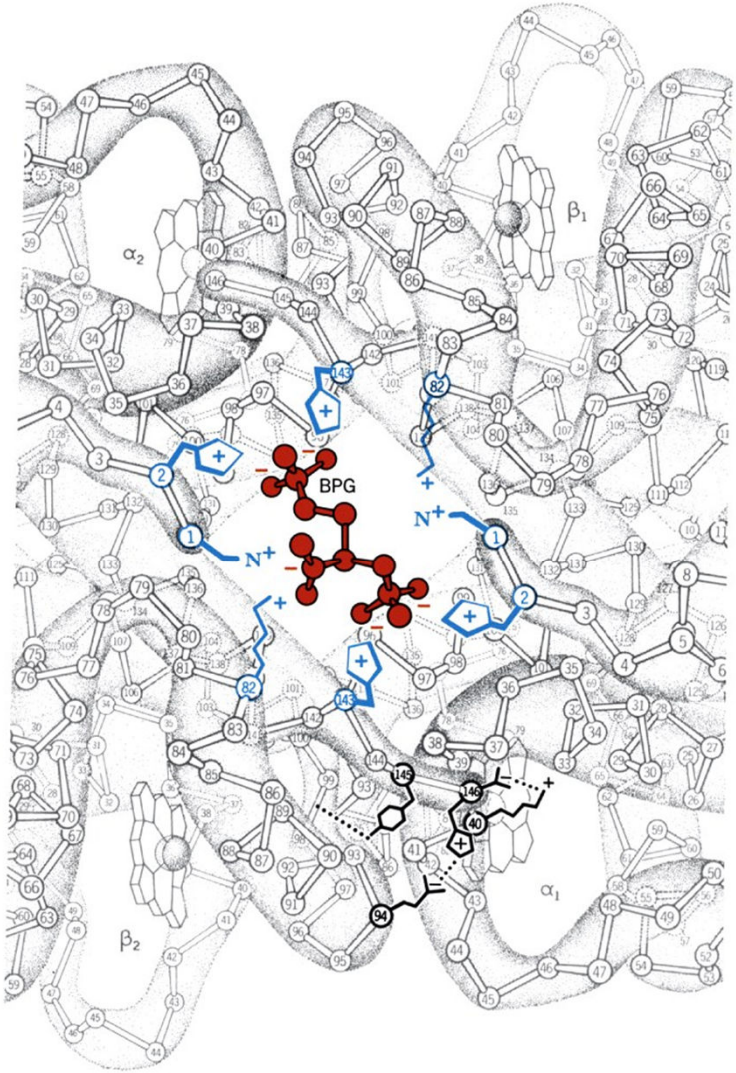
BPG binds in the center of the tetramer, forming salt bridges with + charged groups



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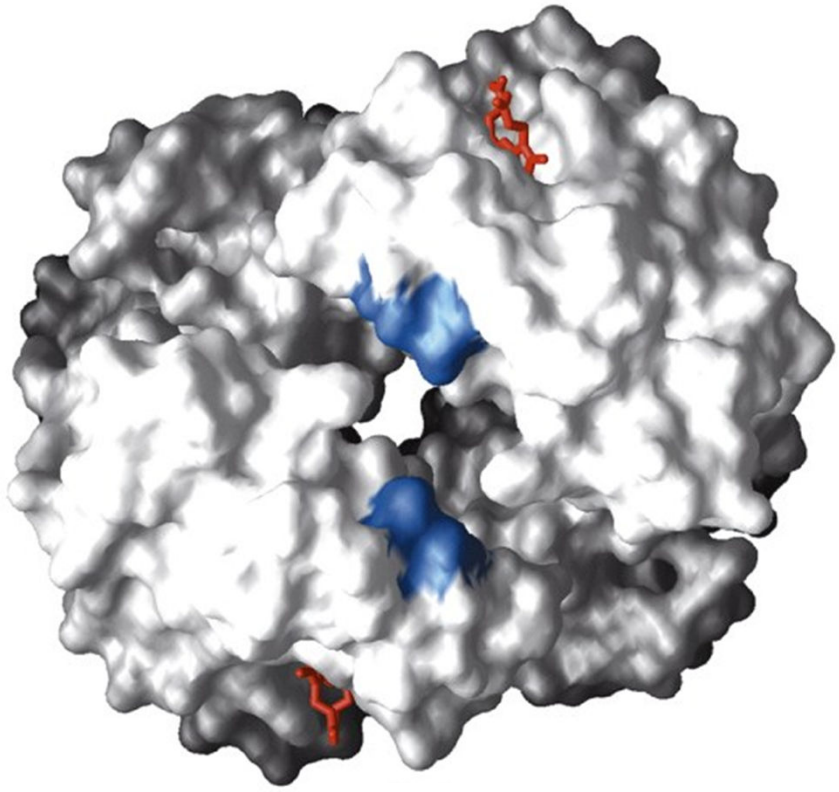
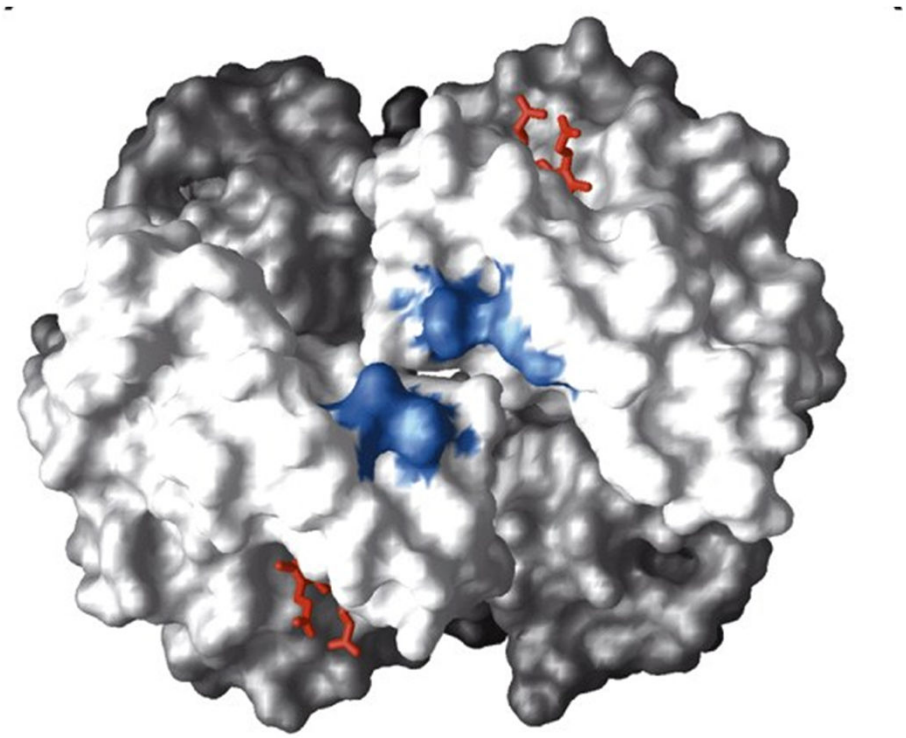
The cavity for BPG binding is only present in the T-state tetramer



T-state



R-state

Figure 5-18
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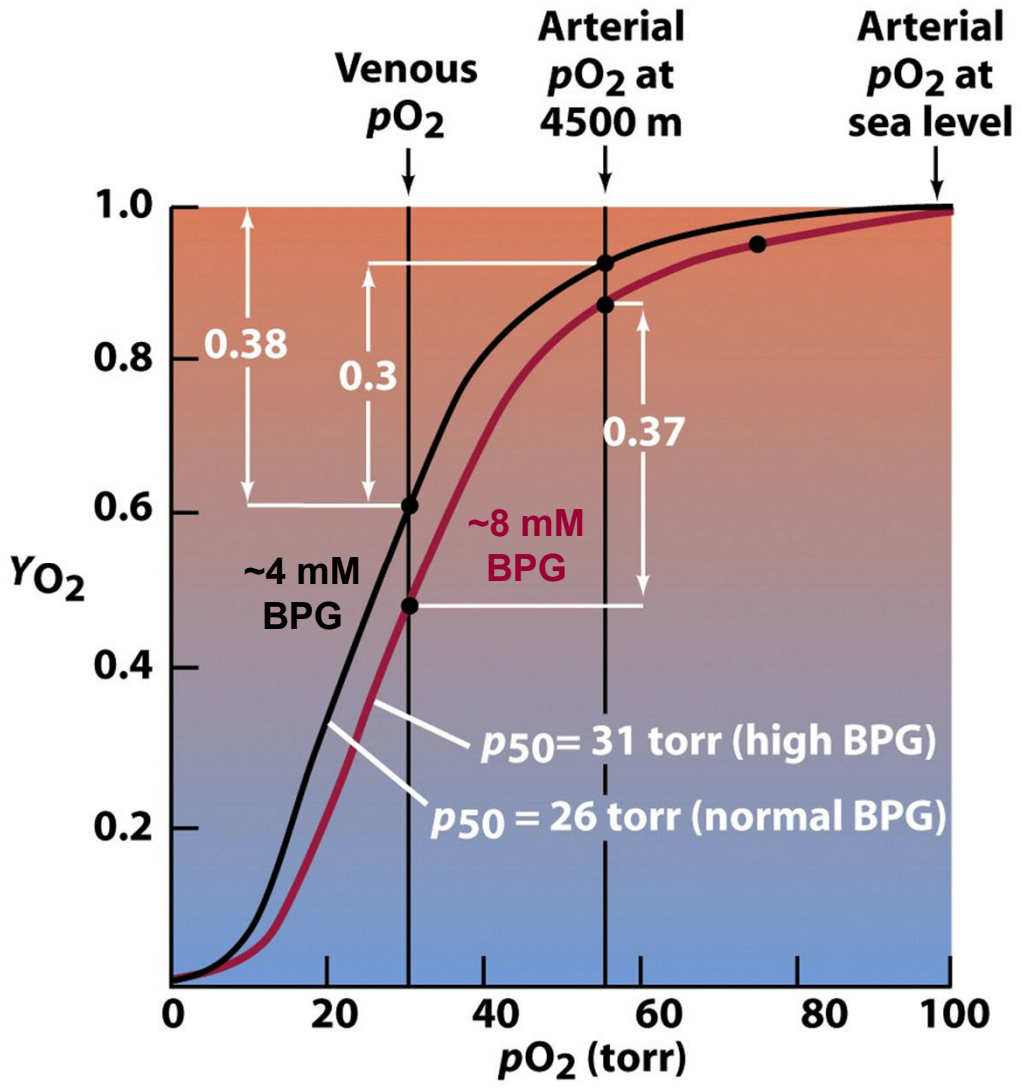
The body can quickly increase BPG levels to enhance oxygen transfer at high altitude



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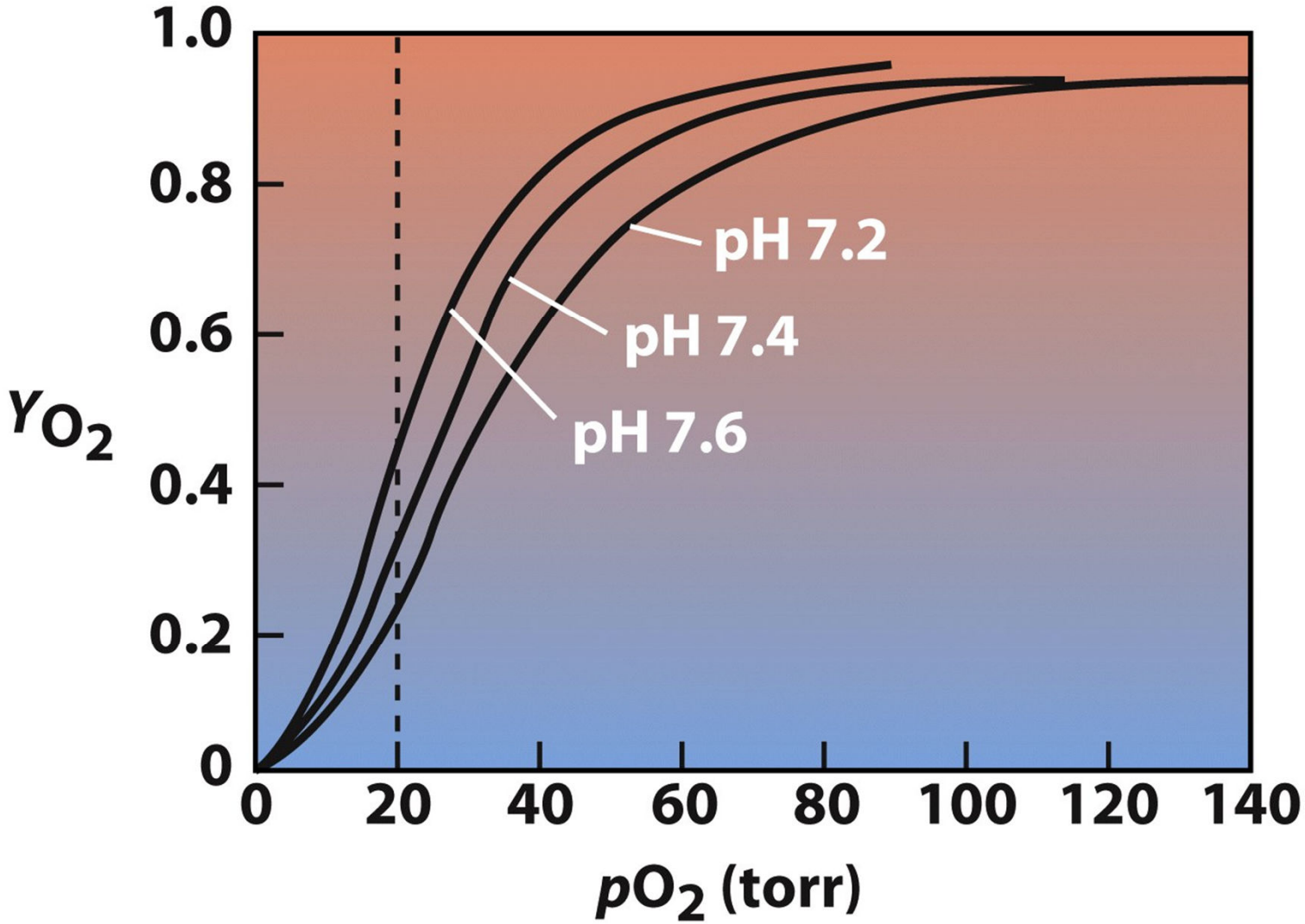
The Bohr effect: Lowering pH reduces Hb's oxygen-binding affinity



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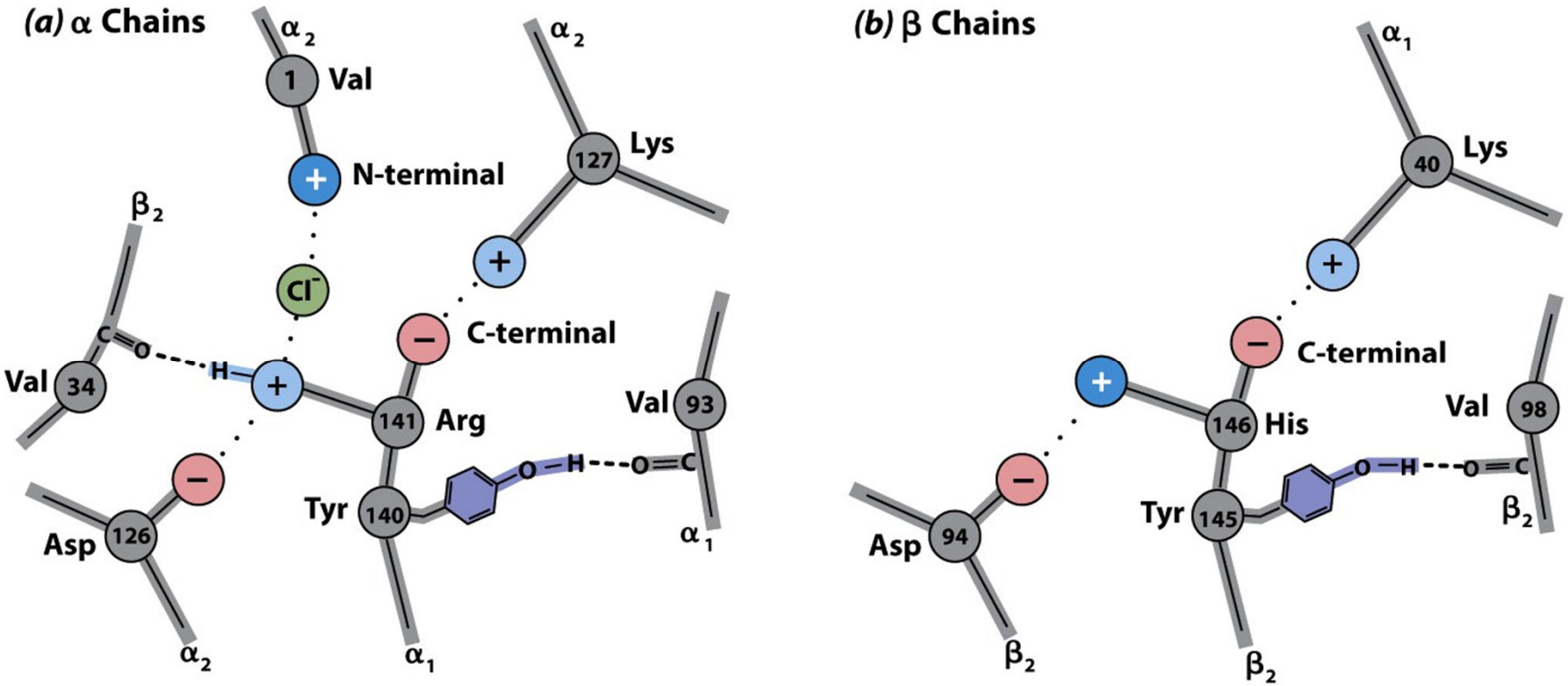
Lower pH increases the liklihood of protonation and salt-bridge formation



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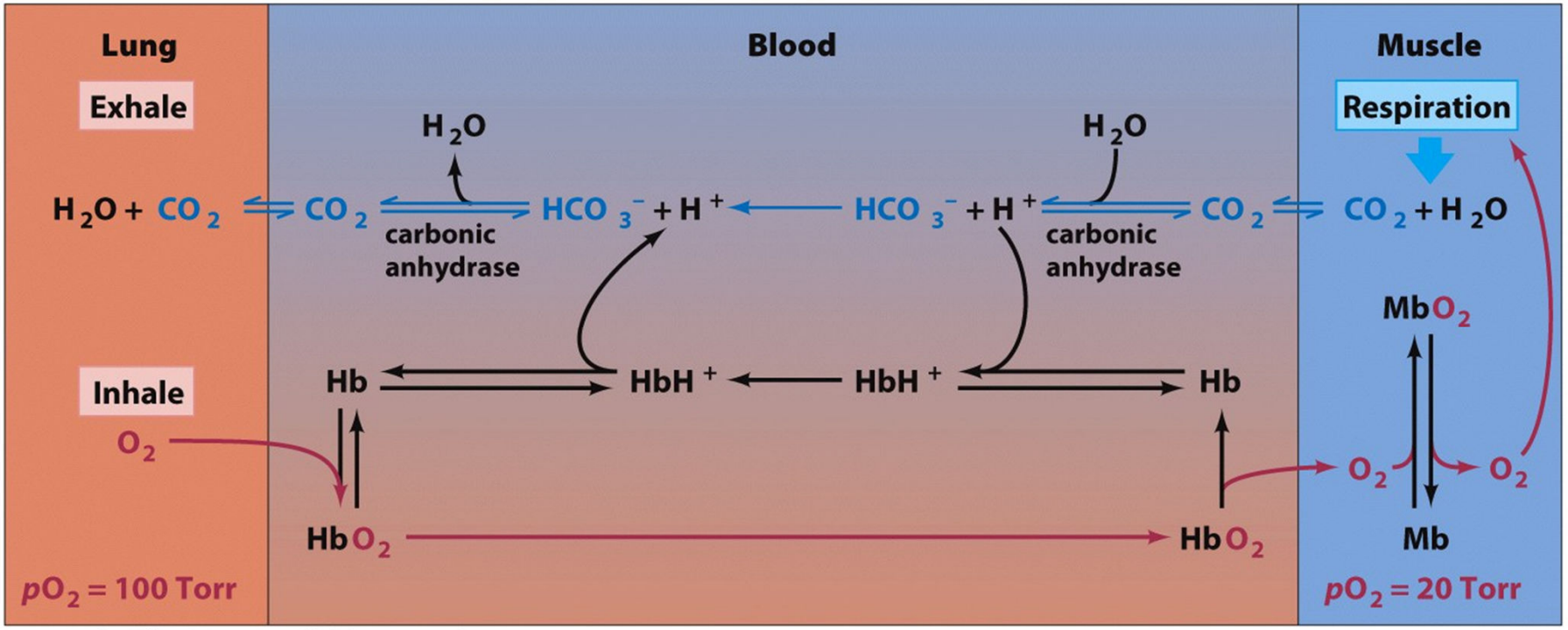
The action of carbonic anhydrase lowers blood pH at the tissues and raises blood pH at the lungs, enhancing O_2 and CO_2 transfer



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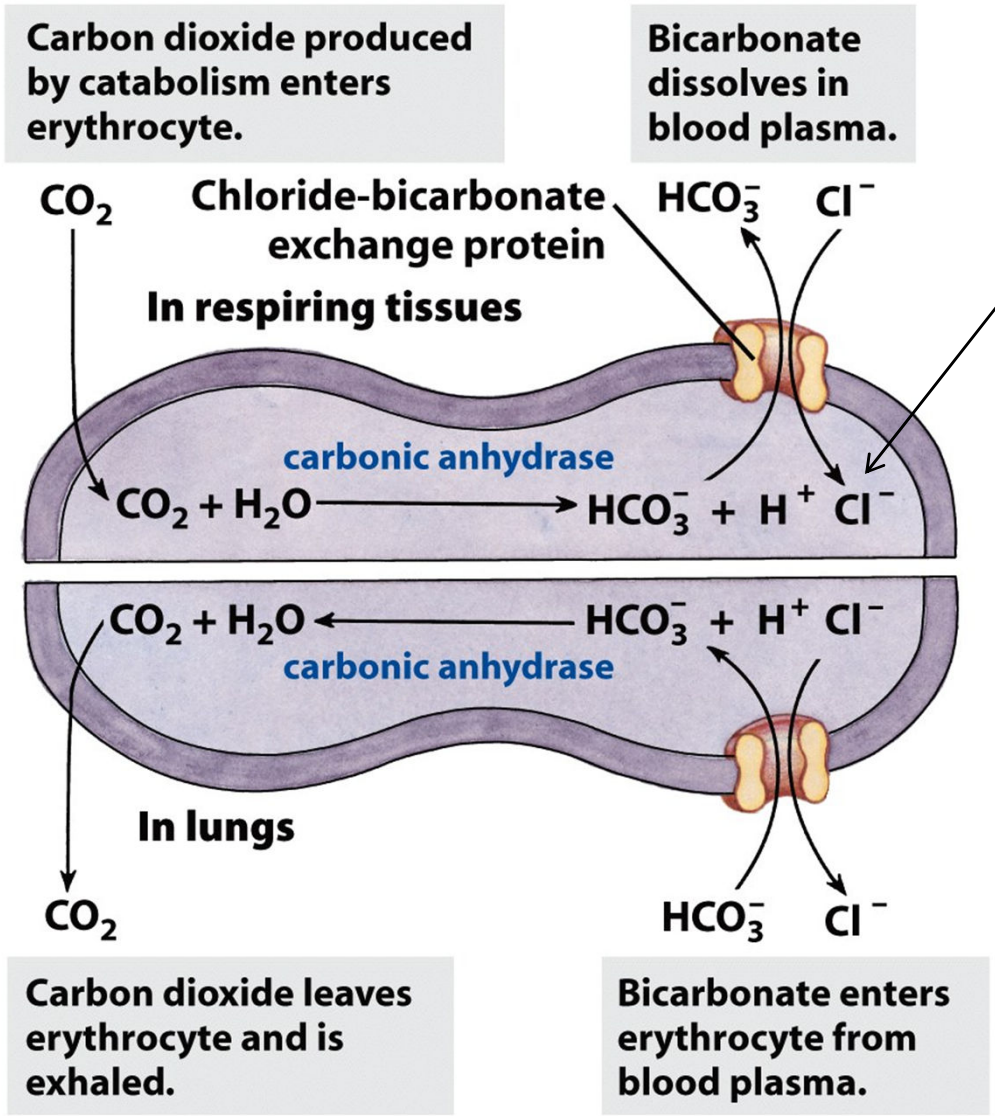
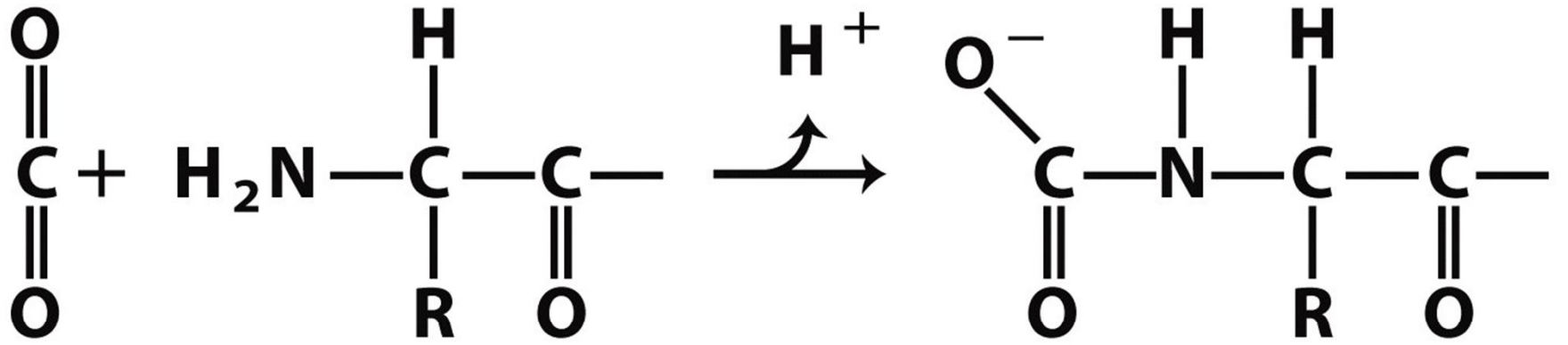
The chloride-bicarbonate exchanger helps increase the CO_2-carrying capacity of blood



Increased [Cl^-] stabilizes T-state (via salt bridges), thus promoting release of O_2

Carbamate formation enhances O_2 and CO_2 transfer between the lungs and tissues



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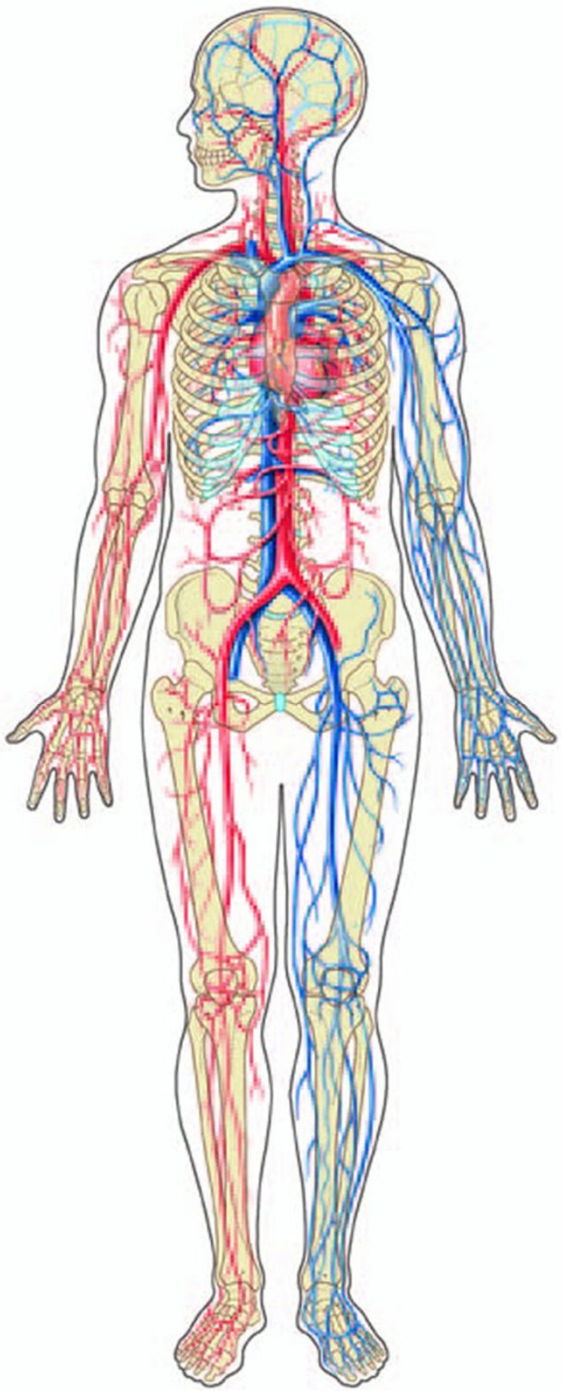

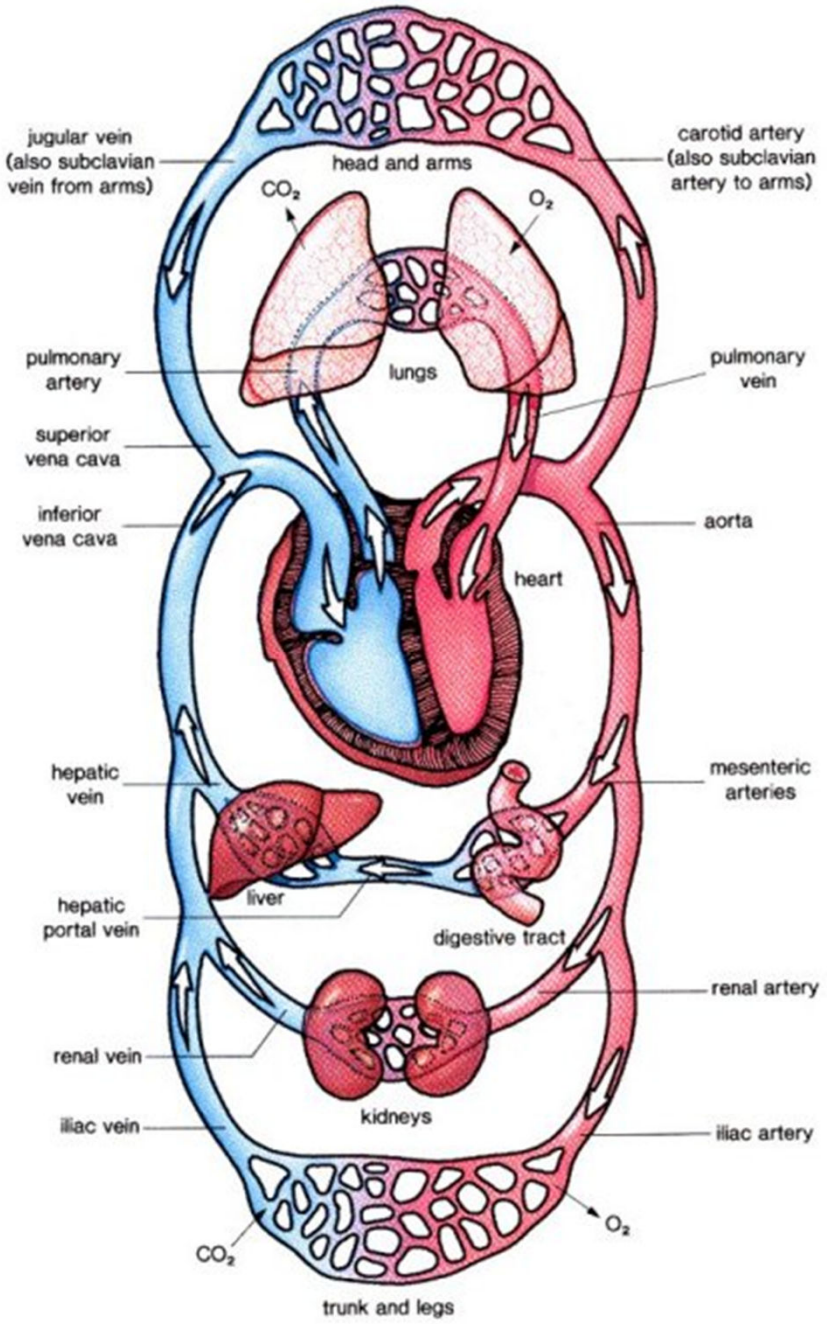
jugular vein
(also subclavian
vein from arms)
head and arms
carotid artery
(also subclavian
artery to arms)
CO_2
O_2
pulmonary
artery
lungs
pulmonary
vein
superior
vena cava
inferior
vena cava
aorta
heart
hepatic
vein
mesenteric
arteries
liver
hepatic
portal vein
digestive tract
renal artery
renal vein
kidneys
iliac vein
iliac artery
O_2
CO_2
trunk and legs

Mutations alter Hb function in different ways

Table 7-1 Some Hemoglobin Variants

Name[a]	Mutation	Effect
Hammersmith	Phe CD1(42)β → Ser	Weakens heme binding
Bristol	Val E11(67)β → Asp	Weakens heme binding
Bibba	Leu H19(136)α → Pro	Disrupts the H helix
Savannah	Gly B6(24)β → Val	Disrupts the B–E helix interface
Philly	Tyr C1(35)β → Phe	Disrupts hydrogen bonding at the α_1–β_1 interface
Boston	His E7(58)α → Tyr	Promotes methemoglobin formation
Milwaukee	Val E11(67)β → Glu	Promotes methemoglobin formation
Iwate	His F8(87)α → Tyr	Promotes methemoglobin formation
Yakima	Asp G1(99)β → His	Disrupts a hydrogen bond that stabilizes the T conformation
Kansas	Asn G4(102)β → Thr	Disrupts a hydrogen bond that stabilizes the R conformation

[a]Hemoglobin variants are usually named after the place where they were discovered (e.g., hemoglobin Boston).

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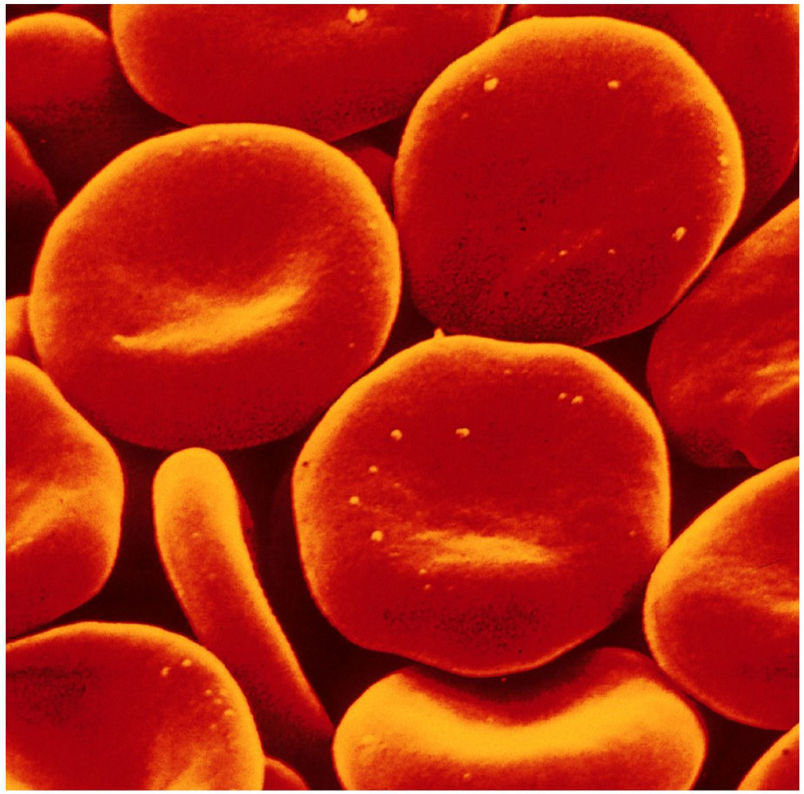
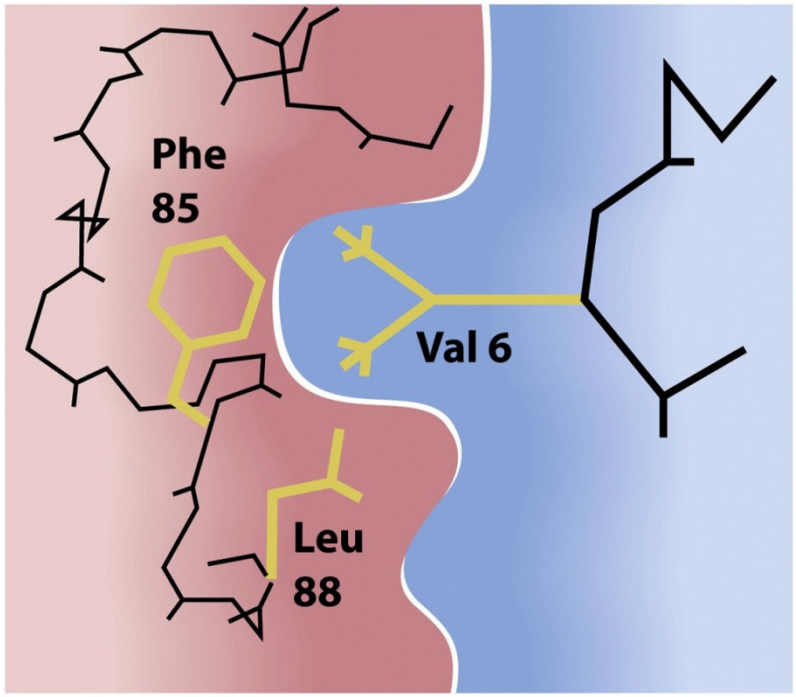
In sickle-cell anemia, mutant Hb can aggregate, leading to sickle-shaped RBCs



David M. Phillips/Visuals Unlimited

The mutant Val of sickle-Hb can bind in a hydrophobic pocket of a T-state β-chain



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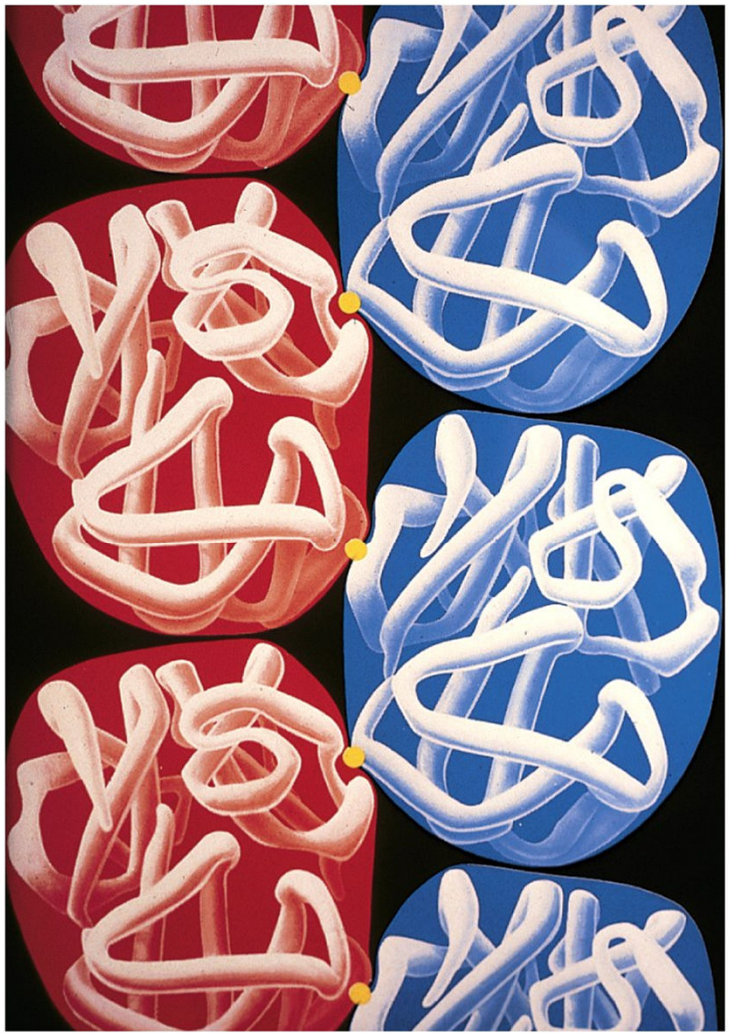
Binding of many T-state tetramers results in the formation of long, rigid fibers



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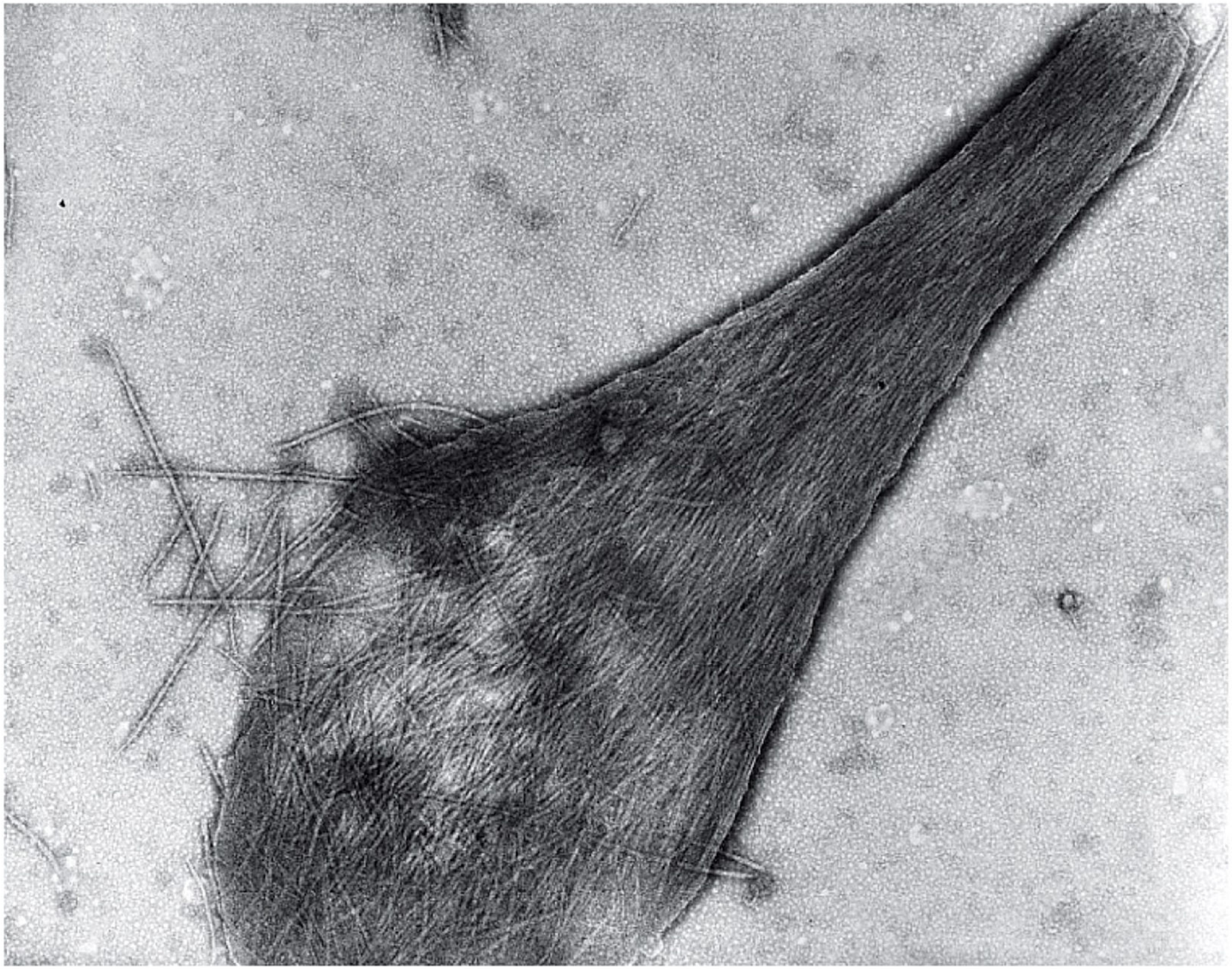
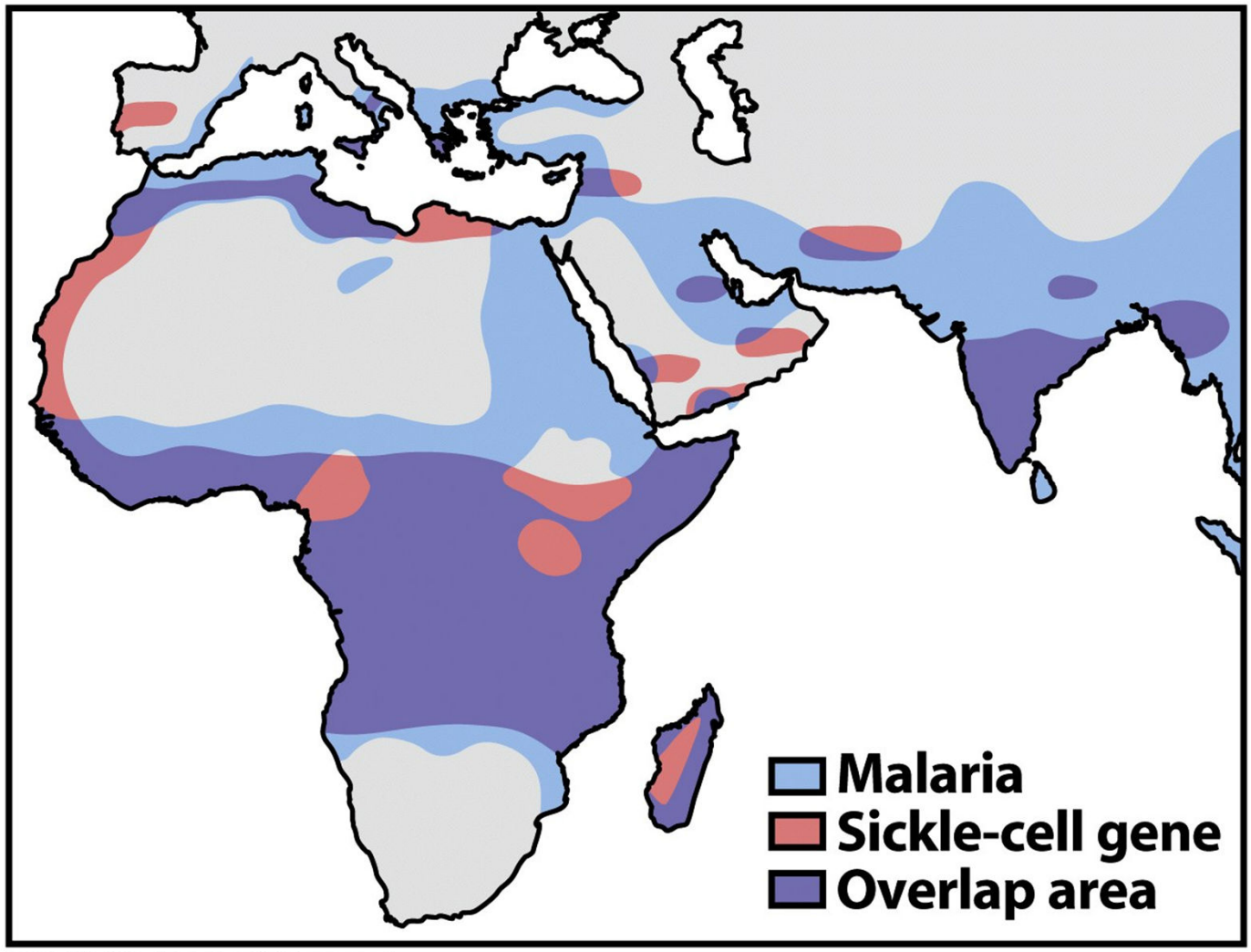
Sickle-hemoglobin fibers can burst the cell



Courtesy of Robert Josephs, University of Chicago

The sickle trait provides resistance to malaria, hence its prevalence in certain populations



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