c. Hypertension Drugs, Propranolol and Nimodipine. These two drugs, which were studied using neutron diffraction, are given to patients suffering from hypertension. The modes of action of these drugs are somewhat different. Nimodipine is a calcium channel blocker that inhibits the flow of calcium ions across the membranes. Propranolol, on the other hand, is a compound that blocks different receptors (the so-called beta adrenergic receptors) in cellular membranes. Activation of these receptors by naturally produced compounds can result in undesirable physiological responses, such as increased cardiac rate. Propranolol has a high affinity for the binding sites of this receptor, and hence it does not allow potentially dangerous affectors to reach the beta adrenergic receptor, causing arrhythmic heartbeats and excessive dilation of the blood vessels. Neutron diffraction was used to determine the non-specific binding location of deuterated nimodipine and propanolol in model membranes. The different profiles gave the location and orientation of the drug molecules in the membranes, and thus helped in understanding their mode of action. Nimodipine is now available for treatment with the trade name Nimtop (Miles) and is given to patients with high blood pressure for improved neurological performance. Propranolol is sold under the trade name Inderal (Wyeth-Ayerst) and is given for the management of hypertension and for the long-term management of angina pectoris.

d. Tissue Plasminogen Activator--New Hope for Stroke Victims. The molecular switches and the conformational changes in enzymes caused by enzymatic regulators can be directly probed under physiological conditions by neutron scattering. An important example of such a study involves the blood clot dissolving enzyme, plasminogen, which is present in an inactive form in human blood serum and becomes activated on contact with the clot forming material, fibrin. The activation of native human plasminogen by lysine was investigated in dilute solution to gain insights into the mechanism that transforms an innocuous enzyme of the blood into an effective protease, capable of dissolving blood clots on contact. The enzyme consists of a single polypeptide chain that forms six domains, five molecular tethers called 'kringles', followed by the functional protease, or protein attacking unit. Researchers using small-angle neutron-scattering at the HFBR discovered that when a particular weak (lysine) binding site in the structure is occupied; the initially compact plasminogen structure unfolds into a string of domains and becomes active. The conformational change is reversible and the largest recorded in any enzyme. Plasmin binds to its substrate, fibrin, through kringle 1. This means that the protease at the opposite end of the flexible, open tether has a large radius within which to cleave fibrin. The determination of the enzyme activation mechanism by ligand induced unfolding was an important step leading to the genetic engineering of a new drug called tissue plasminogen activator (tPA), used to treat stroke victims. This drug, tPA, developed and marketed by Genentech, has been credited with saving the lives of about 17,000 stroke victims in the United States alone.

e. Cyclosporin Increases the Success of Organ Transplants. Human organ transplants, now nearly routine, would be impossible except for the development and use of drugs which 'trick' the immune system into accepting a foreign organ. One of the first highly successful drugs of this kind is Cyclosporin. The high-resolution neutron structure of this drug was examined using neutrons at the HFBR. The study revealed the origin of this molecule's