

## In this issue

### Cellular redox chemistry

The chemistry of the twenty genetically coded amino acid residues determines the structural and functional properties of proteins. Cysteine is unique in possessing a highly reactive, nucleophilic thiol group in its sidechain. The redox characteristics of cysteine, which can oxidize to form disulphide bridges, are a key determining factor in regulating biological processes. Since thiol oxidation is finely controlled by the properties of the milieu in which the protein is located, biological systems have developed exquisite control over redox processes. Inside cells, the environment is largely reducing, most often maintained by the endogenous peptide glutathione, resulting in the absence of disulphide bonds in intracellular proteins. In recent years, other cellular redox buffer systems have been discovered, notably the thioredoxins and glutaredoxins. Considerable current research focuses on the importance of thiol/disulphide exchange reactions in protein folding, following the discovery of the protein disulphide isomerases. This fact of thiol reactivity and related issues are considered by A. Chaudhuri in his review (page 692). Clearly the last word is yet to be said on the rich and fascinating chemistry of thiol groups in proteins.

P. B.

### Shooting at enzyme targets

Therapeutically useful drugs can act at diverse target sites in complex organisms. A central issue

in rational approaches to drug discovery is the identification of key biochemical targets which can be attacked by suitably designed small molecules. Among the best characterized targets are enzymes, which are often crucial for the survival and development of pathogens. A quarter of a century ago the first 'mechanism-based' inhibitors were introduced by Konrad Bloch and his associates. In this approach, the enzyme is tricked into acting upon a pseudo-substrate resulting in a covalent intermediate, which is then incapable of proceeding further down the reaction path. This molecular kamikaze act requires a well-designed inhibitor, whose synthetic construction relies heavily on a clear understanding of mechanistic niceties. The oft-cited success stories in this area are the development of  $\alpha,\alpha$ -difluoromethylornithine as an inhibitor of ornithine decarboxylase, in the treatment of trypanosomiasis or African sleeping sickness, and 5-fluoro-deoxyuridine-monophosphate as an inhibitor of thymidylate synthase in cancer chemotherapy. The design of 'biochemical Trojan horses' affords a fertile meeting ground for chemistry and biology as reviewed by Nangia and Chandrakala on page 699. Unfortunately drug discovery and development do not necessarily follow from biochemical elegance. Enzyme targets in host and pathogen are often so similar that selective inhibition is not easily achieved. Toxicity considerations then determine the course of further development.

P. B.

### Human rotavirus protein

In the midst of all the hubris from the success of Indian satellites, denim and beauty queens it is not hard to be reminded of the reality that surrounds us. Those of us who can and wish to, need but to look around. The others may simply pick up the latest edition of their yearbook or world atlas. Look up a disease and look at the countries that the cartographer colours with a bright pink to denote the highest incidence. Nine chances out of ten India will be amongst the countries where the disease takes its largest toll. By some accounts we are a country with a booming economy and a rapidly growing middle class. But by other harsher and perhaps truer statistics (pardon the oxymoron) we have an unforgivably high infant mortality. A major cause of infant death in India is due to gastroenteritis. The only practical solution to this problem is hygiene combined with simple re-hydration therapy by those affected. This is something that must be taken up on a war footing. Promises of clean water and effective sewage systems surround us in these times of clean elections; but when sewage pipes burst in the nation's capital, the stink speaks louder than a thousand campaign words.

Looking at the problems of diarrhoea as Molecular Biologists, C. Durga Rao and his colleagues from the Indian Institute of Science have been studying a viral pathogen that causes acute gastroenteritis. This virus is a double-stranded RNA virus, a rotavirus, and represents the major cause of infant diarrhoea. In their

detailed study (page 725) reported in this issue of *Current Science*, Rao *et al.* report the nucleotide sequence of one of the regulatory genes of a rotavirus and also express the product of this gene in bacteria to purify the protein product of the regulatory gene. Their work is of general importance because it provides reagents for the analysis of the mechanism of replication of this human virus. Studies on the basic biology of rotaviruses, in particular comparative studies on the evolution of pathogenic and non-pathogenic strains, are of the utmost relevance in understanding the molecular basis of virulence. The importance of such comparative studies with viruses in general cannot be underestimated as it is only by such studies that we can hope to understand how deadly viruses are born and spread.

Biologists today study 'pure' and 'applied' problems. Some use 'model' organisms and others do their work with 'relevant' animals

or plants. The strange thing is that very important basic results (such as the identification of DNA as the genetic material) has come from the study of applied problems and many important results that can be applied have their origin in very basic research (such as methods for sequencing DNA). Thus, while it is difficult to say whether or not the study of the Molecular Biology of rotaviruses will help reduce infant mortality; it is safe to say that studying it is far better than not and, more relevant, it is very likely that a careful study will actually yield valuable information on how the virus invades its host and replicates to cause its deadly effects.

K. VR

#### **Singlet oxygen generation by alkaloids**

In spite of its ubiquitous presence molecular oxygen does not con-

sume our organic world because in its triplet ground state the molecule is quite inert. However, the excited state of oxygen is a very reactive species. Any substance capable of promoting the conversion of triplet oxygen to the singlet form is potentially important in chemical and biological oxidation processes. If, in addition, the compound can intercalate with DNA and happens to be a natural product, it becomes a good candidate for drug screening.

In this context, M. Maiti and A. Chatterjee (page 734) demonstrate the production of singlet oxygen by two alkaloids, sanguinarine and berberine chlorides. The presence of fused aromatic rings evidently is responsible for their ability to function as photosensitizers for singlet oxygen production. The effectiveness of singlet oxygen generation has been quantified by analysing absorption spectral changes.

J. C.