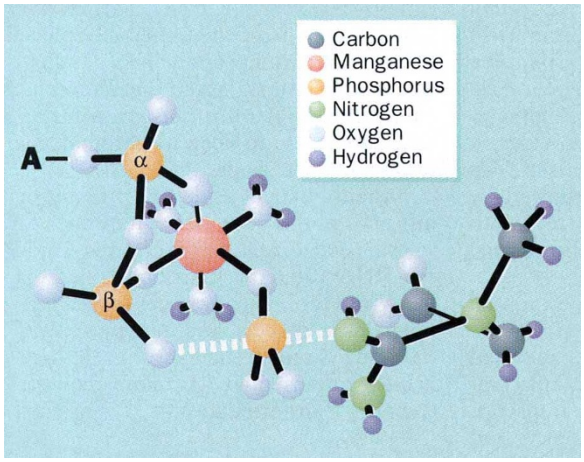

The creatine kinase reaction — putative transition state in the phosphoryl transfer reaction between MnADP (left) and phosphocreatine (right) to form MnATP and creatine. The structure of this activated complex was deduced using electron paramagnetic resonance studies of analogue complexes in the presence of oxygen-17 labelled nucleotides at the α- and β-phosphorus positions[14]. A is the adenosine moiety.

particular, the location of Cys 278 (282) merits comment, as its role in CK's mechanism has been rather controversial[6,7]. It is apparently located at a β-turn[8] between helix α_9 and strand β_6 (Fig. 1*c* of the paper) and, as such, looks to be strategically positioned to participate directly in catalysis. Alternatively, when modified by either relatively bulky or charged sulphydryl blocking agents, it can change the active site's geometry or steric access (or both), effectively obliterating catalysis. A more definitive insight into its involvement will have to await solution of a structure in the presence of either creatine or an analogue. In any case, a mutant RMCK with serine rather than cysteine at position 282 has been shown to be at least partially active (relative rate about 1/500 that of wild-type)[6]. Interestingly, Lys 195 in RMCK can be crosslinked with Cys 282 (ref. 9), indicating that they are close together in the structure. This result again is consistent with the Mi_b-CK crystal structure.

As Fritz-Wolf *et al.* discuss, the function of one of the conserved histidine residues in CK's catalytic mechanism as a possible acid/base catalyst has been the subject of intense scrutiny. Of all of the histidine residues found in the 43 guanidino kinase sequences published to date[10,11], only five are conserved — His 92 (96). l02 (105), l86 (l90), 229 (233) and 29l (295). All of them have been individually changed by mutation to their asparagine (N) counterparts in RMCK[11], each mutant then being overexpressed in *Escherichia coli* and characterized. H105N, Hl90N and H233N all displayed specific activities similar to those of the wild-type enzyme. Clearly, then, these histidines cannot be actively involved in catalysis. Expressed in a crude extract, H96N also had high specific activity, but the mutant seems to be quite unstable and has not yet been further purified. Its corresponding Mi_b-CK residue (His 92) is clearly observable in Fig. l*b* of the paper as being near the γ-phosphate group of the bound ATP. The most interesting mutant is H295N which showed much reduced, but still measurable, catalytic activity. His 291 (295) is near the nucleotide-binding pocket in the crystal structure. Its precise involvement in catalysis, however, will have to await more detailed structural information.

These mutational results with conserved histidine residues reinforce lessons that were predicted by Eigen[12] and dramatically emphasized by mutagenesis studies on thymidylate synthase[13]. It is advantageous for enzymes to have evolved to be robust — that is, mutations of residues even at or near the active site do not necessarily obliterate catalysis, but often have either no or only a minor effect. This is probably especially true of enzymes such as kinases, which rely primarily on proximity to achieve their catalytic effects. The main function of the enzyme is evidently to bring the substrates together intimately so that direct phosphoryl transfer can occur between ATP and the chosen substrate. Of course, the kinase provides the appropriate optimal electrostatic environment to promote charge-stabilization in the transition state (see figure). As Fritz-Wolf *et al.* point out, there is an abundance of positively charged residues at or near the nucleotide binding site to help create just such an environment. □

George L. Kenyon is in the Department of Pharmaceutical Chemistry, University of California, San Francisco, California 94143-0446, USA.

1. Fritz-Wolf, K., Schnyder, T., Wallimann, T. & Kabsch, W. *Nature* **381,** 341–345 (1996).
2. Teicher, B. A. *et al. Cancer Chemother. Pharmacol.* **35,** 411–416 (1995).
3. Chida, K. *et al. Biochem. biophys. Res. Commun.* **173,** 346–350 (1990).
4. Rossman, M. G., Moras, D. & Olsen, K. *Nature* **250,** 194–199 (1978).
5. Rosevear, P. R. *et al. Biochemistry* **26,** 5338–5344 (l987).
6. Chen, L. H. *et al. FASEB J.* **4,** A2119 (1990).
7. Furter, R., Furter-Graves, E. M. & Wallimann, T. *Biochemistry* **32,** 7022–7029 (1993).
8. Maggio, E. T. *et al. J. biol. Chem.* **252,** 1202–1207 (1977).
9. Mahowald, T. A. *Fed. Proc.* **28,** 601 (1969).
10. Mühlebach, S. *et al. Molec. Cell Biochem.* **133/134,** 245–262 (1994).
11. Chen, L. H., Borders, C. L. Jr, Vásquez, J. R. & Kenyon, G. L. *Biochemistry* (in the press).
12. Eigen, M. *Chem. Ser.* **26B,** 13–26 (1986).
13. Carreras, C. & Santi, D. V. *A. Rev. Biochem.* **64,** 721–762 (1995).
14. Leyh, T. S. *et al. Biochemistry* **24,** 308–316 (1985).

DAEDALUS

Shades of health

FACED with almost any complaint, a doctor's prime wish is that he could have seen it sooner. Early diagnosis is the key to cost-effective medicine. Daedalus now has a diagnostic breakthrough.

A tattoo, he remarks, is a pigment-implant about a millimetre under the skin, among the superficial cells of the dermal capillaries. It makes good contact with the circulating blood. Clinical laboratories these days have hundreds of elementary blood tests, each of which indicates the level of some key metabolite by a simple colour change. Daedalus plans to incorporate them all into a novel diagnostic tattoo.

A litmus tattoo, for example, would reveal blood pH. It would go red if the blood went acid, and blue if it went alkaline. Blood oxygen and carbon dioxide, calcium, potassium and iron, glucose and lactic acid, crucial vitamins and hormones, each could similarly be revealed by a suitable indicator. A thermochromic tattoo could show the body temperature. Piezochromic microballoons, collapsing under pressure to eclipse their surface colour, could reveal blood pressure; they might even pulsate visibly to display the heart-rate.

The diagnostic tattoo will probably be most useful on the inside of the wrist. It will be a grid of little coloured squares, each showing the level of a specific blood component. Levels which vary widely will need several squares, changing colour in sequence as the level rises. The wearer need not bother with the details; he can just check the tattoo as a whole against a standard shade card carrying the 'normal' colour pattern. Any deviation will send him to the doctor at once.

If the doctor then prescribes a drug, he need not worry about the dosage. The patient will simply take another tablet whenever the relevant square of the tattoo drifts towards the 'level too low' shade. In the same way, an alcoholic motorist could 'titrate' himself almost up to the legal blood-alcohol limit, and stop drinking when the warning square on the tattoo begins to change colour.

Sexually active women will use the tattoo to check their changing hormone levels. The monthly player of sexual 'Vatican roulette' will at last know her safe period exactly. The Pill-user will have daily reassurance of its adequacy, while the would-be mother will be instantly advised of her pregnancy.

Sadly, the first and most eager customers for the new tattoo will be hypochondriacs. They will spend hours scanning their tattoos for deviations from the shade card, and will reply to the innocent query 'How are you?' in devastating detail. David Jones