transfer; and bound (crosslinked) small molecules (usually ruthenium complexes) to protein electron transfer. The last method, in avoiding the need to determine independently the binding constants and sites of the reagents, is particularly attractive, and it is this method that Isied and collaborators have used to produce their disturbing results.

Before discussing the results of Isied's group in detail, we will briefly describe the ribbon structure of cytochrome *c* (see figure). X-ray diffraction studies of crystals of the protein and nuclear magnetic resonance studies of the protein in solution leave no doubt that the ribbon structure undergoes only a small change from the Fe(II) to the Fe(III) state. Nuclear magnetic resonance additionally provides a dynamic map of fluctuations and their energetics in the protein and has also been used to analyse the structural change and energetics associated with substitution at the iron (see figure). This is a first-order groove-opening reaction dependent on the breaking of the Fe(III)–methionine 80 bond and some small protein rearrangement involving a concerted movement of the section of the protein mainly under the haem. As a result of these studies, the following position was firmly established before the report of Isied's group.

(1) Electron transfer is a reversible phenomenon, which is axiomatic for self-exchange. Provided differences in redox potential are taken into account for forward and back reactions, there is no doubt about reversibility of electron transfer to or from free anions (ferrocyanide), bound cations (ruthenium derivatives) or other proteins (cytochromes *b*). There were no known gated bimolecular reactions involving cytochrome *c*.

(2) A small activation energy is associated with electron transfer for all three types of reaction with some small protein rearrangement (see figure), but electron transfer could not involve a step as energetic as the Fe–Met bond break or ring flips — that is, electron transfer has an activation energy of 10–20 kJ and not of the order of 50–100 kJ.

(3) There is an understandable distance dependence for electron-hop transfer with a rather higher transmission coefficient than expected from theory. This helps to allow long-range (10–15 Å) electron transfer at rates as fast as is commonly found in protein-to-protein electron hopping. Protein–small molecule (free or bound) electron transfer is usually somewhat slower and complicated by solvent relaxation energies, that is, the same type of relaxation, but larger, as that of the small conformation change in the metal protein on redox change, where the protein is the effective solvent.

(4) Electron transfer at these low redox potentials has little dependence on the chemical (amino acid) between the centres, whereas at high potential aromatic groups can act as hopping stations.

The experiments of Isied and collaborators throw all of these conclusions into question. Their results seem to show that the electron-transfer rate, properly corrected for redox potential, can be dependent on the *direction* of electron transfer, that is, it is irreversible. This means that different micro-states are involved for the reaction Ru(II) to Fe(III) and Fe(II) to Ru(III) in cytochrome *c*. Unless there is a gross experimental error in the characterization of species (for example, in structure) this means that this electron transfer can be gated.

The authors offer explanations as to how this could come about and they refer to the conformational states of cytochrome *c* we have described above. It has to be admitted that some states, such as those involved in the flipping of certain aromatic rings and groove openings, do involve activation energies of up to 100 kJ per mole, but it is hard to see how these motions could have anything to do with the electron-transfer steps in only one direction, especially as they are not involved in the other reactions described above. This is not to say that in some proteins, such as cytochrome P-450, electron-transfer reactions are not gated — in the case of P-450 they are gated by substrate binding. But in the very simple case under discussion we have a puzzle on our hands, in that one set of observations is completely out of line with all the others. Clearly the puzzle can be resolved only with a large series of measurements.

Given the importance of the observations of Isied and colleagues it is essential that at least one other group of inorganic chemists makes the same study independently. Until that is done we face the data with bewildered amazement, frankly hoping that they will go away. If they do not, we must re-examine a considerable part of our thinking about protein energy states and not just about electron transfer. □

R.J.P. Williams and D. Concar are in the Department of Inorganic Chemistry at the University of Oxford, South Parks Road, Oxford OX1 3QR, UK.

Dame Honor Fell FRS (1900–1986)

DAME Honor Fell FRS, who died on 22 April, was the pioneer of the technique of organ culture by which small organs or organ rudiments can be successfully grown *in vitro*. In such cultures the various tissue components and their spatial relationship and function are preserved so that the explanted organ closely resembles the parent tissue *in vivo*. In her hands the method proved particularly suitable for the study of developmental processes in fetal organ rudiments but has since been adopted and is still used for the cultivation of adult tissues.

Using this method she made a major contribution in the elucidation of the processes involved in skeletal development. She showed that both avian and murine limb bone rudiments have a remarkable capacity for self-differentiation and will grow and differentiate in the same manner *in vitro* as the organs *in situ*. She further showed that both growth and differentiation could be modified by extrinsic factors, such as vitamins and hormones.

An important example of this modification is the influence of vitamin A on the differentiation of cartilage and ectoderm. She showed that vitamin A added to the culture medium of avian ectoderm modified the direction of epithelial differentiation. The vitamin suppresses normal keratinization and induces mucus-secreting ciliated epithelium instead associated with an increase of sulphur uptake by the metaplastic cells. In embryonic cartilage the vitamin causes a severe breakdown of the matrix with a loss of metachromasia.

This finding formed an important link with her more recent investigations into the mechanisms involved in joint damage in arthritis. To simulate the rheumatoid pannus she grew pig articular cartilage in association with synovium and showed that the synovium, either in direct contact with the cartilage or in medium conditioned by synovial cells, has, like vitamin A, a deleterious effect on the cartilage ground substance, leading to a loss of proteoglycans and collagen, and of metachromasia.

Together with her colleagues at the Strangeways Research Laboratory, Cambridge, United Kingdom, she traced this effect to a factor secreted by the synovial cells, now identified as the polypeptide catabolin/IL1. Her finding constituted a major advance in the understanding of joint destruction in arthritis and forms the basis of much vigorously pursued international research in this field.

Honor Fell obtained her PhD in Zoology at Edinburgh University in 1923 and the same year joined Dr T.S.P. Strangeways at what was then the Cambridge Research Hospital. After his death in 1926 she became Director of the Laboratory now renamed Strangeways Research Laboratory in 1928, a post she held until 1970.

Under her directorship the small laboratory grew to a major institute of worldwide reputation. In the post-war years the laboratory became a focal point for visiting biologists from abroad whom she trained in *in vitro* methods and who came to rely on her advice, guidance and encouragement, which were unstintingly given. She was one of the most outstanding biologists of this century and her death means the end of an era in biomedical science.

Ilse Lasnitzki