news and views

Chinese work on insulin

from Dorothy Crowfoot Hodgkin

Two very beautiful papers on insulin appeared in *Scientia Sinica* in December 1974 (**17**, 752 and 779). They continue a sequence of scientific publications which began in 1961 and includes the total synthesis of sheep insulin, described in 1965. They are published by groups of research workers in China: in Peking in the University (Departments of Biochemistry and Organic Chemistry) and in the Institute of Physics of the Academia Sinica, in Shanghai in the Institutes of Organic Chemistry, Biochemistry and, most recently, Zoology. They provide impressive evidence of integrated researches in different disciplines and laboratories.

The first of the present two papers describes the derivation of an electron density map of insulin in rhombohedral 2-Zinc insulin crystals at 1.80 Å resolution. It gives useful experimental details of the preparation of the crystals and heavy atom derivatives, of the measurement and interpretation of the X-ray diffraction data and of the stages of solution of the structure. The model and electron density map (clearly of very good quality) are illustrated in colour and the atomic arrangement is described in detail. Ramachandran plots and a plot of the distribution of Cγ side chain atoms viewed along Cα–Cβ illustrate some of the stereochemistry observed.

The structure is essentially the same as that found in parallel crystallographic studies in Oxford; indeed, in 1972, in Peking, we compared in detail our earlier electron density maps, both drawn at a scale of 1 cm to 1 Å. There was actually a moment of acute concern when we put the maps together first and they did not fit—until we realised one was upside down compared with the other. We then saw that there was very good correspondence, if not exact agreement, between them. Correspondingly now, in the insulin dimer, molecule I Peking is molecule II Oxford, and molecule I Oxford is molecule II Peking.

One might not wish, in all cases, to see complete duplication of the X-ray analysis of a protein molecule—so much work is involved. But there are great gains in the present case from having two views of the insulin crystal structure. First, insulin is such an odd molecule and the situation in the crystal is very curious. The two insulin molecules in the asymmetric unit are very similar to one another, yet appear to differ in conformation in a number of details; it is comforting to see how closely the molecules described in the Chinese papers agree with Oxford findings. Earlier small differences between us are diminishing; it may well be that the final comparison will give us reliable estimates of the errors we must expect in general in placing atoms from X-ray data on proteins. The present Peking map at 1.80 Å resolution is the most accurate map available of the insulin electron density defined by experimental, isomorphous phase angles—and may well remain so. The calculations we are carrying out at Oxford, designed to show the electron density at 1.50 Å resolution, depend on the extension of the phases from 1.9 to 1.5 Å by various computing procedures, some very experimental. The total cross checking of our operations by the Peking analysis when we come to compare atomic coordinates should be very valuable.

Many of the comments made by the Chinese insulin research group on their findings are similar to ones we have made ourselves, but they often add illuminating details and occasionally recognise quite different features—for example, they realised that the dihedral angles of the glycine residues, B8, B20 and B23, were all in the region allowed for D residues. This led directly to experiments by the Shanghai chemists and biochemists who showed that B23 might be replaced by D-alanine in the insulin sequence with only partial loss of biological activity, whereas activity vanishes when B23 is replaced by L-alanine.

The second paper carries a stage further the study of structure–activity relations in the insulin field through direct measurements of the interaction of insulin and insulin analogues with receptor proteins in liver and fat cells. It, too, parallels and extends work in other laboratories.

Soluble receptor protein preparations were made by the method of Cuatrecasas, of fat cells by a new method avoiding collagenase. It was found that despentapeptide insulin had almost the same binding capacity as insulin, while deshexapeptide insulin and the corresponding molecule with B23 replaced by D-alanine had reduced, but definite, binding capacity. The results strengthen the view that the non-polar residues of the B chain surface, B12, B16, B24 and B25, are important in receptor binding and that the loop B20–B23 and perhaps also the salt bridge A21–B22 assist in stabilising the conformation in this region. There is a nice discussion in the first paper of the part that conformational variability may play in assisting membrane binding in this part of the insulin molecule.

It will be splendid if we can some day soon all meet and talk over the very interesting observations that are accumulating, East and West, on the structure and function of insulin.

Revising the Cainozoic polarity record

from D. H. Tarling

Now that the main plate tectonic band wagon has passed, the dust can be brushed off the marine magnetic anomalies that were so effective in getting it rolling. It is now possible to examine in more detail the record they provide of past geomagnetic changes and to refine the time scale of polarity changes.

The polarity time scale of Heirtzler *et al.* (*J. geophys. Res.*, **73**, 2119; 1968), based on anomalies recorded on profile V-20 SA in the South Atlantic, has stood up remarkably well. Profile V-20 SA was chosen as the longest available with no marked evidence of changes in the rate or direction of spreading, and the anomalies were dated by assuming that the observed spreading rate at the ridge axis—1.9 cm yr^{-1}—had remained unchanged for the past