seismicity is a stationary process on a time scale of thousands of years and that during those years the maximum earthquake has occurred at least once. Finally, implicit in the method is the assumption that the observed geological displacement along the fault is due to earthquakes rather than creep, for any significant component of creep would lead to an overestimation of the maximum expected magnitude.

The need for these assumptions and natural deficiencies in the basic geological data combine to ensure that the method is less than perfect. On the other hand, as Smith points out, it does have the merit over existing techniques of making greater use of geological information. In any event, application of the method predicts maximum magnitudes of 8.2–8.4 for the first order branches (for example, the Calaveras fault) of the San Andreas fault system, 6.3–6.5 for lesser branches (for example, San Simeon) and 6.3 for still lesser branches (for example, West Huasna). Whatever the validity of these figures (compare magnitude 8.3 for the 1906 San Francisco shock) they are certainly more precisely defined than those obtained from fault length–magnitude curves. For a 200 km fault, for example, the conventional technique would only give an upper limit in the looser range 7.3–8.5. □

Poly(ADP-ribose)

from Mark Smulson and Sydney Shall

The fourth International Workshop on poly(ADP-ribose) was held in Hamburg on August 2–4, 1976, was sponsored by the Deutsche Forschungsgemeinschaft and organised by Professor Helmuth Hilz.

THE enzyme poly(ADP-ribose) polymerase requires DNA and catalyses the successive transfer of ADP-ribose units from NAD to histones and other proteins associated with chromatin, the net result being negatively charged, short polymers covalently attached to nuclear proteins.

The workshop concentrated on three main themes; possible biological roles for this modification, definition of the nature and chemistry of the protein acceptors of the polymer, and the purification and characterisation of the enzyme itself. The most exciting advance in the area was experiments suggesting that poly(ADP-ribose) cross-links chromosomal proteins. P. R. Stone and W. R. Kidwell (National Cancer Institute, Bethesda) reported that after incubation of HeLa cell nuclei with NAD, a dimer of histone H1 can be isolated containing one linking chain of 15 ADP-ribose residues. Further evidence for this structure was provided in the previous week in a lecture at the International Congress of Biochemistry in Hamburg by G. Dixon (Calgary Medical School, Canada): he suggested either an inter- or intramolecular covalent linkage by way of poly(ADP-ribose) between glutamic acid residues near the amino terminal and carboxyl terminal ends of trout sperm histone H1. Since the concentration of poly(ADP-ribose) in intact HeLa cells reaches a maximum at the S-G2 phase boundary, Kidwell suggested that the crosslinking property of poly(ADP-ribose) for histone H1 (and perhaps non-histone protein acceptors as well) might function to link widely spaced H1 molecules along internucleosome regions and hence condense chromatin. This model was supported by the finding (M. Smulson, Georgetown University, Washington) that enzyme activity can be detected in internucleosome regions of chromatin and not on isolated nucleosomes.

Extensive purification of the enzyme has been accomplished independently in at least four laboratories. Okayama, Ueda and Hayaishi (Kyoto) have found during their 7,000-fold purification that an endogenous acceptor for ADP-ribose copurifies with the enzyme; and it may not be a simple protein. Histones decrease the K_m for NAD in their preparation. Confirmatory results were reported by K. Yoshihara (Nara Medical School, Japan). Both S. Shall (University of Sussex) and P. Mandel (Centre de Neurochimie du CNRS, Strasbourg) suggest the loss of an inhibitor of the enzyme during their purifications. In addition, Shall and coworkers have estimated the K_i for a number of poly(ADP-ribose) polymerase inhibitors which turn out to be also cyclic AMP phosphodiestrase inhibitors, with higher affinity for the poly(ADP-ribose) polymerase, suggesting that some biological effects attributed to cyclic AMP from inhibitor studies, might really be due to poly(ADP-ribose). Certain NAD analogues were reported to be incorporated into poly(ADP-ribose) chains (R. Suhadolnik, Temple University).

Various new data on chromosomal protein acceptors for poly(ADP-ribose) were presented. M. G. Ord and L. A. Stocken (University of Oxford) find that histone H3 as well as H1 has ADP-ribose. Hilz and coworkers (Hamburg, Germany) have found heterogeneity both in the acceptors among non-histone proteins and in the sensitivity of the covalent linkage to cleavage. The proportion of monomer and polymer varies with changes in cellular proliferation rates. M. Miwa and T. Sugimura (National Cancer Centre, Tokyo) have been able to detect polymer chains with equal (ADP-ribose) units but with different phosphate termini by acrylamide gel electrophoresis.

One frustration has been the heterogeneity in the "tentatively" reported covalent linkage of the first ADP-ribose to histones. The proposed linkages include attachments from C-1 ribose to glutamyl carboxyl and threonyl hydroxyl by way of glycosidic bonds, to seryl phosphate by way of an ester bond or N-glycoside to arginine, and a possible Schiff base linkage. Much work clearly needs to be done in this area, but the heterogeneity of acceptors between histones and non-histone proteins suggests that various covalent attachment sites will ultimately be established.

The development of new ultrasensitive assays, including fluorometric determination (Mandel) and radioimmunoassays (Miwa and Sugimura; Bredehorst and Hilz; Kidwell) for quantitation of poly(ADP-ribose) in cellular extracts, have produced substantial, but still far from definitive progress towards assigning a biological function to this fascinating chromosomal protein modification system. Reports at the workshop suggest that ADP-ribosylation, like other nuclear protein modifications such as phosphorylation, probably has multiple functions all revolving around specific large or small structural pertubations of chromatin. Increases in enzyme activity are noted in SV40 transformation of cells (M. Miwa and T. Sugimura) for example; in induction of globin mRNA in Friend cells (E. Rastl, Ernst-Boehringer-Institut, Vienna) and an interesting correlation was described by A. Caplan (Case Western Reserve University, Cleveland) between intracellular NAD levels, poly(ADP-ribose) polymerase activity and the differentiation of mesenchymal cells either to muscle or cartilage.

Experimental approaches which make use of the effect of cytotoxic DNA-alkylating agents on poly(ADP-ribose) polymerase activity and *vice versa* also indicate that poly(ADP-ribose)–induced changes in chromatin structure may be important in repair of DNA damage. Fragmented sites seem to be a signal for increased *in vivo* activity of poly(ADP-ribose) polymerase (groups at Georgetown and Sussex).

On the basis of data showing accumulation of poly(ADP-ribose) in mid-S phase and again in the G2 phase of the cell cycle (Kidwell) there was also speculation that chromatin repair and housekeeping must occur after the first peak of S phase, perhaps by way of polyADP-ribosylation relaxation of chromatin, and again in early G2 phase for cells to complete a normal cycle.