03. X–1 MOLECULAR STRUCTURE AND BIOLOGICAL ACTIVITY: STRATEGIES FOR INVESTIGATION. A.S. Horn, Department of Pharmacy, University of Groningen, Groningen, The Netherlands.

The process of molecular structure analysis in drug design has multiple facets and may be approached in various ways. This lecture will consider three main areas i.e.

1. What useful information can be derived from a study of conformationally restricted analogues regarding receptor site preferred conformations? How does this information compare to other methods such as N.M.R. and theoretical calculations? Has this approach produced any new drugs?

2. What can an analysis of the molecular structure of agonists and antagonists tell us about the essential pharmacophore and the possible nature of the binding at the receptor site? How can this information be used in drug design?

3. What are the other factors in addition to molecular conformation which play a role in drug action? What are the roles of multiple receptors, lipophilicity and metabolism? What are the "pharmacological pitfalls" that a crystallographer may encounter in this type of work?

03. X–2 THE USE OF CRYSTAL STRUCTURE DATA IN MEDICINAL CHEMISTRY. By P.Murray-Rust, Glaxo Group Research, Greenford, Middx., UB6 0HE, U.K.

Most drugs are known (or believed) to act by binding to macromolecules (enzymes, receptors, DNA, etc.) but the precise nature of this binding is normally unknown, particularly when the drug molecule is flexible. Knowledge of the crystal structures of biologically active molecules might thus seem to be of little use in the search for new drugs. In practice, however, when we can compare the structure of an active molecule to those of chemically related molecules we can often answer the questions:

- How flexible is the molecule?
- What groups in the molecule are likely to be involved in strong intermolecular contacts?
- Are there other molecules which, though chemically different, possess the same pharmacophoric groups in the same spatial positions?

Over 30 000 organic compounds are now on the Cambridge Data File, many of which are of biological interest. The crystal environment of a molecule can easily be calculated and can throw new light on the intermolecular interactions of a pharmacophore. An important aspect is the ease with which a non-crystallographer can review the structural aspects of a group of compounds. The file can also been seen as a library of molecular geometries and can be used to search for compounds containing groups of atoms which might be used as new frameworks onto which to attach pharmacophores.

03. X–3 X-RAY CRYSTALLOGRAPHIC CONFORMATION AND CENTRAL NERVOUS SYSTEM ACTIVE COMPOUNDS. By J.P. Tollenaere, Department of Theroretical Medicinal Chemistry, Janssen Pharmaceutica Research Laboratories, 2340 Beerse, Belgium.

It is now widely accepted that the 3-D structure of CNS active drugs is of major importance towards an understanding of how molecules interact with their receptor. The knowledge of their preferred conformation in the solid, dissolved and isolated state may offer a means of tentatively classify the various drugs in terms of their 3-D characteristics. The underlying rationale for this is that a given receptor will recognize and interact with a molecule in its biologically relevant conformation. It should be stressed that conformation analysis pertaining to any of the three classical aggregation states of matter remains an approximation to the conditions prevailing at the receptor site or its environment. Nevertheless the solid state conformation is a minimum energy conformation or one of the intrinsically probable conformations.

Since the early seventies, a great number of crystal structures of CNS agents became available (J.P. Tollenaere, H. Moereels and L.A. Raymaekers (1979), Atlas of the Three-Dimensional Structure of Drugs). Based on the analysis of the solid state conformations of anticholinergics, $H_1$-antihistamines, dopamine antagonists and analgesics, it can be shown that the emerging pharmacophoric pattern for each of these classes of CNS agents is not impressively precisely defined.

Thus, although useful information can be gathered from X-ray data, it is apparent that the solid state conformation of flexible molecules as most CNS agents are, is necessary but surely not sufficient knowledge towards our better understanding of the pharmacophoric requirements for the various CNS receptors.

03. X–4 ION TRANSPORT ANTIBIOTICS. M. Dobler Organic Chemistry Laboratory, Swiss Federal Institute of Technology, ETH-Zürich, CH-8092 Zürich, Switzerland.

Ion transport antibiotics have the ability to selectively complex metal cations, especially of alkali and alkaline earth metals, and to transport them through biological and artificial membranes. Such ionophoric antibiotics are conveniently divided into two groups, distinguished both by structural differences and by differences in their effect on mitochondrial respiration. The valinomycin group consists of macrocyclic molecules built from regular sequences of aminoacid or hydroxyacid units. They are neutral molecules with no ionizable groups and little or no ability to catalyze proton transport across membranes. The nigericin group are polycyclic polyethers with a terminal carboxyl group at one end and one or two hydroxyl groups at the other. The carboxyl group is ionized, giving the molecule a negative charge. A cyclic conformation is maintained by hydrogen bonding between hydroxyl groups and carboxylate anion. The nigericin group antibiotics are able to couple $H^+/K^+$ transport across membranes.

Results of crystallographic, spectroscopic and theoretical investigations enable us to relate the structures of these compounds to their ion-specific properties. Crystal structure analyses of such antibiotics in both uncomplexed and complexed form have lead to tentative models for the complexation process.