

Our knowledge of biological receptors is mainly derived from a knowledge of the size, shape and other characteristics of molecules producing a particular biological response and the characteristics of the activated state are ignored. Examples of accumulation of evidence to help to define several biological receptors are described.

Antibodies may be considered as model biological receptor sites, and hapten-antibody association used to study the importance of size and shape of molecules in the surface interactions. Stereo-selective adsorbents prepared from silica may also be used as simple drug-receptor models. Physico-organic measurements and modern conformational principles facilitate a representation of size and shape of molecules under biological conditions. Effective molecular size may be altered by hydration, aggregation and micelle formation and thus the biological action of a particular type of molecule affected.

Many enzymatic processes are stereo-selective. Penetration of certain membranes is under stereo-selective control. The action of many drugs is partly dependent upon their geometry. Side effects of drugs may be largely attributed to the molecules being adsorbed at "undesirable" as well as at "desirable" receptor sites of slightly differing size and shape requirements. One approach to the search for clinically more selective drugs should therefore involve minor modifications on a three dimensional plan of molecules with known biological actions.

### 23 Chemical Structure, Physical Properties, and Biological Activity. A. BURGER (U.S.A.).

This lecture will explore the possibilities that medicinal chemists now have to influence the activity of different chemicals during their paths to their receptor sites and their duration and selectivity of action at these sites. The first problem is to study structural variations or temporary alterations of compounds known to possess a given biological activity if their potency or specificity is inadequate. Protective alterations may keep a reactive compound from being absorbed randomly and prematurely and from being excreted, or they may activate an unreactive molecule so that it will be properly absorbed and distributed. The methods available in these areas will be reviewed.

Analogous considerations are applied to improve the actual reactions or to block alternate metabolic reactions at receptor sites. Following a "lead", the molecule can be changed by increasing or decreasing those binding forces which affect the attachment and maintenance of the drug at the receptor. Apart from the few successful methods of producing irreversible inhibitors by covalent binding, one has to rely on minute and mostly empirical methods of balancing reversible polar, electronic and short-range forces in the molecule. A summary of contemporary work in this field will be given.

Drug activity at receptor sites can also be affected by altering metabolic and blocking reactions. This leads to the intellectually most challenging aspect of medicinal chemistry, the rational design of new biologically active structures. At present, most of the pertinent working hypotheses are still in formative stages, and there are too many exceptions to make them really satisfactory. Theories of metabolite antagonism are overlayed with stereochemical ideas to accommodate various advanced forms of the lock and key fit explanations of drug mechanisms. Since several stereochemical observations have been reviewed by Beckett in the preceding paper, other aspects of reactivity, that is, of various chemical and physical properties, will be dealt with here. How far have we come since the early days of isosterism? How can we get out of the shackles of minor alterations imposed by small molecules as the only acceptable classical procedure? How much should one adhere to biochemical analogy, and how can unorthodox structures be reconciled with metabolite analogues? An attempt will be made to illustrate such cases with established observations as a basis of predictability of novel drug structures.

### 24 Discussion of Previous Papers. P. JANSSEN (Belgium) and G. B. MARINI-BETTOLO (Italy).

#### 25a Inhibiteurs de la Monoaminoxidase et Potentialisation du Sommeil Expérimental. P. LECHAT et M. LEMEIGNAN (France).

Les effets sur le sommeil expérimental de l'administration préalable d'inhibiteurs plus ou moins puissants de la mono-amino-oxydase ont été étudiés chez la souris et chez le rat. Les trois hypnotiques utilisés ont été choisis de structure chimique différente: chloral, hexobarbital et méthyl-4- $\beta$ -chloréthyl-5-thiazole (Hémicineurine). Les trois inhibiteurs ont été: isoniazide (100 mg/kg), iproniazide (100 mg/kg) et JL 1314 (10 mg/kg). A ces doses, seuls les deux derniers exercent un pouvoir inhibiteur puissant et sensiblement égal sur la MAO. Ils ont été administrés par voie péritonéale, 30 min avant les hypnotiques, ceux-ci étant injectés par voie veineuse.

En considérant comme seule significative d'une potentialisation, une multiplication par deux au moins de la durée du sommeil témoin, on constate dans ces conditions expérimentales, que: (1) l'hexobarbital est potentialisé d'une façon sensiblement identique par les trois substances chez la souris et chez le rat; (2) le chloral n'est potentialisé que par le JL 1314 chez la souris; (3) le méthyl-4- $\beta$ -chloréthyl-5-thiazole n'est potentialisé que par l'iproniazide chez la souris.

On peut en conclure qu'inhibition de la MAO et augmentation de l'effet des hypnotiques ne vont pas systématiquement de pair, puisque suivant leur nature chimique, les hypnotiques se trouvent ou non potentialisés par des substances dont le pouvoir inhibiteur sur la MAO est très différent.