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166 Passage of Drugs Across the Gastro-intestinal Epithelium. L. S. SCHANKER (U.S.A.).

Absorption studies with the stomach, small intestine, and colon have revealed that the gastro-intestinal epithelium behaves as a lipid-like barrier to the passage of many drugs and other foreign organic compounds. Drugs administered in true solution are readily absorbed in their lipid-soluble, undissociated form, and very slowly absorbed in their lipid-insoluble, ionized form. Moreover, with drugs that are mainly undissociated, the rate of absorption is roughly related to the lipid/water partition coefficient of the undissociated form—the greater the coefficient, the more rapid the rate of absorption. In the stomach, where the contents are strongly acid, acidic drugs like the salicylates and barbiturates exist as undissociated molecules and are readily absorbed; in contrast basic drugs, including many plant alkaloids, exist largely as ions and are very slowly absorbed. In the small intestine and colon, where the contents have a pH of 6 to 8, most weak acids and bases are at least partially undissociated and are absorbed at various rates depending on their lipid-solubility. Slowest rates of intestinal absorption are observed with completely ionized drugs like quaternary ammonium compounds and sulphonic acids, and with lipid-insoluble molecules like sulphaguanidine and mannitol.

Although the gastro-intestinal absorption of most foreign organic compounds may be explained in terms of simple diffusion across a lipid-like boundary, there is evidence that a drug may also be absorbed by a specialized transport process if its chemical structure is similar enough to that of the natural substrate. For example, the foreign pyrimidines, 5-fluorouracil and 5-bromouracil, are actively transported across the intestinal epithelium by the process which transports the natural pyrimidines, uracil and thymine.

167 Biliary Excretion and Choleresis. I. SPERBER (SWEDEN).

The transport mechanism handling bile salt in the liver appears closely similar to the renal tubular mechanism secreting, e.g. phenol red and hippuric acid. This mechanism may transfer into the bile (in addition to bile salt) a great number of other substances, mostly aromatic acids of a molecular wt. of 350–700. Several of these compounds are excreted in comparatively large amounts, and have a choleretic effect. To obtained information concerning the nature of this choleretic effect the concentration of such substances in bile has been examined. To reduce, if possible, the influence of variations in bicarbonate secretion and reabsorption, and the basal excretion of bile salt, only those experiments are included, where the bile flow has been more than doubled by the choleretic effect of the substance examined.

In experiments with chicken, cholate, taurocholate, dehydrocholate, phlorizin, phenol red and polyethylene glycol have been used. Further experiments have been made in the turkey, pigeon, goat, rat, rabbit and guinea pig. The concentration of these substances is usually between 25 and 60 mM/a., except for the micelle-forming cholate and taurocholate, which show decidedly higher concentrations, and polyethylene glycol (usually lower concentration).

The results obtained are considered to be in satisfactory agreement with the hypothesis that the secretion of bile salt (and similarly handled compounds) into the bile capillaries is the primary event in bile formation. The osmotic effect of these large ions may be supposed to result in the inflow of water and dissolved small ions and molecules.

168 Renal Excretion of Weak Organic Acids and Bases. G. H. Mudge (U.S.A.).

The renal excretion of certain organic acids and bases is determined by filtration, active secretion and passive back diffusion. Secretion involves a minimum of two separate mechanisms, one for acids and one for bases. With the increasing number of compounds which are being demonstrated to be actively transported, specific structural requirements for transport remain difficult to define. Competitive inhibition of apparent secretion is the most reliable criteria for identifying an active transport component. The degree of tubular reabsorption varies greatly, from (for example) *p*-aminohippurate, which is virtually non-reabsorbed, to probenecid, which is normally completely reabsorbed. Within series of analogues the rate of urinary excretion is a function of four independent variables. Acid strength (p*Ka*) and lipid solubility are inherent chemical characteristics; urine pH and volume are biological variables. There is no convincing evidence that any of these factors determines the rate of active secretion. The experiments are consistent with the hypothesis that each of these factors influences the rate of non-ionic back diffusion through a lipid membrane, presumably the distal tubule, but not necessarily excluding the proximal tubule. The concept of continuous and simultaneous active secretion and passive reabsorption imposes rigid experimental restrictions on the study of active transport by either the clearance or tissue slice techniques. Most products of drug metabolism are less lipid soluble than the parent compound and, hence, appear to be eliminated by the kidney as a result of decreased reabsorption.

169 Effect of Drugs on Renal Transport Mechanisms. R. W. BERLINER (U.S.A.).

The wide variety of transport processes in the kidney and the fact that they may be modified by a number of drugs and hormones makes it necessary

to limit the scope of the material to be covered in this presentation. Consideration will be limited, therefore, to those agents which have major influences on the transport and excretion of strong monovalent electrolytes. Although these transport processes are subject to modification by the effects of many drugs, and these effects are frequently utilized for therapeutic purposes, information concerning the mechanisms by which these effects are produced is, at best, fragmentary. The effects of several agents are of particular interest because they relate these transport processes to others in systems which are more easily subjected to direct study. Among these are: (1) the agents derived from or related to the glycosides of digitalis; (2) inhibitors of carbonic anhydrase; and (3) pituitary antidiuretic hormone. Two other groups, the mercurial diuretics and the benzothiazide derivatives, are of particular importance because of the intensity and therapeutic usefulness of their effects but, unfortunately, virtually nothing is known of their mechanism of action and even the locus of this action is in dispute. Discussion will be concerned with what may be inferred about the nature of renal tubule electrolyte transport from the effects of these drugs.

170 Discussion of the Previous Paper. F. BERGLUND (Sweden).

171 New Aspects of Cardiac Glycosides. Introductory Remarks. W. WILBRANDT (Switzerland).

172 Stereochemistry of Glycosides as Related to Biological Activity. C. TAMM (Switzerland).

The aglycone moiety is responsible for the physiological effect of the cardiac glycosides. Therefore, the stereochemistry of the cardenolides and the bufadienolides (toad poisons) is discussed with emphasis on the conformational aspects. The cardiac aglycones differ in their structure from the steroids of other biological activity in a characteristic manner.

On the basis of the geometric mean of the cat lethal doses (LD) a detailed analysis of the activities of the various structural types of glycosides is presented: (1) Effect of the sugar unit if combined with the same aglycone; (2) Effect of the aglycone unit if combined with the same sugar; (3) Influence of the number of sugars; (4) Effect of the nature of the unsaturated lactone group; (5) The role of the position and the stereochemistry of the functional groups in the aglycone; (6) The importance of the nature of the glycosidic linkage in the glycosides; (7) Activity of chemical derivatives of aglycones and glycosides.—Unpublished results are included in this consideration.

Finally, the scope and limitation of the assay method used above and the relationship to other biological methods are discussed. Furthermore, the possibilities of employing such results for the evaluation of therapeutical use are considered.

173 Possibilities of Further Development in the Glycoside Field by Modifying the Glycoside Structure. K. K. CHEN (U.S.A.).

More than 30 years ago we started to investigate the chemistry and pharmacology of Chinese toad poison.[1] Our interest was focused on digitalis-like substances. This was followed by isolation of similar products from 14 species of toads, all of *Bufo* genus. Our work was soon extended to glycosides and aglycones of plant origin. To date, cat-assay results and other observations on about 300 compounds, mostly supplied by Reichstein and Stoll, have been accumulated suitable for consideration of structure–activity relationship. As a rule, cardenolides are weaker than bufadienolides of the same configuration. The glycosides of cardenolides are generally more active than their parent aglycones, but those of bufadienolides frequently have a potency equal to or lower than their aglycones. Among the cardenolides, acetylation of the OH-group at C_3 or C_{16} has a favourable influence on cardiotonic activity. The aldehydes at the angular C_{10} are stronger than the methyl analogues. Epimerization at C_3, α-orientation at C_5 or saturation in the lactone ring results in a decrease or disappearance of action. Thirty-eight compounds were tested in patients with ventricular fibrillation, but they are all less easily absorbed through the gastrointestinal tract than digitoxin. The renotropic effect, speed of action, absorbability, and emetic action of glycosides will be discussed.

1. CHEN, K. K. (1929), *Proc. Soc. Exper. Biol., N.Y.*, **26,** 378.

174 Metabolism of Cardiac Glycosides. K. REPKE (Germany).

This review considers the metabolic fate of cardenolides but only in so far as facts may be related to their mode of action.

The double bond in the lactone ring may be reduced, but this reaction proceeds slowly and irreversibly so that this part of the molecule cannot serve as a hydrogen carrier in intermediary metabolism. Hydroxylation at C_{12} is not a necessary prerequisite for activity. The glycosides may undergo fission in the body to produce the corresponding genins as intermediary products. The aglycones may function as coenzymes of a transhydrogenase, but it has been shown that this effect has no relation to their mode of action. The glycosides are acting directly as such. The importance of the sugar component consists in favouring enrichment of the molecules in the heart and in preventing rapid inactivation by epimerization and conjugation at C_3-OH.

Digitoxin is not more enriched in the heart and, in part, even less than in other organs. The subcellular distribution has not been clarified beyond doubt as yet. The overall distribution will not