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INTRODUCTORY REMARKS

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The study of interactions of organic molecules with plasma proteins began in the 1930s and was reviewed extensively by Goldstein in 1949. Early research on the binding of anionic dyes to plasma proteins from patients with poor renal function revealed decreases in the binding (Bennhold 1932, Onishi and Sugs 1940 (cited in Baker 1951), and Ehrstrom 1937). Thus, study of drug-protein binding in disease was part of the early investigation of this phenomenon.

Several investigators in the 1960s found that sulfonamide binding was decreased in the plasma of uremic patients (reviewed in Reidenberg 1976). Odar-Cederlof, Lunde, and Sjoqvist (1970) were the first to observe decreased binding of phenytoin in plasma from a patient with uremia.

The first systematic study of drug-protein binding in renal disease was published in 1971 (Reidenberg et al.). Phenytoin binding was observed to decrease in proportion to the degree of renal impairment as measured by blood-urea nitrogen (BUN), serum creatinine, or clinical state of the patient. Since phenytoin, the sulfonamides, and the dyes are all acidic drugs, it seemed clear at that time that acidic drug binding was decreased in uremia. Desmethylimipramine was then studied as a prototype organic base and found to have normal binding in uremia. This differentiation of drugs into anionic or cationic classes for binding studies has been a useful classification in subsequent studies of many investigators studying many different aspects of drug-protein binding.

Evidence that cationic drugs bind to protein other than albumin came from studies of quinidine binding by Nilsen and Jacobsen (1975) and Fremstad et al. (1976). These workers found that quinidine was bound to alpha$_1$-acid glycoprotein, an acute phase reactant, and that

the binding went up after surgery in parallel with the increase in this protein. Piafsky and Borgå (1977) subsequently confirmed the importance of base binding to alpha$_1$-acid glycoprotein using alprenolol and imipramine as the test compounds.

Studies of drug-protein binding have been so extensive that several symposia have been held and many review articles have been written on the subject. The symposia include one held by the New York Academy of Sciences in 1973 (Anton and Solomon 1973) and one held by the Swedish Academy of Pharmaceutical Sciences in 1980 (Danielsson 1980) on the general subject of drug-protein binding, and one on clinical implications of drug-protein binding sponsored by the Syva Company in 1983 (Levy and Shand 1984).

There are a number of reasons why the subject of drug-protein binding has achieved such great popularity. The studies can be technically easy and inexpensive to perform. Thus many investigators can do them. These studies can easily be carried out in patients and so appear to have clinical and medical relevance. Because there are so many different drugs and different physiologic states, one can usually identify a match that has not been published previously and thus do "original" research in this subject. Additionally, studies of drug-protein binding can reveal information about fundamental biological phenomena and disease processes. These studies can also give important information that is immediately relevant to the practice of medicine and proper patient care.

The purpose of this symposium is to bring together experts on drug-protein binding to discuss basic biologic and biochemical mechanisms and disease processes to gain insight into the subject. In addition, the clinical consequences of drug-protein binding and its changes in physiology or disease will be considered. We hope that this symposium will enhance our overall understanding of drug-protein binding and its importance as well as provide a stepping stone toward greater knowledge of biology and medicine in the future.

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