pKa for Medazepam

In the July issue of this Journal, le Petit[1] reported the pKa for medazepam in the Communications section. Since the data reported were not "new findings of outstanding importance," I assume that the impetus for publication was "corrections and reinterpretations of previously published reports."

By spectroscopic and solubility measurements, le Petit determined the pKa for medazepam to be 6.17 at 37°. He stated that "the findings disagreed with previous results." Two previous studies are cited. One[2] was a spectroscopic determination (pKa 4.4) at 20°. Thermodynamically, the pKa of a charged weak acid is expected to increase with a temperature increase. Thus, the difference between the two values is not surprising and no literature "correction" is necessary. The second study[3] reported a polarographic pK′ value of 8.7 (room temperature assumed). This value cannot be compared to the thermodynamic pKa of medazepam attributable to the azomethine functional group. Because of these erroneous comparisons, the paper is not scientifically valid, and I am surprised at the failure of our reviewing system to detect its inadequacies.

Additionally, if the comparisons had been valid and literature "corrections" necessary, I feel that the corrections should be published in the journal where the original error or misinterpretation was presented. Publication in the *Journal of Pharmaceutical Sciences* of data from other journals in need of correction is inappropriate and delays publication of original contributions.

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Structured Water in Biology: A Revolution in the Making

The controversy over the role of structured water in cell physiology is steadily increasing in the literature[1]. The controversy is no longer about the existence of structured water in the cell but over the extent of its role in cell physiology. However, little of this controversy has appeared in the pharmaceutical literature.

Limitation of space precludes more than a resume of the contending positions. The classic position in biology holds that the cell is an aqueous medium in which various aggregates of molecules and ions are suspended, the whole of which is contained within a membrane. The membrane is a separate sac-like structure, which selectively permits reversible diffusion. Cytoplasm is considered to be in the same thermodynamic state as the extracellular aqueous medium in which the cell exists.

Therefore, when an entity such as the sodium ion is present in the extracellular fluids at a higher concentration than it is in the intracellular fluids under invariant conditions, it is necessary to postulate a mechanism, *i.e.*, a "pump," to maintain steady-state conditions. Since "pumping" is against a concentration gradient, it is also necessary to postulate the use of energy. Energy is considered to be available from metabolism.

An alternative view, referred to as "water structuring," maintains that the cytoplasm is in a different thermodynamic state, *i.e.*, lower dielectric constant, different colligative properties, *etc.*, than is the surrounding extracellular plasma. In this case, the concentration difference of intra- and extracellular sodium ions exists in equilibrium because the cytoplasm and plasma are in different thermodynamic states.

As an analogy, one may cite olive oil in contact with bulk water. If sodium chloride is introduced into this two-phase system and an equilibrium is reached, the concentration of salt in the oil will be much less than in the water. No energy-consuming pumps need be postulated to explain this equilibrium. The equilibrium is a function of chemical potential differences. The oil is thermodynamically analogous to the structured water (cytoplasm), and the bulk water is thermodynamically analogous to the bulk water of extracellular fluids.

Any critically decisive test of these concepts must involve the role of energy. Thus, how can the following fact be accounted for? The body is a perfect calorimeter, and an intake of 2000 calories in foodstuffs produces 2000 calories as heat. From the foregoing fact, the second law of thermodynamics would state that, in a reversible invariant system such as the body, there can be no energy available for work such as is required by the sodium pump[2].

A modification of the water structure concept, which has developed historically, regards the cytoplasm and all of its component molecules as being in a structured equilibrium. This structured cytoplasmic matrix is known as a coacervate phase. The membrane is an integral part of the cytoplasm and is the interface between the cytoplasm and the extracellular fluids. Since all of the components of the cytoplasm contribute to the equilibrium structure, a virtually infinite number of structural configurations are possible; these, in turn, explain the subtle solvent and other highly specific properties of the cell[3]. The growing acceptance of the concept that the membrane is a liquid structure fits more readily into the coacervate model than it does the sac-like classic model.

The basic concepts on which virtually all of the pharmaceutical sciences operate are involved in this controversy. This fact should be reflected in the pharmaceutical literature.

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