The only variable was the dialysis method, that is, equilibrium dialysis (2) and dynamic dialysis (1). These findings are essentially an indication that the two dialytic methods may give equivalent results. Curve D, representing results using bovine serum albumin are not relevant since bovine serum albumin was not used in my work. Curve A, for 1% human serum albumin, suggests that binding characteristics change with protein concentration. Curve C, representing human serum albumin in phosphate buffer, suggests that protein concentration is of no consequence in phosphate buffer, although it is in tromethamine buffer. Figure 1 (1) thus leads to the conclusions that results with tromethamine buffer are different from those obtained with phosphate buffer and that protein concentration is of consequence in tromethamine buffer but not in phosphate buffer. These conclusions are not in disagreement with my findings because I made no claims about the generality of results in tromethamine buffer.

Figure 2 (1) is very difficult to interpret as presenting conflicting data because it represents data of experiments using 1% human serum albumin in phosphate and 1% bovine serum albumin in phosphate while only 2% human serum albumin was used in my work. In the experiments (2), the sulfonylureas usually were bound to the extent of 80% or higher at all concentrations of sulfonylurea used with the exception of the highest (81–84 $\times$ 10^{-8} mole) at which 40–60% binding was found, which is a rather substantial interaction.

A comment (1) was made that estimation of binding constants from extrapolation of the linear portion of Scatchard plots may be inaccurate. There is no disagreement on this point. The binding constants (2) were approximations because of this reason and, more basically, because of the limited number of data points. However, there is reasonable agreement in Table I between the n value for tolbutamide with 2% human serum albumin in tromethamine and that determined by Crooks and Brown. The difference between the n values for tolbutamide with 2% human serum albumin in tromethamine (2) and in Reference 1 is less than that shown in Meyer and Guttman's paper (3) comparing k_1 for their kinetic method and literature values for ultrafiltration.

I cannot accept the conclusion of Crooks and Brown that there is questionable significance to my data on drugs competing with the binding of sulfonylureas to human serum albumin. Given that tromethamine may bind to human serum albumin, the amount of tromethamine was constant in each cell and the reduction in binding caused by the presence of competitor drugs was beyond that possibly caused by tromethamine. The reduction in binding caused by these competitor drugs was significant, and the results clearly have qualitative significance. Quantitative conclusions in terms of the amount of reduction in binding of sulfonylureas to human serum albumin caused by a number of moles of competitor drug would not be absolute if tromethamine also acts as a competitor drug; but with a constant amount of tromethamine in each system, the quantitative conclusions would be relative.

I believe Crooks and Brown (2) make two important contributions which do not represent disagreement with

my findings (1) but actually extend our knowledge of binding of sulfonylureas to human serum albumin and, perhaps, protein binding in general. First, buffer systems may have significant effect on binding and more than one buffer system should be employed to ascertain these effects. Second, protein concentration may affect binding characteristics, although this finding is not new. Brunkhorts and Hess (4) found differences in binding parameters at different concentrations of albumin in studies of the interaction of the latter with cortisol. Perhaps this phenomenon, not yet satisfactorily explained, may be more general than is now appreciated.

(1) M. J. Crooks and K. F. Brown, J. Pharm. Sci., 62, 1904(1973).
(2) J. Judis, ibid., 61, 89(1972).
(3) M. C. Meyer and D. E. Guttman, ibid., 57, 1627(1968).
(4) A. Brunkhorts and B. Hess, Arch. Biochem., 111, 54(1965).

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Importance of Considering Variables when Using Magnetic Basket Dissolution Apparatus

Sir:

In several recent articles (1, 2), the versatility and adaptability of the magnetic basket were demonstrated. This apparatus was initially developed to yield reproducible dissolution profiles for capsules. The adaptability of the magnetic basket apparatus to tablet dissolution was also discussed (2). By using several sets of specially formulated tablets as the control, the magnetic basket was shown to differentiate between the common tablet parameters of hardness, particle size, and formulation changes, thereby illustrating its possible use in quality control. However, to use the concept of the magnetic basket as a means of correlating in vitro dissolution with the in vivo performance of a drug, further adaptability of the basket must be considered. Since the above-mentioned tablet parameters are not appreciably changed and remain constant after initial clinical testing demonstrates the effectiveness of the dosage form, the dissolution system must be able to show further versatility in its ability to provide an in vitro dissolution profile which approximates the in vivo behavior of the drug. Adjustment of the in vitro conditions, such as propeller height and revolutions per minute, or a change in the mesh or size of the basket

would seem to be the means of achieving this approximation.

To test this hypothesis partially, two new magnetic baskets were built. The first conformed to the original specifications (1) but was made of 16-mesh instead of the original 8-mesh stainless steel wire. The second basket was constructed with 8-mesh wire and had larger dimensions: an inner diameter of 12 mm. and a length of 38 mm. instead of the 11 × 25-mm. dimensions of the original basket.

A tablet and capsule were selected to be tested. Pentobarbital tablets were prepared in our laboratories, which allowed control of the ingredient and manufacturing variables. Commercially prepared sodium butabarbital capsules were selected since a previous publication (1) showed that capsules manufactured in an automated manner show less variance than hand-packed capsules.

The pentobarbital tablets were tested in the three different size baskets and showed no clogging of the pores in any case. At least five tablets of the same formulation and hardness were run in each basket. The T_{50} percent values increased in the expected order as the dimensional and pore size of the baskets decreased. The T_{50} values of 10, 14, and 21 min. were found for the bigger basket, regular basket, and smaller pore basket, respectively. In varying the revolutions per minute of the stirring propeller from 60 through 150 for the pentobarbital tablets in the regular basket, a distinct difference can be seen. The T_{50} at 150 and 120 r.p.m. is very close at an average of 2.5 and 3.25 min.

Decreasing the revolutions per minute to 90 and to 60 shows a significant reduction and difference, with the T_{50} equal to 7.5 and 14 min., respectively.

A comparison of the dissolution of the sodium butabarbital capsules in the three baskets shows little difference between the bigger and regular baskets, with the T_{50} equal to 26 and 29 min., respectively. The smaller pore basket did show an increase in the T_{50} to 38 min. The difference in the T_{50} in the regular basket as a function of revolutions per minute was small at 150 and 120, producing average times of 15 and 16 min., respectively. Decreases in propeller speed to 90 and 60 r.p.m. showed T_{50}'s of 21 and 30 min., respectively.

In conclusion, the adjustment of basket pore size and propeller revolutions per minute can produce significantly different dissolution profiles, which should be considered when comparing in vitro dissolution results from the magnetic basket in quality control or as a means of correlating in vitro–in vivo data.

(1) R. E. Shepherd, J. C. Price, and L. A. Luzzi, J. Pharm. Sci., 61, 1152(1972).

(2) T. E. Needham, R. E. Shepherd, and L. A. Luzzi, ibid., 62, 470(1973).

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BOOKS

REVIEWS

The Prostaglandins, Volume I. Edited by PETER W. RAMWELL. Plenum, New York, NY 10011, 1973. 526 pp. 17 × 25.5 cm. Price $22.50.

Respected scientists have collaborated in this treatise to report on the present status of prostaglandin data and hypotheses in chemistry, physiology, and pharmacology. The chemistry of prostaglandins is presented in a functional manner. The chemical, metabolic, physiological, and pharmacological implications of altering bonds, specific groups, and steroidal configurations on this complex molecule are discussed. Methods of in vitro and in vivo synthesis of the primary prostaglandins and analogs from various chemicals are described.

Prostaglandins synthetase, its assay, and the hypotheses regarding physiological production of various prostaglandins in vivo are discussed. Working hypotheses are presented and defended by data for the physiological role of various prostaglandins in peripheral, central, and autonomic neurotransmission; renal, respiratory, GI, ocular, cardiovascular, lipid, and endocrine homeostasis; and male and female reproductive function. Data and hypotheses for pos-

sible roles of various prostaglandins in pathological states such as hypertension, asthma, inflammation, anaphylaxis, glaucoma, ocular trauma, and endocrine disorders are presented.

The possibilities of treating neurological, respiratory, GI, cardiovascular, renal, and lipid diseases with exogenous prostaglandins are explored. Results of using PGE_2 and $PGF_{2\alpha}$ for induction of term labor by the intravenous route and for induction of artificial abortions by the intravenous, subcutaneous, vaginal, extraovular, and intraamniotic routes are presented to demonstrate the practicability of prostaglandins for terminating pregnancy at all stages of gestation. In this rapidly developing field of research and development involving the chemist, physiologist, pharmacologist, and clinician, this volume is valuable to scientists in all of these disciplines in summarizing what often appear to be conflicting data and applying them to hypotheses.

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