Table I—Cumulative Excretion (Milligrams) of Nitrofurantoin for Six Subjects under Propantheline and Control Conditions

Subject	Control (Nitrofurantoin Only)	Nitrofurantoin and Propantheline
1	17.2	30.2
2	29.0	34.7
3	12.3	19.5
4	15.2	31.8
5	13.0	33.6
6	16.0	22.3
Mean ± *SE*	17.1 ± 2.49	28.7 ± 2.57

versed. All subjects fasted overnight and for 4 hr after drug administration. Total urine specimens were collected for 24 hr. Nitrofurantoin in the urine was determined by a spectrophotometric method (5) specific for unchanged drug.

The results (Table I) indicate a statistically significant increase in nitrofurantoin excretion when propantheline was coadministered as compared with the control condition ($p < 0.01$ as determined by paired t-test). No statistical significance was observed for differences in urinary volume or urinary pH between the two conditions. Thus, the results are consistent with the hypothesis that a delay in gastric emptying possibly will increase the bioavailability of nitrofurantoin and indicate that this effect might explain why food produces similar effects.

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Simple Method for Monitoring Flow Rate during Gravity Perfusion

Keyphrases □ Flow rates—apparatus for continuous monitoring during perfusion studies □ Perfusion studies—apparatus for continuous monitoring of flow rate □ Equipment—apparatus for monitoring flow rate during gravity perfusion

To the Editor:

The apparatus described here fills the need for an inexpensive, easily constructed device for continuously monitoring flow rates during perfusion studies. Although extremely simple in design, it can be employed to advantage with modern electronic recording equipment.

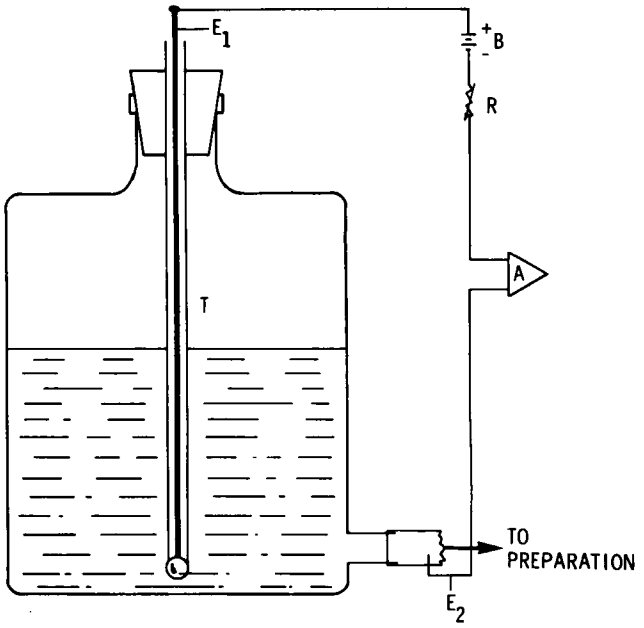

Figure 1—*Components of device for continuously monitoring flow rates during perfusion studies.*

The device makes use of the familiar air bubbles which emerge from the pressure regulating tube (T) of the well-known Marriotte bottle. The last 1 or 2 cm of this tube is coated on both the inner and outer surfaces, most simply by dipping the tubing in melted paraffin. One electrode (E_1)—essentially a length of stainless steel wire insulated except at the tip—is passed down the glass tubing (Fig. 1). A second electrode (E_2), which can be much shorter, is placed in the perfusion solution, usually through a piece of rubber tubing leading from the outlet of the reservoir.

Leads from these two electrodes are connected to the input of the recorder amplifier (A) with an ordinary 1.5-v flashlight battery (B) and variable resistor (R) placed in the circuit as indicated. As the perfusion proceeds, the column of air in the glass tubing (T) descends and "breaks off" in the form of air bubbles. These bubbles serve to break the circuit, and this breakage is registered on the recorder. Changes in flow caused by interventions that alter the perfusion rate are rapidly indicated on the chart. This system avoids the time-consuming process of collecting and measuring the effluent to determine whether a change in flow has actually occurred. The amount of change can thus be measured, either by collecting the effluent or counting the marks on the chart recorder over a specific length of time.

By its nature, a tracing provides a stronger visual impact than does a number, and this advantage is particularly noticeable when other parameters are being recorded simultaneously on the same strip chart. The system has been very valuable also for demonstrations to large classes, using closed circuit T.V. with the camera focused on the chart. The apparatus described here has been employed extensively

to study the effects of drugs or procedures on isolated perfused hearts, lungs, and blood vessels. The very small current employed (approximately 0.2 mamp) has no observable effects on either the preparation or the actions of the drugs studied.

In short, this apparatus provides a method for rapidly detecting changes in flow by using the Marriotte bottle to provide graphic information as well as to serve simply as a reservoir for the perfusion solution. Ease of construction and low cost make it particularly useful for teaching purposes, since each group of students can be supplied with one of these devices.

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Controlled Release from Matrix Systems

Keyphrases □ Matrix systems—controlled release of ethynodiol diacetate from silicone rubber devices, comments □ Silicone rubber matrix—release of ethynodiol diacetate, comments on controlled release □ Release, controlled—ethynodiol diacetate from silicone rubber devices, comments

To the Editor:

Two publications by Chien and coworkers (1, 2) described the release of ethynodiol diacetate from silicone rubber devices. These authors treated two cases for the matrix release process: matrix-controlled and partition-controlled drug release mechanisms. The equations describing the diffusional process were previously presented by Higuchi (3) and Roseman and Higuchi (4). With the assumptions that (*a*) the matrix acts as the diffusion medium, (*b*) a pseudo-steady-state condition exists during the release process, and (*c*) the drug particles are uniformly distributed throughout the matrix and are quite small relative to the average distance of diffusion, Higuchi (3) derived the following relationship for the release of drug from a planar homogeneous matrix:

$$Q = [D_s C_s (2A - C_s)t]^{1/2} \quad \text{(Eq. 1)}$$

where Q = amount of drug released per unit area, D_s = diffusion coefficient of drug in the homogeneous matrix phase, C_s = solubility of drug in the matrix phase, t = time, and A = total amount of drug present per unit volume of matrix.

When $A \gg C_s$, Eq. 1 reduces to:

$$Q = (2AD_s C_s t)^{1/2} \quad \text{(Eq. 2)}$$

Chien *et al.* (1), however, incorrectly quoted the Higuchi equation as:

$$Q = [D_s C_s (2A - C_a)t]^{1/2} \quad \text{(Eq. 3)}$$

where C_a is the solubility of drug in the elution medium[1]. Although the $(2A - C_a)$ term does not appear to have any physical significance (except, of course, when $C_a = C_s$), Eq. 3 does yield Eq. 2 when $2A$ is much greater than C_a.

The equations derived by Roseman and Higuchi (4) are an extension of the concepts discussed by Higuchi (3) for the specific case where diffusion from the surface of the device is considered in series with the diffusional step through the matrix. In this instance, the release of drug from a planar matrix is given by the following expressions, when $A \gg C_s$:

$$Q = Al \quad \text{(Eq. 4)}$$

$$l^2 + \frac{2D_e h_a l}{D_a K} = \frac{2D_e C_s t}{A} \quad \text{(Eq. 5)}$$

where[1] l = diffusional distance in the matrix (depleted zone); K = partition coefficient (C_a/C_s); h_a = diffusional distance in the boundary diffusion layer; $D_e = D_s\epsilon/\tau$ where ϵ and τ are the volume fraction and tortuosity of the matrix,respectively; and D_a = diffusion coefficient of drug in the elution medium. The other terms were defined previously.

Except for consideration of the boundary diffusion layer, the basic assumptions in the derivation of these equations are the same as those used to derive Eq. 2. Equations 4 and 5 describe a general case for matrix release, which was termed the matrix-boundary diffusion layer model (4). This nomenclature corresponds to the partition-controlled and matrix-controlled cases subsequently used by Chien and Lambert (2) for the two limiting cases. When $l \gg 2D_e h_a/D_a K$, Eqs. 4 and 5 yield Eq. 2 (matrix-controlled case)[2]. Conversely, when $l \ll 2D_e h_a/D_a K$, Eqs. 4 and 5 yield:

$$Q = \frac{D_a C_a t}{h_a} \quad \text{(Eq. 6)}$$

which is boundary layer controlled release (partition-controlled release).

In the publication by Chien and Lambert (2), the Higuchi equation is again misquoted as the authors derived a series of equations following the theoretical treatment resulting in Eqs. 4 and 5. For the limiting condition that yields Eq. 6, Chien and Lambert (2) presented the following expressions[1]:

$$Q = \frac{KD_a C_s t}{h_a} \quad \text{(Eq. 7)}$$

$$Q = \frac{KD_a C_a t}{h_a} \quad \text{(Eq. 8)}$$

Equation 7 is correct since it reduces to Eq. 6 (note that $K = C_a/C_s$). However, Eq. 8 is only valid for the trivial case when $C_s = C_a$. But the data on ethynodiol diacetate indicate that C_s does not equal C_a; therefore, analysis of the data does not support the contention that Eq. 8 is valid.

I hope this communication clarifies the discrepancies between the original equations reported in Refs.

[1] Symbols used for the various parameters differ among authors. In this communication, each term is defined to avoid confusion. For example, in Ref. 1, D_m, C_p, and C_s are equivalent to D_s, C_s, and C_a, respectively, while in Ref. 2, D_s, δ_D, and δ_m are equal to D_a, h_a, and l, respectively.

[2] Equation 2 was derived for a homogeneous matrix; therefore, ϵ and τ were unity.