Influence of Administration Route on Drug Delivery to a Target Organ

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Abstract □ Mathematical relationships describing the delivery of drug to a target organ after intra-arterial, intravenous, and oral administration are presented. This discussion clearly demonstrates that administration into a blood vessel leading to the target organ often is superior to intravenous administration. However, this superiority is not clear from traditional plasma concentration monitoring data.

Keyphrases □ Drug delivery—to a target organ, influence of administration route, mathematical relationships □ Administration routes—influence on drug delivery to a target organ, mathematical relationships □ Mathematical models—influence of administration route on drug delivery to a target organ

When the rate and extent of drug absorption is of concern, the first choice for drug delivery is usually the intravenous route. Intravenous administration delivers drug directly into the bloodstream and virtually assures almost immediate delivery to the target organ(s). Because there is no drug loss at the administration site, a drug delivered intravenously is considered to be completely available to the body. However, if a drug were to precipitate during an intravenous injection due to poor solubility in plasma, distribution of the drug would be delayed. The precipitated drug would eventually redissolve and be distributed to the remainder of the body. Thus, the site of precipitation can be viewed as a site of retention rather than a site of loss.

Although no drug is lost at the administration site, there exists the possibility for drug loss in the body prior to its reaching the site of measurement or the target organ. For example, if a drug is administered intravenously, the drug must first traverse the lungs before it can be further distributed in the body. Thus, any drug eliminated in the lungs reduces the amount of drug available to the other organs (1). Furthermore, only a fraction of the drug not metabolized by the lungs leaves the left ventricle for the target organ. The remaining drug leaving the left ventricle circulates to other tissues and organs where elimination can occur before recirculation to the target organ is possible.

One way to circumvent the potential for drug loss is to administer the drug intra-arterially, *i.e.*, directly into an artery leading to the target organ (2, 3). Although intra-arterial injections are more difficult than venipuncture to perform, as well as being more uncomfortable for the patient, it is sometimes the preferred route (3–7). Intra-arterial drug administration ensures that the entire dose administered will reach the target organ.

Because little information exists in this area, no clearcut parameters have been established to determine the superiority of one administration route over another. Utilization of pharmacokinetic principles may prove to be useful.

The following report discusses mathematical relationships describing: (*a*) the amount of drug delivered to the target organ by both intra-arterial and intravenous administration routes, and (*b*) the amount of drug reaching the liver after an oral dose if the liver is the target organ. This latter situation parallels that of an intra-arterial injection into an artery leading to a target organ except that the drug must traverse the GI tract where loss can occur prior to its reaching the liver.

KINETIC MODEL

A flow model for drug disposition, described in Scheme I, is used in this discussion. Compartment 1 is the lungs, receiving blood from the right ventricle; compartments 2 through n represent the remainder of the body, compartmentalized and receiving blood from the left ventricle. Compartments 2 through m are all capable of eliminating the drug and comprise the liver (Compartment 3), the mesenteric vascular bed (Compartment 2), the kidneys, *etc.*; compartment $m + 1$ to n represents the organs and tissues incapable of eliminating the drug and are, therefore, considered to be storage compartments.

The blood clearance of any compartment (Cl_i) reflects the elimination rate with respect to the whole blood concentration entering the compartment (C_{in}) and not the concentration in the compartment itself (which would represent the intrinsic clearance of the compartments). From steady-state values, this is expressed as:

$$Cl_i = \left(\frac{dA_i/dt}{C_{in}}\right)_{ss} \qquad \text{(Eq. 1)}$$

where dA_i/dt is the rate of elimination in compartment i, and ss denotes steady-state conditions. More important, however, is the fact that clearance can be determined from the total amount eliminated from time zero to time infinity by the organ $[\int_0^\infty (dA_i/dt)\,dt]$ and the total area under the blood concentration *versus* time-curve from time zero to time infinity ($\int_0^\infty C_i\,dt$) entering the organ; *i.e.*:

$$Cl_i = \frac{\int_0^\infty (dA_i/dt)\,dt}{\int_0^\infty C_{in}\,dt} \qquad \text{(Eq. 2)}$$

Therefore, the arterial concentration (or left ventricle concentration) is used as a reference blood concentration for most organs. This procedure is identical to using the venous blood concentration from a storage compartment as the reference concentration. However, pulmonary clearance is defined with respect to the right ventricle concentration, although it is relatively easy to convert pulmonary clearance from its present definition (Cl'_1) to one with respect to left ventricle concentration (Cl_1) by using the following relationship:

$$Cl_1 = Cl'_1 \Big/ \left(1 - \frac{Cl'_1}{Q_1}\right) \qquad \text{(Eq. 3)}$$

where Q_1 is the pulmonary blood flow that is equal to the total cardiac output (Q_C). If the pulmonary clearance is low, the two clearances are essentially the same. Only if the pulmonary clearance is large is it necessary to make the conversion.

Intra-Arterial Injection into Artery Leading to Target Organ—If the target organ is m, the amount delivered to this organ ($A_{E,m}$) from time zero to time infinity is equal to:

$$A_{E,m} = D + \int_0^\infty C_L Q_m\,dt \qquad \text{(Eq. 4)}$$

where D is the dose administered, C_L is the left ventricle blood concentration, and Q_m is the blood flow to the target organ. Blood flow is assumed to be time and concentration independent. The term $\int_0^\infty C_L\,dt$ can be obtained by the following development:

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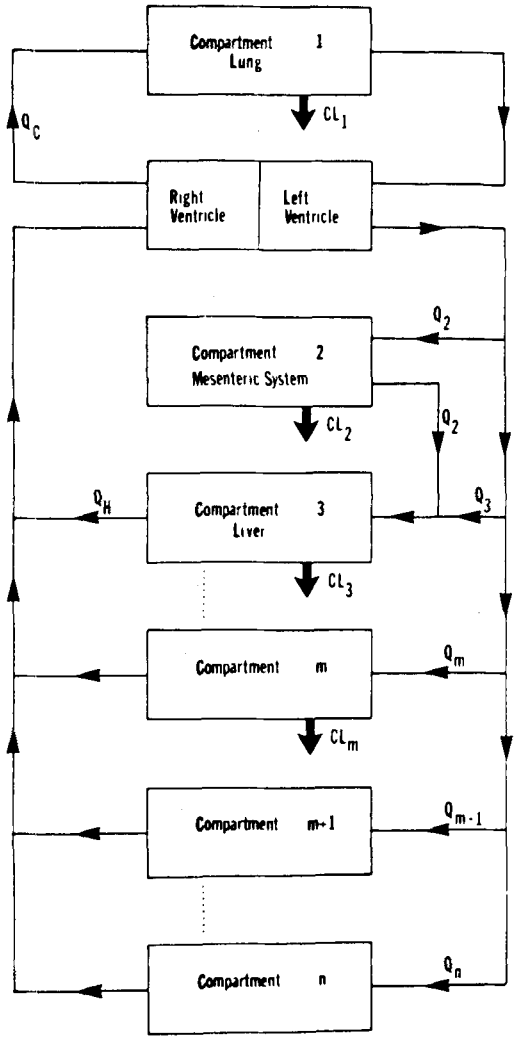

Scheme I—Pharmacokinetic model of drug disposition.

The fraction ($F_{L,i}$) of the drug delivered to an eliminating organ that leaves the same compartment is:

$$F_{L,i} = 1 - \text{fraction lost} = 1 - \frac{A_{\text{lost},i}}{A_{E,i}} = 1 - \frac{\int_0^\infty (dA_i/dt)\,dt}{\int_0^\infty Q_i C_{\text{in}}\,dt} \qquad \text{(Eq. 5)}$$

From Eqs. 2 and 5:

$$F_{L,i} = 1 - \frac{Cl_i}{Q_i} \qquad \text{(Eq. 6)}$$

The amount leaving the left ventricle ($A_{L,L}$) from time 0 to time infinity is equal to:

$$A_{L,L} = \sum_{i=2}^{m} \int_0^\infty C_L Q_i\,dt = Q_C \int_0^\infty C_L\,dt \qquad \text{(Eq. 7)}$$

where Q_C is the cardiac output.

The total amount entering the left ventricle ($A_{E,L}$) is expressed by:

$$A_{E,L} = \int_0^\infty C_R Q_C \left(1 - \frac{Cl_1'}{Q_C}\right) dt = (Q_C - Cl_1') \int_0^\infty C_R\,dt \qquad \text{(Eq. 8)}$$

where C_R is the blood concentration in the right ventricle. The amount leaving the right ventricle ($A_{L,R}$) can be expressed by:

$$A_{L,R} = \int_0^\infty C_R Q_C\,dt = Q_c \int_0^\infty C_R\,dt \qquad \text{(Eq. 9)}$$

By using the fraction lost in each eliminating compartment as expressed in Eq. 6, the total amount entering the right ventricle ($A_{E,R}$) can readily be obtained:

$$A_{E,R} = \int_0^\infty C_L \left[Q_2\left(1 - \frac{Cl_2}{Q_2}\right) + Q_3\right]\left(1 - \frac{Cl_3}{Q_2 + Q_3}\right) dt + \left[\sum_{i=4}^{m} C_L Q_i \left(1 - \frac{Cl_i}{Q_i}\right) dt\right] + \left(\sum_{i=m+1}^{n} \int_0^\infty C_L Q_i\,dt\right) + D\left(1 - \frac{Cl_m}{Q_m}\right) \qquad \text{(Eq. 10)}$$

The first part of the right-hand side of Eq. 10 takes into account that part of the hepatic blood flow which must pass through the GI tract *via* the mesenteric system before reaching the liver *via* the portal vein.

With the assumption that no elimination occurs in the ventricles, the amount leaving each ventricle from time zero to time infinity is equal to the amount entering. By combining Eqs 7–10 and defining $Q_2 + Q_3$ as the hepatic blood flow (Q_H), the following is obtained:

$$\int_0^\infty Cl\,dt = \frac{D\left(1 - \frac{Cl_m}{Q_m}\right)}{\frac{Cl_1' Q_C}{Q_C - Cl_1'} + \left(\sum_{i=2}^{m} Cl_i\right) - \frac{Cl_2 Cl_3}{Q_H}} \qquad \text{(Eq. 11)}$$

By combining Eqs. 4 and 11, the total amount entering the target organ after an intra-arterial injection into an artery leading to this organ is:

$$A_{E,m} = D\left(1 + \frac{Q_m - Cl_m}{\frac{Cl_1' Q_C}{Q_c - Cl_1'} + \left(\sum_{i=2}^{m} Cl_i\right) - \frac{Cl_2 Cl_3}{Q_H}}\right) \qquad \text{(Eq. 12)}$$

Furthermore, by combining Eqs. 3 and 12 to express all clearances with respect to the left ventricle concentration, the following is obtained:

$$A_{E,m} = D\left(1 + \frac{Q_m - Cl_m}{\left(\sum_{i=1}^{m} Cl_i\right) - \frac{Cl_2 Cl_3}{Q_H}}\right) \qquad \text{(Eq. 13)}$$

As can be seen from Eq. 13, the total amount reaching the target organ after an intra-arterial injection depends not only on the dose but also on the blood flow to this organ, its clearance, portal blood flow, and cardiac output, as well as the various clearances in the different parts of the body (see *Discussion*).

Intra-Arterial Injection into Artery Not Leading to Target Organ—In this case, the amount administered is assumed to be injected into Compartment $m - 1$ instead of the target organ, Compartment m. Thus, the amount delivered to Compartment m is:

$$A_{E,m} = \int_0^\infty C_1 Q_m\,dt \qquad \text{(Eq. 14)}$$

Similarly to Eq. 13, $A_{E,m}$ can be expressed as:

$$A_{E,m} = D\frac{Q_m\left(1 - \frac{Cl_{m-1}}{Q_{m-1}}\right)}{\left(\sum_{i=1}^{m} Cl_i\right) - \frac{Cl_2 Cl_3}{Q_H}} \qquad \text{(Eq. 15)}$$

Intravenous Bolus Dose Administration—This situation is equivalent to delivering the drug directly into the right ventricle. In this case, by using similar development as in the two previous sections, the amount delivered to the target organ can be shown to be equal to:

$$A_{E,m} = \frac{DQ_m}{\left(\sum_{i=1}^{m} Cl_i\right) - \frac{Cl_2 Cl_3}{Q_H}} \qquad \text{(Eq. 16)}$$

Oral Dose When Target Organ Is Liver—The amount of an oral dose delivered to the liver ($A_{E,3}$) is equal to the amount leaving the GI tract [$D(1 - G)$] and escaping elimination in the GI wall. It is assumed that this amount is equal to the fraction that usually escapes elimination in the mesenteric system, $1 - (Cl_2/Q_2)$, plus the amount delivered *via* the vascular system through recirculation:

$$A_{E,3} = \int_0^\infty C_L \left[Q_2\left(1 - \frac{Cl_2}{Q_2}\right) + Q_3\right] + (1 - G)\left(1 - \frac{Cl_2}{Q_2}\right) \qquad \text{(Eq. 17)}$$

Using a similar development as for Eq. 10 and defining $(1 - G)$ [$1 - (Cl_2/Q_2)$] as $(1 - E)$, one obtains:

$$A_{E,3} = D\,(1-E)\left[1+\frac{(Q_H - Cl_2)\left(1-\frac{Cl_3}{Q_H}\right)}{\left(\sum_{i=1}^{m} Cl_i\right)-\frac{Cl_2Cl_3}{Q_H}}\right] \qquad \text{(Eq. 18)}$$

Intravenous Dose When Target Organ is Liver—The amount of drug delivered to the liver in this situation is equal to:

$$A_{E,3} = \int_0^\infty C_L\left[Q_2\left(1-\frac{Cl_2}{Q_2}\right)+Q_3\right] \qquad \text{(Eq. 19)}$$

By using a similar development as before, it can be demonstrated that:

$$A_{E,3} = \frac{D(Q_H - Cl_2)}{\left(\sum_{i=1}^{m} Cl_i\right)-\frac{Cl_2 - Cl_3}{Q_H}} \qquad \text{(Eq. 20)}$$

DISCUSSION

Intra-Arterial Injection Leading to Target Organ *versus* Intravenous Injection—The ratio of the amount of drug entering the target organ from the intra-arterial to the intravenous injection (Y_T) can be obtained from Eqs. 13 and 16:

$$Y_T = 1+\frac{\left(\sum_{i=1}^{m-1} Cl_i\right)-\frac{Cl_2Cl_3}{Q_H}}{Q_m} \qquad \text{(Eq. 21)}$$

Because Q_H always is larger than Cl_2 or Cl_3, this relationship is always greater than one as long as $\sum_{i=1}^{m-1} Cl_i$ is not zero. Therefore, Eq. 21 demonstrates that an intra-arterial injection of a drug into an artery leading to the target organ always delivers more drug to the target organ than an intravenous bolus dose. The single exception is when only the target organ eliminates the drug since then the two modes of administration are identical.

The advantage of intra-arterial administration increases under the following circumstances:

1. Lung clearance is high. In this case, the intravenously administered drug has to pass through the lungs and be partially metabolized before it can reach the target organ.
2. Elimination by other organs is high in comparison to target organ blood flow. In this case, a large amount of drug leaving the left ventricle per heart beat circulates to various organs where possibilities for elimination exist. Therefore, only a fraction of the drug is returned to the general circulation for recirculation to the target organ. This conclusion, however, is not readily determined from regular concentration monitoring data or from evaluation of bioavailability.

Bioavailability is practically determined as the amount delivered to the site of measurement from a test dose to that of a control dose. By considering the intra-arterial dose as the test dose, the intravenous dose as the control, and, for simplistic reasons, the sampling site as the venous side of storage compartment n, the bioavailability (F) can be expressed as:

$$F_T = \frac{\left(\int_0^\infty ClQ_n\,dt\right)\text{ intra-arterially}}{\left(\int_0^\infty ClQ_n\,dt\right)\text{ intravenously}} \qquad \text{(Eq. 22)}$$

Derivation yields:

$$F_T = 1-\frac{Cl_m}{Q_m} \qquad \text{(Eq. 23)}$$

This result indicates that an intravenous dose always delivers more drug to the sampling site than an intra-arterial injection. Therefore, use of this site to evaluate various drug administration routes may be inadequate and misleading.

A similar conclusion can be drawn from the theoretical evaluation of intra-arterial *versus* intravenous administration of chemotherapeutics by Chen and Gross (8). They evaluated a slightly different kinetic flow model, and their clearances were defined in terms of the intrinsic clearance values of the various organs at steady state. Again, however, an advantage of intra-arterial injections with respect to delivery to the target organ was observed (Y_T), in conjunction with a decreased systemic availability (F_T).

Intra-Arterial Injection Not Leading to Target Organ *versus* Intravenous Injection—In this case, the ratio of the amount delivered to the target organ from the various administration routes (Y_N) can be obtained from Eqs 14 and 15:

$$Y_N = 1-\frac{Cl_{m-1}}{Q_{m-1}} \qquad \text{(Eq. 24)}$$

and bioavailability is expressed by:

$$F_N = 1-\frac{Cl_{m-1}}{Q_{m-1}} \qquad \text{(Eq. 25)}$$

In this situation, it is clear that an intravenous dose delivers more drug to the target organ than an intra-arterial dose. The intra-arterial dose has to pass to a nontarget organ ($m-1$) where it can be partially eliminated before it reaches the venous circulation. However, the intravenous dose reaches the venous circulation directly; *i.e.*, if the decision is made to administer a drug intra-arterially, it is imperative to identify the target organ to ensure that the drug is administered into an artery leading to that target organ.

The use of venous drug concentration monitoring or traditional bioavailability determination accurately reflects the relative amounts reaching the target organ by these two administration routes only when intra-arterial administration is into an artery not leading to the target organ.

Oral Dosing *versus* Intravenous Injection When Target Organ Is Liver—From Eq. 18, it can be seen that the ratio of drug delivered to the liver by these two routes (Y_0) is equal to:

$$Y_0 = (1-E)\left[1+\frac{\left(\sum_{i=1}^{m} Cl_i\right)-Cl_3}{Q_H - Cl_2}\right] \qquad \text{(Eq. 26)}$$

Thus, it is possible to predict when oral administration is advantageous over intravenous injection if the target organ is the liver. However, extensive knowledge of the various clearances for a drug is required. In principle, the larger the fraction of the dose that reaches the liver in its first pass [$(1-E) \rightarrow 1$] and the larger the extrahepatic clearance is in comparison with hepatic blood flow, the greater is the likelihood for an oral dose to be superior to an intravenous injection.

Bioavailability (F_0) is equal to:

$$F_0 = (1-E)\left(1-\frac{Cl_3}{Q_H}\right) \qquad \text{(Eq. 27)}$$

This relationship always predicts that the intravenous route is superior to the oral route provided E and Cl_3 are not zero.

Using traditional bioavailability determinations to decide on an optimal drug delivery route may sometimes be misleading. Based on this discussion, it appears that when blood (or plasma) concentration in a peripheral vein is used for determining the best administration route, the choice will invariably be the intravenous route. However, alternative routes are sometimes able to delivery more drug to the target organ than an intravenous dose. Therefore, care should be taken in drug plasma monitoring or the use of steady-state plasma concentrations or bioavailability data when different administration routes are considered for optimization of drug therapy.

On the other hand, if two dosage formulations given *via* the same route are compared, such reservation is not necessary. In this case, the drug traverses the same path before it reaches the measurement site or the target organ. Therefore, the ratio of the amount delivered to the measurement site accurately reflects the ratio reaching the target organ.

This discussion should not be considered as being limited to the two special examples provided. The same conclusions can be reached in other situations, such as intramuscular injection when the muscle is the target organ, inhalation when the lung is the target organ, and intrathecal injection when the spinal nerves are the target.

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Determination of Flurbiprofen and Ibuprofen in Dog Serum with Automated Sample Preparation

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Abstract □ Methods for the determination of flurbiprofen and ibuprofen in dog serum were developed using high-performance liquid chromatography and automated serum extraction. Sample extraction was automated by use of cartridges packed with a styrene–divinylbenzene macroreticular resin in a microprocessor-controlled centrifugal system. The average recoveries were 98.9% for flurbiprofen and 94.5% for ibuprofen. The limits of detection were ~0.04 μg/ml for flurbiprofen at 254 nm and 0.5 μg/ml for ibuprofen at 230 nm. The relative standard deviations for the determination of a laboratory standard between days was 2.4% (20 μg/ml) for flurbiprofen and 1.7% (13 μg/ml) for ibuprofen. Peak height ratios were linear with concentrations of 0.04–100 μg/ml for flurbiprofen and 1.0–50 μg/ml for ibuprofen. These methods are simple, rapid, sensitive, and specific. The use of an automated sample preparation procedure improved the between-day precision by a factor of two when compared to a manual extraction procedure. These methods were applied to bioavailability studies in dogs.

Keyphrases □ Flurbiprofen—determination in dog serum with automated sample preparation □ Ibuprofen—determination in dog serum with automated sample preparation □ Bioavailability—determination of flurbiprofen and ibuprofen in dog serum with automated sample preparation

Flurbiprofen [*dl*-2-(2-fluoro-4-biphenylyl)propionic acid] and ibuprofen [*dl*-2-(*p*-isobutylphenyl)propionic acid] are nonsteroidal anti-inflammatory drugs. Several gas chromatographic (GC) procedures were previously developed for flurbiprofen (1) and ibuprofen (2–4). Methods using high-performance liquid chromatography (HPLC) were previously developed for ibuprofen (5, 6) and similar compounds: indoprofen (7), ketoprofen (8), and naproxen (8). To reduce the amount of labor and time involved in performing assays for flurbiprofen or ibuprofen in serum, an HPLC procedure using an automated sample processor[1] was developed. The previously developed GC procedures use manual liquid–liquid sample preparations and derivatization prior to analysis. Sample extraction with the automated sample processor uses a liquid–solid extraction with a cartridge packed with a styrene–divinylbenzene macroreticular resin in a microprocessor-controlled centrifugal system, resulting in reduced analysis effort and improved assay precision.

[1] Prep I, Dupont Co, Wilmington, Del.

EXPERIMENTAL

Reagents and Materials—Reagents were of at least analytical reagent grade quality, and acetonitrile[2] was distilled-in-glass grade. Stock solutions of flurbiprofen[3] and ibuprofen[3] were prepared in pH 7.2 phosphate buffer (0.05 *M*).

Instrumentation—A variable-wavelength detector[4], a solvent pump[5], and an autoinjector[6] were used for the chromatographic analysis. Preparation of samples was performed with an automated sample processor.

Chromatographic Conditions—Chromatography took place on a 0.46-cm i.d. × 25-cm long column packed with octadecylsilane bonded to microparticulate silica[7] (10 μm). The precolumn, 4.2 cm × 0.3-cm i.d., was packed with octadecylsilane bonded to microparticulate silica[8] (30 μm). The mobile phase was acetonitrile–0.05 *M* acetic acid (40:60).

The flow rate was 2.0 ml/min, the column temperature was ambient, and the column back-pressure was ~1500 psi. The approximate retention times of flurbiprofen and ibuprofen were 14 and 19 min, respectively. Preliminary work was performed with the acetonitrile–water ratio at 50:50 and the flow rate at 1.2 ml/min. The mobile phase was filtered and deaerated by vacuum sonication prior to use.

Automated Extraction—The automated sample processor is designed to perform automatic extractions simultaneously of up to 12 liquid samples in 30 min or less. Centrifugal force is used to move solvents through an extraction resin bed. The system is composed of an inner rotor, which holds extraction columns, and a larger outer rotor, which holds the corresponding effluent and recovery cups. The extraction column is comprised of a sample reservoir and a resin bed. The rotor first spins clockwise to force the sample through the resin bed. A predetermined amount of wash solvent is forced through the resin bed and into an effluent cup. In this manner, unwanted components are removed from the column. The rotor direction is then reversed so that the extraction column is positioned over the recovery cup.

An aliquot of a second solvent elutes the component of interest and is collected in the recovery cup. If desired, the extract is then heated and blown to dryness. The dried extract is manually reconstituted and transferred to another instrument. Fifteen programs are currently available which vary timing, compartment temperature, and the option of sample evaporation.

Assay Procedure—Blank serum spiked with 100 μl of flurbiprofen or ibuprofen solutions in 0.05 *M* phosphate buffer (pH 7.2) was used to prepare standards to obtain a calibration curve for each chromatographic run. One milliliter of blank or sample serum was pipetted into the car-

[2] Burdick & Jackson, Muskegon, Mich.
[3] The Upjohn Co, Kalamazoo, Mich.
[4] Perkin-Elmer LC-55B, Norwalk, Conn.
[5] Model 100A, Altex Scientific, Berkeley, Calif.
[6] WISP model 710, Waters Associates, Milford, Mass.
[7] RP-8, Rheodyne, Berkeley, Calif.
[8] Permaphase ODS, Dupont, Wilmington, Del.

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