when d is zero or negative. Unless the value of j_1 equals $X_1(0)\{(d + \mu_1)^2/(ab)\}$, the two roots of Eq. 30 will be distinct.

DEFINITION OF SYMBOLS

μ_σ = decay constants of exponentials
r_σ = roots of cubic equation (Eq. 19)
V_σ = volume of distribution of the compartments
C_σ = integration constants proportional to dose
t_1^* = time at which minimum occurs in $X_1(t)$
t_1^{**} = time at which maximum may occur in $X_1(t)$
t_2^* = time at which maximum occurs in $X_2(t)$
t_3^* = time at which maximum occurs in $X_3(t)$; $X_3(t_3^*) = X_1(t_3^*)$
$t(0)$ = time at which extremum occurs in $F(t)$
X_σ = concentration in Compartment σ
i_σ = intercepts of three resolved plots whose sum depicts $\ln X(t)$
δ_{12} = permeability of drug across the barrier between Compartments 1 and 2
$\alpha_{12} = (\delta_{12}/V_1) + (\delta_{12}/V_2)$

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Hydrodynamic Analog Model for Pharmacokinetics II: Critical Examination of Model and Its Contribution to Pharmacokinetics

V. S. VAIDHYANATHAN

Abstract □ A comparison of the conventional pharmacokinetic models and the previously proposed hydrodynamic diffusion analog model is presented. A significant result that an n-compartment system can exhibit at best $(n - 1)$ extremum times in the concentration–time plot of the central compartment under appropriate values of physiological parameters is presented. The observation of kinks experimentally in certain physiological–drug systems is thus shown to be amenable to explanation.

Keyphrases □ Models, hydrodynamic diffusion analog—proposed for pharmacokinetics, critical examination, equations □ Diffusion model, hydrodynamic, analog—proposed for pharmacokinetics, critical examination, equations □ Pharmacokinetics—hydrodynamic diffusion analog model proposed and critically examined, equations

The hydrodynamic analog of the multicompartment model presented previously (1) leads to certain significant conclusions, which agree with the results of the familiar pharmacokinetic models and provide new insights. This article presents a critical examination of this contribution to pharmacokinetics and a possible observation of aperiodic oscillatory phenomena similar to the kink observed in the case of the dicumarol system.

ANALYSIS

Mathematically, both the hydrodynamic analog and familiar multicompartment models essentially involve solutions of coupled first-order linear differential equations of the kind (2):

$$\dot{X}(t) = AX(t) \qquad \text{(Eq. 1)}$$

where X is an n-component vector whose elements represent concentrations at time t of the n-compartment diffusion model (1).

In the familiar pharmacokinetic model, these vector elements represent the amount of substance present in each compartment. The super dot in Eq. 1 denotes the first time derivative. The time-independent elements of matrix A of Eq. 1 represent the permeabilities of the drug in barriers between connected compartments in the hydrodynamic diffusion model. Thus, when there is no connection between Compartments i and j, the corresponding matrix element A_{ij} is zero.

In the familiar pharmacokinetic model, the elements of the corresponding matrix are linear combinations of assumed first-order rate constants. For example, the partial contribution (due to the existence of connectivity with Compartment j) to the rate of decrease in the amount of material in Compartment i is assumed to be given by:

$$\dot{Y}_i = -k_{ij}Y_i + k_{ji}Y_j \qquad \text{(Eq. 2)}$$

where Y_j and Y_i are the amounts in Compartments j and i, respectively, at time t; and the k_{ij}'s are the assumed first-order rate constants.

Thus, volumes of distribution of various compartments are not introduced in the formulation of the familiar pharmacokinetic model and these need to be extracted from experimental data on the basis of *ad hoc* assumptions. The decay constants of conventional pharmacokinetics are considered not as functions of volumes of distribution. Since volumes of distribution of various compartments in an n-compartment model definitely play a role in the material distribution in various compartments at arbitrary finite

time, t, such volumes of distribution lie buried in the expression of familiar pharmacokinetics, which is a solution of Eq. 1, namely that the amount of material of Compartment j is given by:

$$Y_j(t) = \sum_{i=1}^{n} A_{ji} \exp(\lambda_i t) \qquad \text{(Eq. 3)}$$

In the diffusion model (1), one defines the partial contribution to the rate of decrease in concentration of Compartment i, due to connectivity with Compartment j, by the relation (see Eqs. 9 and 10 of Ref. 1):

$$V_i \dot{X}_i(t) = \delta_{ij}[X_i - X_j] \qquad \text{(Eq. 4)}$$

In this manner, the influence of volumes of distribution of various compartments on the time course of concentrations in various connected compartments are explicitly introduced in the formulation of the differential equations in the hydrodynamic (diffusion) analog (1). This approach has the advantage of precisely incorporating the influence of the volumes of distribution, the permeability properties of barriers between connected compartments to drug, and the elimination rate constants with the decay constants experimentally measurable and the coefficients of the solution of Eq. 1—*viz.* (see Eqs. 17, 22, and 26 of Ref. 1):

$$X_j(t) = \sum_{\sigma=1}^{n} S_{j\sigma} \exp(\mu_\sigma t) \qquad \text{(Eq. 5)}$$

Thus, there are no uncertainties about the role played by characteristic parameters of the physiological system in the determination of the time course of concentrations of drug in any compartment. This aspect may be considered the salient feature of the diffusion analog. In addition, the exact relationships existing between coefficients $S_{j\sigma}$ and $S_{i\sigma}$ can be expressed in terms of eigenvalues.

Returning now to another aspect of the pharmacokinetic problem, one recognizes that concentrations in compartments other than the central one (Compartments 2 and 3 of the three-compartment model of Ref. 1) are zero at initial time and at $t = \infty$. Since concentrations are positive definite quantities for intermediate finite times, there must exist a finite time t_σ^* when $\dot{X}_\sigma = 0$. Thus, the concentration–time plot of the $(n - 1)$ compartments of n-compartment systems should all exhibit maxima. If the nth central compartment also exhibits extremum times at which $\dot{X}_1(t)$ vanishes, then the observation of kinks and shoulders becomes amenable to explanation within the context of the diffusion model of pharmacokinetics.

DESCRIPTIVE ANALYSIS OF BEHAVIOR OF $X_1(t)$

The time dependence of concentrations in the three compartments as depicted by the theory (1) are schematically presented in Fig. 1. Curves II and III represent the time dependence of concentrations of Compartments 2 and 3, respectively, exhibiting extrema at times t_2^* and t_3^*. These are the shapes of concentration–time curves that will be observed for a three-compartment system with no chemical reactions.

Figure 1 also shows three alternative curves, I*a*, I*b*, and I*c*, which are mutually exclusive for the time dependence of concentration of drug in Compartment 1. Plot I*a* is the familiar monotonic curve experimentally observed for $X_1(t)$ in many systems. This can be resolved into three distinct exponential functions by the well-known procedure of resolution of the plot of ln $X_1(t)$ into three linear plots with positive intercepts i_1, i_2, and i_3 on the concentration axis. The procedures of obtaining the permeability coefficients, volumes of distribution, and elimination rate constants from such experimental data were presented previously (1).

Plots I*b* and I*c* of Fig. 1 are schematic examples of $X_1(t)$, which exhibit one extremum and two extremum times, respectively. Plot I*c* is similar to the case of dicumarol behavior upon intravenous administration, exhibiting the "kink." Plot I*b* may be considered as a special case of plot I*c*, where the two extremum points t_1^* and t_1^{**} as well as the inflection time coincide such that the time derivative of $X_1(t)$, while remaining negative most of the time, momentarily approaches zero. Such a behavior occurs when the rate of gain of material from Compartment 3 by Compartment 1 equals the rate of loss to Compartment 2 from Compartment 1.

For the three-compartment system, the time t_2^* at which concentration in Compartment 2 attains maximum value is given by:

$$p = (C_2/C_1) = (\mu_1 - \mu_3 F)/(\mu_3 F - \mu_2 G) \qquad \text{(Eq. 6a)}$$

$$F = \exp(\mu_3 - \mu_1)t_2^* \qquad \text{(Eq. 6b)}$$

$$G = \exp(\mu_2 - \mu_1)t_2^* \qquad \text{(Eq. 6c)}$$

Similarly, the time t_3^* at which concentration in Compartment 3 reaches a maximum value is given by:

$$p = (\mu_1 R_1 - \mu_3 R_3 H)/(\mu_3 R_3 H - \mu_2 R_2 I) \qquad \text{(Eq. 7a)}$$

$$H = \exp(\mu_3 - \mu_1)t_3^* \qquad \text{(Eq. 7b)}$$

$$I = \exp(\mu_2 - \mu_1)t_3^* \qquad \text{(Eq. 7c)}$$

$$R_\sigma(\sigma = 1, 2, 3) = [1 + m\{r_\sigma + (V_1/\delta_{13})M_\sigma\}] \qquad \text{(Eq. 7d)}$$

Thus, the characteristic times t_2^* and t_3^* are independent of dose and are related to each other and constant parameters of the system by:

$$\mu_1\mu_3(R_3H - R_1F) + \mu_1\mu_2(R_1G - R_2I) + \mu_2\mu_3(R_2IF - R_3GH) = 0 \qquad \text{(Eq. 8)}$$

CONDITIONS FOR OBSERVATION OF KINK

Assume that a system obeying the three-compartment hydrodynamic model exhibits a kink similar to I*c* of Fig. 1 in the concentration–time plot of the central compartment concentration. Thus, both t_1^* and t_1^{**} exist for this system and are observable. When two such extremum times exist, evidently an inflection point $t_1^\dagger$ should also exist. When these three real times exist, one has from Eqs. 20*a*–20*e* of Ref. 1:

$$\mu_1 S_1 + p\mu_2 S_2 Y_2^* = (1 + p)\mu_3 S_3 Y_3^* \qquad \text{(Eq. 9a)}$$

$$\mu_1^2 S_1 + p\mu_2^2 S_2 Z_2 = (1 + p)\mu_3^2 S_3 Z_3 \qquad \text{(Eq. 9b)}$$

$$\mu_1 S_1 + p\mu_2 S_2 Y_2^{**} = (1 + p)\mu_3 S_3 Y_3^{**} \qquad \text{(Eq. 9c)}$$

where:

$$S_\sigma = 1 + r_\sigma m \qquad \text{(Eq. 10a)}$$

$$Y_2^* = \exp(\mu_2 - \mu_1)t_1^* \qquad \text{(Eq. 10b)}$$

$$Y_3^* = \exp(\mu_3 - \mu_1)t_1^* \qquad \text{(Eq. 10c)}$$

$$Z_2 = \exp(\mu_2 - \mu_1)t_1^\dagger \qquad \text{(Eq. 10d)}$$

$$Z_3 = \exp(\mu_3 - \mu_1)t_1^\dagger \qquad \text{(Eq. 10e)}$$

$$Y_2^{**} = \exp(\mu_2 - \mu_1)t_1^{**} \qquad \text{(Eq. 10f)}$$

$$Y_3^{**} = \exp(\mu_3 - \mu_1)t_1^{**} \qquad \text{(Eq. 10g)}$$

Similar to the existence of the critical point in van der Waals' isotherm, when the three times t_1^*, $t_1^\dagger$, and t_1^{**} equal each other, one has the expression:

$$\exp\{(\mu_2 - \mu_3)t_1^*\} = [(1 + p)S_3\mu_3(\mu_1 - \mu_3)]/[pS_2\mu_2(\mu_1 - \mu_2)] \qquad \text{(Eq. 11)}$$

The conclusion that one arrives at from Eqs. 9 and 11 is that these critical times are independent of dose. This conclusion is substantiated by the case of dicumarol where the time at which kink occurs is essentially independent of the dose of drug.

Since the left-hand side of Eq. 11 is positive definite, in order that t_1^* exists and is real and observable, the necessary condition is:

$$(1 + p)S_3/(pS_2) = -C_3(1 + r_3 m)/[C_2(1 + r_2 m)] > 0 \qquad \text{(Eq. 12)}$$

When t_1^*, $t_1^\dagger$, and t_1^{**} exist and are distinct, one has:

$$-j_3/j_2 = (\mu_1 Y_2^* - \mu_2 Z_2)/(\mu_1 Y_3^* - \mu_3 Z_3) \qquad \text{(Eq. 13a)}$$

$$= (Y_2^* - Y_2^{**})/(Y_3^* - Y_3^{**}) \qquad \text{(Eq. 13b)}$$

For the sake of brevity, the following discussion to explain the possibility of experimentally observing curves of types I*b* and I*c* of Fig. 1 is limited to systems in which α_{13} is greater than k_{20}. It can be shown (see *Appendix*) that C_1 and C_3 are negative definite for

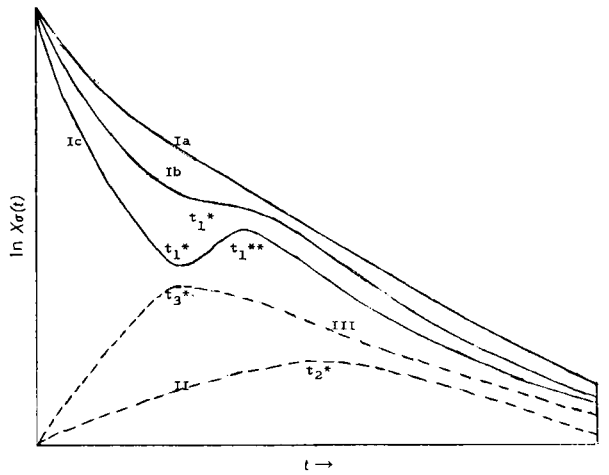

Figure 1—*Curves II and III represent time dependence of concentrations in Compartments 2 and 3, respectively, of the three-compartment hydrodynamic model. The time dependence of concentrations of Compartment 1 is represented schematically by plot Ia when there is no extremum time, by plot Ib when there is one extremum time at* t_1^**, and by plot Ic when there are two extremum times.*

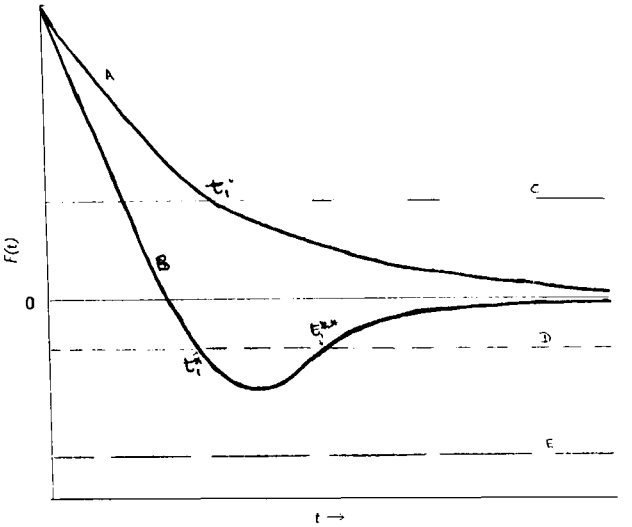

Figure 2—*Time dependence of the function* F(t) *is shown schematically by curve A when there is no extremum and by curve B when there is an extremum. Curves C, D, and E represent three possible values of* $(-C_3S_3)$.

this system. Recall from Eqs. 17*a* and 20*e* of Ref. 1 that one has:

$$\alpha_{12} + \alpha_{13} + k_{20} = -(\mu_1 + \mu_2 + \mu_3) > 0 \quad \text{(Eq. 14)}$$

The parameters α_{12}, α_{13}, μ_σ's, k_{20}, and r_σ's have dimensions of reciprocal seconds. Thus, all of these parameters can be expressed as proportional to k_{20}, the proportionality constants being simple numbers.

When specifically considering the case of r_1 and r_2 being negative and r_3 positive, both S_1 and S_2 are negative provided that the magnitudes of r_1m and r_2m are greater than unity; S_3 is positive definite. The requirement that both S_1 and S_2 are negative is assured when $(\delta_{12}/V_2) < \alpha_{12} < k_{20}$.

Under these conditions, both C_1S_1 and C_3S_3 are positive, while C_2S_2 is negative. With these preliminaries, one is now in a position to discuss the existence or nonexistence of t_1^*, the time at which time derivative of $X_1(t)$ vanishes.

A function $F(t)$, defined by:

$$F(t) = C_1S_1(\mu_1/\mu_3)\exp[(\mu_1 - \mu_3)t] + C_2S_2(\mu_2/\mu_3)\exp[(\mu_2 - \mu_3)t] \quad \text{(Eq. 15a)}$$

$$F(t_1^*) = -C_3S_3 \quad \text{(Eq. 15b)}$$

has the behavior of either plot A or B of Fig. 2. Note that $F(0) = \dot{X}_1(0)/\mu_3$ is positive. It can be shown that $F(t)$ can be either monotonic with time or at best can have one and only one extremum point. When no extremum point exists, the behavior of $F(t)$ is schematically represented by plot A of Fig. 2.

When an extremum point exists in $F(t)$, the behavior of $F(t)$ is represented by plot B of Fig. 2. The extremum point of $F(t)$, t_0, is given by:

$$t_0 = (\mu_2 - \mu_1)^{-1}\ln|[-C_1S_1\mu_1(\mu_1 - \mu_3)]/[C_2S_2\mu_2(\mu_2 - \mu_3)]| \quad \text{(Eq. 16)}$$

In order that t_0 exists, the quantity within the brackets of Eq. 16 should be positive and greater than unity. Figure 2 also shows plots C, D, and E, drawn parallel to the time axis and representing three possible magnitudes of C_3S_3; C_3S_3 is negative in curve C and positive in plots D and E.

The condition that $X_1(t)$ is positive definite for all finite times requires that C_3S_3 is positive definite. The intersection point between $F(t)$ and the line drawn parallel to the time axis with magnitude C_3S_3 evidently denotes the time t_1^*, at which time $\dot{X}_1(t) = 0$. Thus, when $F(t)$ for a system is monotonic with time, no extremum point in $X_1(t)$ occurs. Also, when for a system $F(t)$ has an extremum and has the shape of curve B, if the magnitude of C_3S_3 is large so that no intersection occurs, then no extremum point occurs in $X_1(t)$. Thus, experimental exhibition of the kink in the plot of $X_1(t)$ of a drug in a physiological system, simulating a three-compartment model, is critically dependent on the magnitude of C_3S_3 (hence on i_3) and on the existence of t_0 of $F(t)$.

Observation of kinks in the plot of $X_1(t)$, as in the case of dicumarol, is not excluded by the hydrodynamic diffusion analog of compartment models in pharmacokinetics. Since extremely stringent conditions of the relations among physiological parameters need to be satisfied for the observation of such kinks, it is no wonder that most systems exhibit only plot Ia of Fig. 1.

AN ILLUSTRATIVE CALCULATION

One may compute that $k_{20}m = 2.50$ for a system having the following magnitudes for the various parameters: $(\delta_{13}/V_1) = 0.1733\ k_{20}$, $(\delta_{12}/V_1) = 0.36\ k_{20}$, $\alpha_{12} = 0.76\ k_{20}$, and $\alpha_{13} = 1.24\ k_{20}$. One may also compute by the methods described that, for this system, $\mu_1 = -1.6\ k_{20}$, $\mu_2 = -1.2\ k_{20}$, and $\mu_3 = -0.2\ k_{20}$; $p = -1.1577$ for this system. One may verify that for this system the plot of $X_1(t)$/dose resembles plot I*b* of Fig. 1, with one extremum point occurring slightly above $2.3\ (k_{20})^{-1}$.

DISCUSSION

The presented analysis can be extended to n-compartment systems, with arbitrary choice of connectives. The main results of such deliberations are that the time dependence of concentrations of any compartment can be expressed in the form of Eq. 5 with n exponential terms. The decay constants are related to the volumes of distribution and permeabilities of barriers between compartments for the drug, by relations analogous to Eqs. 17 and 27 of Ref. 1, except that one has to find the roots of an nth order polynomial.

However, with appropriate values for the physiological parameters of the system to the drug, corresponding functions $F_n(t)$ can have more than one extremum time. Thus, with appropriate value of C_nS_n, which should be positive definite, the plot of the concentration of the central compartment in which drug is introduced initially can, in principle, exhibit $(n - 1)$ extremum times (3–5) at which $\dot{X}_1(t) = 0$. However, since $\dot{X}_1(t)$ is negative definite for very small times and for very large times, the number of physically realizable extremum points should be an even number. Therefore, observation of two such kinks for a specified drug in the plot of ln $X_1(t)$ requires that the physiological system behave for this drug as a five-compartment system.

If the drug participates in a chemical reaction in the barriers connecting compartments, then these have the effect of altering the corresponding matrix element of matrix A of Eq. 1. Thus, active transport of a drug across a specified barrier has the effect of changing the magnitude and sign of the corresponding matrix element.

If the drug participates in a chemical reaction in the compartment fluid phase of the physiological system, such effects may contribute to either alteration of corresponding element of vector X of Eq. 1 or, in principle, change an n-compartment model to behave as an $(n + 1)$-compartment model. These considerations will be discussed in future publications; for the present, it is concluded that such a phenomenon is capable of possibly explaining certain types of "aperiodic biological oscillatory" after effects observed with certain drugs in physiological systems.

APPENDIX

Defining the quantities ϵ and ζ by:

$$\epsilon = \alpha_{12} + (\delta_{13}/V_1) \quad \text{(Eq. A1}a\text{)}$$

$$\zeta = \epsilon + k_{20} \quad \text{(Eq. A1}b\text{)}$$

one has:

$$\omega = k_{20} - \epsilon \quad \text{(Eq. A2)}$$

Equations 22a–22c of Ref. 1 can now be expressed as:

$$C_1(J_1/\eta) = -(\mu_3 + \mu_2) - \zeta \quad \text{(Eq. A3}a\text{)}$$

$$C_2(J_2/\eta) = (\mu_1 + \mu_3) + \zeta \quad \text{(Eq. A3}b\text{)}$$

$$C_3(J_3/\eta) = -(\mu_1 + \mu_2) - \zeta \quad \text{(Eq. A3}c\text{)}$$

$$J_1 = (\mu_1 - \mu_2)(\mu_1 - \mu_3) \quad \text{(Eq. A3}d\text{)}$$

$$J_2 = (\mu_1 - \mu_2)(\mu_2 - \mu_3) \quad \text{(Eq. A3}e\text{)}$$

$$J_3 = (\mu_1 - \mu_3)(\mu_2 - \mu_3) \quad \text{(Eq. A3}f\text{)}$$

The J_σ's, η, and ζ are positive definite. The decay constants are distinct and are negative definite. They may be ordered such that their magnitudes satisfy the inequalities of $|\mu_1| > |\mu_2| > |\mu_3|$.

It is evident that both C_1 and C_3 are negative when the magnitude of ζ is greater than $-(\mu_1 + \mu_2)$ [greater than $-(\mu_2 + \mu_3)$]. Because of the constraint expressed by Eq. 21b of Ref. 1, C_2 should be positive definite, which is assured by Eq. A3b.

The condition imposed by Eq. 12 for the existence of t_1^* is that the ratio $(1 + r_3m)/(1 + r_2m)$ should be positive. This condition is evidently satisfied if the roots of cubic Eq. 19 of Ref. 1, r_2 and r_3, are both positive and have a magnitude less than k_{20}. This condition is also satisfied if both r_2 and r_3 are negative, provided the magnitudes of r_2m and r_3m are greater than unity. It is also satisfied if either r_2 or r_3 is negative, provided the product of negative root and m has a magnitude less than unity.

When α_{13} is greater than k_{20}, from Eq. 17c of Ref. 1 it follows that $R = -(r_1r_2r_3)$ is negative. This requires that, when r_1 is negative, r_2 and r_3 must have opposite signs.

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Potential Anticancer Agents II: Antitumor and Cytotoxic Lignans from *Linum album* (Linaceae)

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Abstract □ A phytochemical study of *Linum album* (Linaceae), guided by bioassay with the 9KB cell culture, resulted in the isolation of podophyllotoxin and a new lignan, 3′-demethylpodophyllotoxin; α- and β-peltatins were identified by comparative TLC.

Keyphrases □ *Linum album* (Linaceae)—isolation and identification of antitumor and cytotoxic lignans □ Lignans—isolation and identification from *L. album*, screened for anticancer and cytotoxic properties □ Anticancer agents, potential—isolation and identification of antitumor and cytotoxic lignans from *L. album*, screened for activity

Linum album was found to be active against the P-388 leukemia and 9KB cell assay system in a random collection screening program for new anticancer agents. The chloroform extract of *L. album* yielded podophyllotoxin, α- and β-peltatins, and a new lignan, 3′-demethylpodophyllotoxin. Based upon spectroscopic data, a structure was proposed for 3′-demethylpodophyllotoxin, which was verified by preparation of a derivative of known structure. The lignans podophyllotoxin, α- and β-peltatins, and 3′-demethylpodophyllotoxin were shown to be at least partially responsible for the antitumor and cytotoxic activity of *L. album* extracts.

EXPERIMENTAL[1]

Biological Activity—An ethanolic extract of *L. album* was evaluated for cytotoxicity; it was found active against Eagle's 9KB carcinoma of the nasopharynx in cell culture (ED_{50} = 2.3, 2.5, and 1.4 μg/ml)[2] and showed *in vivo* activity against the P-388 lymphocytic leukemia in mice (T/C 136, 126, and 108 at 133, 88, and 88 mg/kg, respectively)[3]. Test methods employed were those of the Drug Research and Development Branch of the National Cancer Institute (1).

[1] The plant material used in this investigation consisted of the whole plant of *L. album* Kotschy ex Boiss. (Linaceae), collected in Iran during July 1970 and provided by Dr. T. Fakouhi, Department of Pharmacology, Pahlavi University, Medical School, Shiraz, Iran. Voucher specimens were identified by R. E. Perdue and are deposited in the Herbarium of the U.S. Department of Agriculture, Beltsville, Md.

[2] An active fraction is one that exhibits an $ED_{50} \leq 20$ μg/ml.

[3] An active fraction is one that exhibits a T/C of ≧125%.