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Lymphatic Transport of Griseofulvin in the Rat and the Possible Factors Determining the Extent of Lymphatic Absorption[1]

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Lymphatic and plasma levels of griseofulvin were determined in the rat after intraluminal administration as an oil-in-water emulsion dosage form.

Compared with oral administration, peak plasma levels are attained in a very short time. This finding supports the proposed mechanism that the bioavailability of orally administered griseofulvin was improved by inhibition of gastric motility. Although peak lymphatic level is reached more slowly than the peak plasma level, griseofulvin peak concentration is almost as high, suggesting that the lymphatic appearance of griseofulvin is due to its distribution in the body water, of which lymph is a part.

The possible factors determining the extent of lymphatic absorption of lipid-soluble compounds have been discussed with the special reference to their dissolution characteristics *in vitro*.

Two groups (lymph/plasma$>$1 and lymph/plasma$\leqslant$1) related to the ratio of dissolution rates in an oil-in-water emulsion and in 6% BSA solution are distinguished. It is suggested that one of the major factors determining the extent of lymphatic absorption is the affinity with carriers in the portal route rather than that with lymphatic ones.

Keywords——lymphatic absorption; griseofulvin; rat; oil-in-water emulsion dosage form; lipid-soluble compounds; factors determining the lymphatic absorption; ratios of dissolution rate

The absorption of griseofulvin has been studied extensively in man and laboratory animals. It has been shown that variable and incomplete absorption of griseofulvin occurs after oral administration, probably due to its extremely low solubility in water. Based on measurements of the area under the curve for plasma concentration *versus* time, Carrigan and Bates[3] reported that the bioavailability of micronized griseofulvin in rats given as an oil-in-water emulsion was 2.5 and 1.6 times greater than that of an oil suspension and an aqueous suspension, respectively. Improvement of bioavailability of lipid-soluble compounds by using an oil-in-water emulsion has been reported by Wagner, *et al.*[4] It was recently reported by Bates and Sequeira[5] that a mechanism based on the ability of the linoleic and oleic acids liberated during the digestion of corn oil to inhibit gastrointestinal (GI). motility and stimulate gallbladder evacuation may explain the marked enhancing effect of emulsified corn oil on griseofulvin absorption in humans. It can also be considered that oil is useful for accelerating the dissolution and the absorption of poorly water-soluble compounds.

Moreover, there is also the possibility that griseofulvin may be absorbed by the lymphatic route from an oil-in-water emulsion, since many lipophilic compounds are known to enter the organism through lymphatic absorption. Cholesterol,[6] long chain fatty

1) *a*) This paper constitutes the 10th report in the series of "Mechanism of the Intestinal Absorption of Drugs from Oil-in-Water Emulsions"; *b*) Preceding paper, Part IX: T. Noguchi, K. Taniguchi, S. Muranishi, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **25**, 434 (1977).
2) Location: *Yoshida Shimoadachi-cho, Sakyo-ku, Kyoto.*
3) P.J. Carrigan and T.R. Bates, *J. Pharm. Sci.*, **62**, 1476 (1973).
4) J.G. Wagner, E.S. Gerard, and D.G. Kaiser, *Clin. Pharmacol. Therap.*, **7**, 610 (1966).
5) T.R. Bates and J.A. Sequeira, *J. Pharm. Sci.*, **64**, 793 (1975).
6) C.R. Treadwell and G.V. Vahouny, "Handbook of Physiology," Section 6, Alimentary Canal. III Intestinal Absorption, ed. by C.F. Code, Washington, D.C., 1968, pp. 1407—1438.

acids,[7] lipid-soluble vitamins[8] and other dietary fats[9] are mainly absorbed by the lymphatics. However, few systematic studies of the mechanism of the lymphatic absorption of lipid-soluble compounds have been made.[10,11]

We have reported about the mechanism of the intestinal absorption and the lymphatic transport of lipid-soluble compounds from oil-in-water emulsions and showed that the absorption characteristics of lipid-soluble compounds were influenced by that of oils to some extent.[1b,12] In this paper, lymphatic and plasma levels of griseofulvin have been examined in the rat administered as an oil-in-water emulsion and an aqueous suspension in the intestinal loop where the factor of gastric emptying can be neglected. Furthermore, possible factors determining the extent of lymphatic transport have been discussed from the data of several lipid-soluble compounds.

Experimental

Materials——Griseofulvin was supplied by Takeda Chemical Ind. Ltd., and was micronized from benzene solution by the freezing dry method (specific surface area=21.6 m^2/g). Oil Red XO, Sudan Blue (Tokyo Kasei Co., Ltd.), triolein, bovine serum albumin fraction V, vitamin A acetate, diethylstilbestrol propionate (Sigma Chemical Co., Ltd.), diethylstilbestrol, testosterone, testosterone propionate (Nakarai Chemicals, Ltd.), and egg lecithin (Merck and Co., Ltd.) were used as supplied. Sodium taurocholate was synthesized by the method of Norman[13] with slight modification. Other chemicals were of reagent grade.

Animal Experiments——Male Wistar rats (190—220 g) were used in all experiments. Before an operation rats were fed *ad libtum*. Under sodium pentobarbital anesthesia the abdomen was exposed by a middle line incision, and the small intestine was cannulated at the end of pylorus with silicone tube. After carefully washing out the intestinal contents with saline warmed at 37°, the cannula was removed and the whole small intestine was made into loop by ligature.

Major intestinal lymphatic was cannulated by the heparin-filled polyethylene cannula (i.d. 0.50 mm, o.d. 0.80 mm, Dural Plastics and Eng. Pty. Ltd., Australia). A drop of tissue cement, Aron Alpha A® (Sankyo Co., Ltd.), was applied to the hole in the lymphatic to seal it and to fix the cannula in place. The accessory lymphatic was intentionally disrupted by forceps and occuluded with the cement to increase the return through the cannulated main lymphatic. To secure the cannulation 10 mm^2 of abdominal muscle was attached on the cement.

Emulsions containing 2 mg/ml of griseofulvin, 4% v/v of triolein and 0.2% w/v of Tween-80 in distilled water were prepared. The mixture of these components was shaken vigorously and sonicated at 20 kHz, 100 W for 5 min by a sonicator (No. 5202, Ohtake Seisakusho, Japan) under ice cooling. Five milliliters of this emulsion were administered in the intestinal loop and the lymph was collected every hour in a heparinized tube. Systemic blood was sampled from the cannula of cervical artery, and centrifuged immediately to get the plasma.

Determination of Solubility——Lipid-soluble compounds were agitated in various solvents at 25° for two days until no further change in their concentration was observed. Samples were centrifuged then, the supernatant layers were extracted with various organic solvents and the concentration of lipid-soluble compounds was determined.

Determination of Dissolution Rate——Thirty milligrams of griseofulvin or vitamin A acetate or 100 mg of Oil Red XO, Sudan Blue or testosterone, or 119 mg of testosterone propionate were dissolved in 10 ml of chloroform–petroleum ether (1: 1). The solution was poured into a petri dish with a flat bottom and a membrane filter (Sartorius SM-11309, 90 mm) was placed in the solution. The petri dish was tilted slightly until the membrane filter was uniformly saturated. Then the excess liquid was allowed to drip off and the

7) W.J. Simmonds, T.G. Redgrave, and R.L.S. Willix, *J. Clin. Invest.*, **47**, 1015 (1968).
8) *a*) D.G. Cornwell, F.A. Kruger, and H.B. Robinson, *J. Lipid. Res.*, **3**, 65 (1962); *b*) M.T. MacMahon, G. Neale, and G.R. Thompson, *Europ. J. Clin. Invest.*, **1**, 288 (1971); *c*) D.L. Yeung and M.J. Veen-Baigent, *Can. J. Physiol. Pharmacol.*, **50**, 753 (1972); *d*) H.E. Gallo-Torres, F. Weber, and O. Wiss, *Internat. J. Vit. Nutr. Res.*, **41**, 504 (1971).
9) *a*) C.E. Rubin, *Gastroent.*, **50**, 65 (1966); *b*) A. Nilsson, *Biochim. Biophys. Acta*, **152**, 379 (1968).
10) S.M. Sieber, V.H. Cohn, and W.T. Wynn, *Xenobiotica*, **4**, 265 (1974).
11) J.D. Kamp and H.-G. Neumann, *Xenobiotica*, **5**, 717 (1975).
12) *a*) T. Noguchi, C. Takahashi, T. Kimura, S. Muranishi, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **23**, 775 (1975); *b*) T. Noguchi, Y. Jinguji, T. Kimura, S. Muranishi, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **23**, 782 (1975); *c*) T. Noguchi, Y. Tokunaga, H. Ichikawa, S. Muranishi, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **25**, 413 (1977).
13) A. Norman, *Arkiv. Kemi.*, **8**, 331 (1955).

filter was pressed between the blotter pads using a hand roller. Pressing was repeated once more using the new blotter pads. The solvent was evaporated during these procedures and the filter was then stored at 4°.

Three types of solvents were used: distilled water, 6% bovine serum albumin (BSA) solution (a model of cytoplasmic protein) and an oil-in-water emulsion (a model of chylomicrons and very low density lipoproteins), which contains 2.5% v/v of triolein, 5.04 mg/ml of egg lecithin and 3.36 mg/ml of sodium taurocholate in distilled water.

The filter maintaining lipid-soluble compounds was placed in position between the plates of the diffusion chamber of Sartorius Absorption Simulator® (Sartorius-Membranefilter, GmbH), and the plates screwed together. Two chambers were connected by the glass tube to make the effective surface area for dissolution double. In the case of griseofulvin, vitamin A acetate, testosterone and testosterone propionate, the single perfusion method was used (Fig. 1-A). Fifty milliliters of solvent were maintained at 37°, and were introduc-

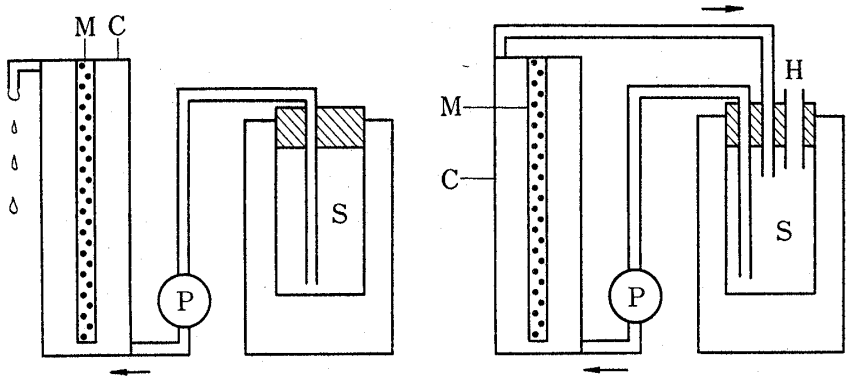

Fig. 1. Schematic Diagram of the Apparatus for Dissolution Rate Studies

Key: C, the diffusion chamber of Sartorius Absorption Simulator®; M, Sartorius Membranefilter SM-11309 maintaining lipid-soluble compounds; S, solvents maintained at 37° (A: 50 ml, B: 35 ml); P, circulation pump (flow rate=3.0 ml/min); and H, sampling hole.

ed into the diffusion chamber by a circulation pump at the flow rate of 3.0 ml/min. The eluted solvent was collected every minute and the concentration of lipid-soluble compounds in it was determined.

In the case of Oil Red XO and Sudan Blue, the recirculation method was used (Fig. 1-B) owing to the sensitivity of assay method. Thirty-five milliliters of solvents were recirculated through the diffusion chamber and 0.5 ml of solvent was sampled up from the sampling hole at 5, 10, 15, 20, 25, 30, 45 and 60 min after the start of experiment.

Analytical Methods——For griseofulvin the specific spectrofluorometric procedure of Shah, *et al.*[14] was slightly modified for handling *in vivo* and *in vitro* samples. The plasma, lymph and various solvents of *in vitro* experiments were extracted with 6 ml of ether and an aliquot of the organic phase was subsequently evaporated to dryness under N_2 at 50°. The residue was dissolved in 3 ml of methanol–water (1: 1), shaken with 3 ml of hexane. The fluorescence of the hydroalcoholic phase was measured on a spectrofluorometer (Hitachi Model 512, Hitachi Ltd., Japan) using activation and emission wavelengths of 300 and 420 nm, respectively. Subsequently, 3 drops of concentrated sulfuric acid was added to the cuvette and the fluorescence was determined. The difference between the two readings was used to calculate the concentration of griseofulvin from the standard curve.

Vitamin A acetate was also determined spectrofluorometrically by the slightly modified method of Hansen and Warwick.[15] A 0.5 ml of sample was placed in a separate centrifuge tube. A 0.5 ml of double distilled water, 3 ml of distilled ethanol, and 5 ml of cyclohexane were added to each tube. After shaking and centrifugation, upper organic phase was pipetted and the fluorescence of the sample was read at 460 nm with activation at 330 nm.

Testosterone was determined by two methods. In the case of 6% BSA solution and an aqueous solution, it was determined spectrophotometrically at 231 nm after being extracted with petroleum ether. In the case of an oil-in-water emulsion, an aliquot of petroleum ether layer was evaporated to dryness under N_2 at 50°. The residue was dissolved in 4 ml of methanol–water (1: 1), shaken with 4 ml of hexane. The hydroalcoholic phase was measured spectrophotometrically at 231 nm. Testosterone propionate was determined

14) P.V. Shah, S. Riegelman, and W.L. Epstein, *J. Pharm. Sci.*, **61**, 634 (1972).
15) L.G. Hansen and W.J. Warwick, *Am. J. Clin. Pathol.*, **50**, 525 (1968).

by the same method as testosterone except that ethanol–water (3 : 1) was used instead of methanol–water (1 : 1).

Diethylstilbestrol and its propionate were extracted with ether and aliquots of ether layer were evaporated to dryness under N_2 at 50°. The residue was dissolved in 4 ml of 0.1 M K_2HPO_4–ethanol (1 : 1) and determined spectrophotometrically at 418 nm after ultraviolet (UV) irradiation for 2.5 hr. Diethylstilbestrol propionate was hydrolyzed with 0.4% KOH–ethanol at 65° for 30 min before addition of K_2HPO_4–ethanol solution.

Oil Red XO and Sudan Blue were determined spectrophotometrically at 484 and 646 nm, respectively, after being solubilized with ethanol.

Results

Lymphatic and Plasma Levels of Griseofulvin after Intraluminal Administration of an Oil-in-Water Emulsion

Figure 2 represents the lymphatic and plasma concentration of griseofulvin versus time plots obtained following the intraluminal administration of a single 10 mg dose of micronized griseofulvin to individual rat as an oil-in-water emulsion dosage form. The curve reveals a delay in the attainment of peak lymphatic level following administration of the emulsion as compared with that of peak plasma level. The peak heights of both levels, however, are almost equal. Same results were obtained in the case of an aqueous suspension of griseofulvin.

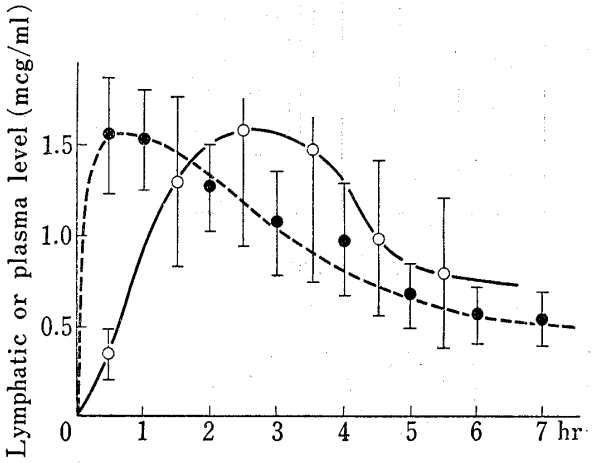

Fig. 2. Lymphatic and Plasma Levels of Griseofulvin after Intraluminal Administration of an Oil-in-Water Emulsion

Key: —○— lymphatic level; ---●---, plasma level. Emulsions containing 2 mg/ml of griseofulvin, 4% v/v of triolein and 0.2% w/v of Tween-80 in distilled water were administered 5 ml/rat in the loop of the small intestine. Each value represents the mean ± S.D. of at least three animals.

These results mean that griseofulvin is not absorbed exclusively through lymphatics. In our previous study,[12a] Oil Red XO, a highly lipid-soluble and poorly water-soluble dye, was not detectable in the mesenteric lymph in spite of its negligible metabolism during absorption.

It was well recognized that highly lipophilic compounds were accumulated much in the epithelial cells.[12b,16] So, it can be considered that the rate determining step of their absorption is their release from

Table I. Solubility of Lipid-Soluble Compounds in Various Solvents

Compound	Solubility (mcg/ml) in			
	Dist. water	6% BSA	Triolein	Liposome[a]
Oil Red XO	0.00	8.9	2.20×10^4	1.05×10^2
Sudan Blue	0.00	1.0	1.01×10^4	9.92×10
Vit. A acetate	0.40	2.7		
Griseofulvin	1.47×10	1.47×10^2	2.61×10^2	4.01×10
Testosterone	1.83×10	8.93×10	4.80×10^3	8.57×10
Diethylstilbestrol	4.63	8.48×10^2	3.76×10^4	
Diethylstilbestrol propionate	0.00	7.13	1.46×10^4	

The samples were agitated at 25° for two days until no further change in concentration of compounds was observed. Each value represents the mean of at least three samples.
a) Egg lecithin 230 mg + sodium taurocholate 0.25 mmol + distilled water 40 ml, sonicated for 10 min at kHz, 100 W.

16) D. Hollander, K.S. Muralidhara, and E. Rim, *Am. J. Physiol.*, **230**, 251 (1976).

the epithelial cell membrane and/or cytoplasmic particles through binding to cytoplasmic proteins or being entrapped in chylomicrons. Factors determining the extent of lymphatic absorption was investigated from this viewpoint.

Solubility and Dissolution Rate of Lipid-Soluble Compounds

Lipid-solubility has been considered to be the major factor for the lymphatic transport of small molecules.[10,11] Solubility of lipid-soluble compounds in various solvents were measured and shown in Table I. In these model compounds Sudan Blue and vitamin A acetate were demonstrated to show higher lymph/plasma ratios than one.[8c,12b] Testosterone as well as Oil Red XO and griseofulvin had the ratio of less than one.[10] Also diethylstilbestrol, reported to be highly excreted in bile,[17] can be considered to have the ratio of less than one. All of these compounds show high solubility in triolein but low one in distilled water, which seems to have no relationship with their extent of lymphatic transport. On the other hand, their solubility in 6% BSA solution partly indicates that protein binding may play an important role in their portal transport.

Since the absorption process is a dynamic one, it is better to measure the dissolution rate rather than solubility. The dissolution rate was determined using the apparatus shown in Fig. 1. In the conventional methods a pellet of compound must be prepared and the effective surface area of the pellet is usually very small. In the present method, however, the preparation of membrane maintaining lipid-soluble compounds is very simple and its effective surface area is very large. So, the dissolution experiment can be done in a short period. The typical pattern of dissolved griseofulvin *versus* time curve is shown in Fig. 3.

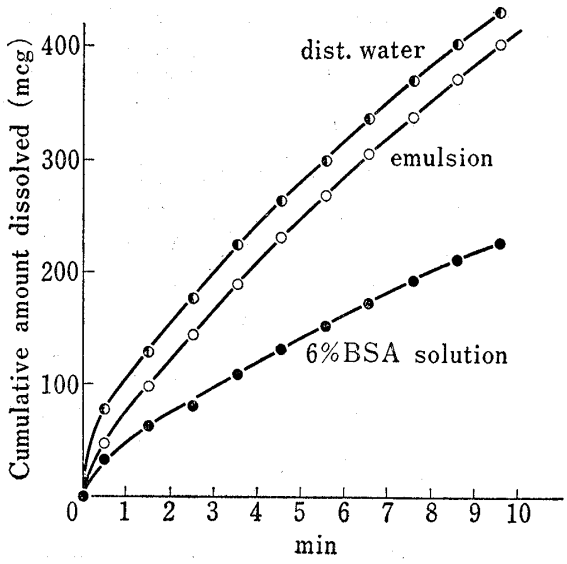

Fig. 3. Dissolved Amount *versus* Time Curves of Griseofulvin

The figure represents the typical pattern of dissolution in three solvents. Little or no variabilities were observed in the same experiment.

For these dissolution profiles, the dissolution rate may be expressed as the following equation which was derived by Shah and Ochs[18] for the continuous fluid flow system:

$$J = V\frac{dC}{dt} + nC \qquad \text{(Eq. 1)}$$

where J is the dissolution rate, V is the fluid volume in the diffusion chamber, C is the concentration of a compound in the dissolution medium at time t, and n is fluid flow rate. As the volume of diffusion chamber is very small relative to effective surface area in the present apparatus, the attainment of equilibrium could be rapid and C would be almost constant in an initial period of experiment. Then $dC/dt \fallingdotseq 0$ and Eq. 1 becomes

$$J = nC \qquad \text{(Eq. 2)}$$

After a minute's lag time, the curve shows the linear line, which means that the dissolution is the apparent zero order process, which is reasonable from Eq. 2. The dissolution rate of griseofulvin was then determined from the slope of curves shown in Fig. 3. Dissolution rate of other lipid-soluble compounds was also determined in the same way and summarized in

17) A.G. Clark, L.J. Fischer, P. Millburn, R.L. Smith, and R.T. Williams, *Biochem. J.*, **112**, 17 (1969).
18) A.C. Shah and J.F. Ochs, *J. Pharm. Sci.*, 63, 110 (1974).

Table II. Apparently no good relationship is observed between the solubility and the dissolution rate.

Table II. Dissolution Rate of Lipid-Soluble Compounds in Various Solvents (37°)

Compound	Method	Dissolution rate (mcg/min) in		
		Emulsion	6% BSA	Dist. water
Oil Red XO	Recirculation	1.24×10 (2)	1.72×10 (2)	
Sudan Blue	Recirculation	2.12×10 (2)	2.62 (2)	
Vit. A acetate	Single perfusion	2.86×10 (2)	3.91 (2)	
Griseofulvin	Single perfusion	3.60×10 (2)	1.88×10 (2)	3.38×10 (2)
Testosterone	Single perfusion	9.06×10 (2)	1.80×10^2 (3)	2.00×10^2 (2)
Testosterone propionate	Single perfusion	2.57×10 (3)	1.24×10 (2)	0.00 (1)

Dissolution rate was calculated from the dissolution curve *e.g.* shown in Fig. 3, which could be postulated as the pseudo-zero order process. The number of experiments was shown in the parenthesis. Little or no variabilities were observed in the same experiment.

To elucidate the factors which decide the extent of lymphatic absorption, various ratios of dissolution rates are compared in Table III, where the values are represented as the relative ratio to griseofulvin. As is clearly shown in Table III, six lipid-soluble compounds are classified into two groups by the ratio of dissolution rates in an emulsion and in 6% BSA solution, namely >1 and $\leqslant1$ of A/B or A/C.

Table III. Ratios of Dissolution Rates of Lipid-Soluble Compounds

Compound	Ratio of dissolution rates	
	A/B	A/C
Oil Red XO	3.78×10^{-1}	6.74×10^{-1}
Sudan Blue	4.24	7.56
Vit. A acetate	3.83	6.83
Griseofulvin	1.00	1.00
Testosterone	2.63×10^{-1}	4.23×10^{-1}
Testosterone propionate	1.08	1.94

Key: A, dissolution rate in an emulsion; B, dissolution rate in 6 % BSA solution; C, same value of B except griseofulvin and testosterone, in the case of which dissolution rate in distilled water was used instead of that in 6 % BSA solution.
Values are represented as the relative ratio to griseofulvin.

Discussion

From this study it was clarified that the lymph/plasma ratio of griseofulvin administered intraluminally as an oil-in-water emulsion dosage form was not larger than one. The ratio is not much different from water-soluble compounds, such as *p*-aminosalicylic acid,[19] cardiac glycosides[20] and sugars,[21] and is smaller than the cases of macromolecules, such as parotin.[22]

Compared with the results of Carrigan and Bates[3] it takes very short time to attain peak plasma level, supporting their proposed mechanism that triolein is useful to inhibit gastric

19) T.J. De Marco and R.R. Levine, *J. Pharmacol. Exptl. Therap.*, **169**, 142 (1969).
20) W. Forth, E. Furukawa, and W. Rummel, *Naunyn-Schmiedebergs Arch. Pharmak.*, **264**, 406 (1969).
21) J. Seifert, H. Pröls, K. Messmer, R. Bücklein, G. Lob, H. Mehnert, and W. Brendel, *Digestion*, **12**, 221 (1975).
22) H. Manita, T. Sudo, and H. Asano, *Endocrinol. Jpn.*, **20**, 463 (1973).

motility and thus improve the bioavailability of orally administered griseofulvin. This concept is also supported by the fact that when administered intraluminally no difference was observed between an oil-in-water emulsion and an aqueous suspension (not shown).

As is known anatomically[23] and from the case of vitamin K,[24] the thoracic lymph dose not reflect the true lymphatic absorption from the intestine. The concentration of compounds absorbed *via* intestinal lymphatic is always lower in thoracic lymph than that in mesenteric one. Though the mesenteric lymph was investigated in this paper, the peak lymphatic concentration of griseofulvin is equal to plasma one (Fig. 2) and it is suggested that the lymphatic appearance of griseofulvin is due to a kind of distribution in the body water, of which lymph is a part. It is well explained from the dissolution rate of griseofulvin in distilled water (Table II) that the dissolution of griseofulvin seems not to be the rate determining step in its release from the epithelial cell, though its solubility in distilled water is very small (Table I).

Recently, a serum albumin-liposome complex was proposed as a model of lipoprotein membrane[25] and the mechanism of lymphatic transport was examined using the model of this complex.[26] Same experiments have been done using animal chylomicrons by Sieber, *et al.*[10] They concluded that lipid solubility of the compounds and its metabolite during absorption process appeared to be an important factor for the extent of lymphatic transport. However, these studies dealed only with the steady-state and their theory can not explain the phenomena that Oil Red XO, highly lipophilic dye, is not absorbed through the lymphatics.[12b] As shown in Table I, solubility of four compounds in liposome cannot explain the lymphatic affinity, either.

Pocock and Vost[27] reported that once absorbed by the lymphatics some dichlorodiphenyltrichloroethane (DDT) was transported from chylomicrons to albumin or other plasma proteins before tissue uptake. Considering with the higher flow of portal vein than of lymphatics[28] it is well posturated, therefore, that the major factor determining the extent of lymphatic absorption is not the affinity with chylomicrons or Golgi apparatus as has been considered before, but is the affinity with such as cytoplasmic proteins which play an important role in carrying lipid-soluble compounds into the portal system.

Table III clearly demonstrates the rightness of this hypothesis. Considering with the difference of effective surface area among compounds and the balance of two routes, the lymphatic and the portal ones, it must be better to deal with the ratio of dissolution rates in an emulsion, the model of chylomicrons and very low density lipoproteins, and in 6% BSA

Table IV. Dissolution Rate of Griseofulvin in Various Solvents and Their Relative Viscosities

Solvent	Dissolution rate (mcg/min)	Relative viscosity
Dist. water	3.38×10	1.00
6% BSA soln.	1.88×10	1.17
3% BSA soln.	4.58×10	1.05
Emulsion	3.60×10	1.08

Relative viscosities were measured at 37° with B type viscometer (Tokyo Keiki Seizosho, Japan).

23) N.L. Tilney, *J. Anat.*, **109**, 369 (1971).
24) J.A. Mezick, R.K. Tompkins, and D.G. Cornwell, *Life Sci.*, **7**, 153 (1968).
25) B.V. Sogol and J.E. Zull, *Biochim. Biophys. Acta*, **375**, 363 (1975).
26) Y. Aso, M. Agata, and K. Mishima, Seventh Symposium on Drug Metabolism and Action, Sapporo, Oct., 1975.
27) D.M.-E. Pocock and A. Vost, *Lipids*, **9**, 374 (1974).
28) B.M. Hendrix and J.E. Sweet, *J. Biol. Chem.*, **32**, 299 (1917).

solution, the model of cytoplasmic proteins. In the case of rather water-soluble compounds (in the virtue of the dissolution rate) such as griseofulvin and testosterone, it is better to use the dissolution rate in distilled water rather than that in BSA solution, since the former is faster than the latter probably because of higher viscosity of BSA solution than that of distilled water and such compounds seem to be diffused into the portal vein with little aid of cytoplasmic proteins. The relationship between a viscosity of solvents and dissolution rate of griseofulvin in it is shown in Table IV. Dissolution of griseofulvin in 6% BSA solution seems to be partly accelerated by protein binding and be partly suppressed by its higher viscosity.

Although the contribution of the lymphatic system in the intestinal absorption of most drugs appears to be minor due to its little flow, if the technique of pro-drugs was applied to such drugs, their absorption by the intestinal lymphatics would permit their direct distribution to the lymphatic system and to the entire body without the first-pass effect by the liver. The differences in the amount of lymphatic transport among various derivatives of α-tocopheryl esters have been reported recently.[29] It was also known that the distribution of α-tocopherol was much differed by its carriers.[30] However, propionates of testosterone and diethylstilbestrol were not transported into lymph (not shown). Compared with testosterone and diethylstilbestrol, their solubility in 6% BSA solution decreased by one order, but they are still higher than that of Sudan Blue and vitamin A acetate.

Though the absorption process of lipid-soluble compounds from an oil-in-water emulsion involves various factors, the diffusion rate theory proposed in this paper can give some information about the extent of lymphatic transport by the simple routine work. However, many drugs and pro-drugs of diverse categories must be examined to substantiate the above remarks.

29) T. Nakamura, Y. Aoyama, T. Fujita, and G. Katsui, *Lipids*, **10**, 627 (1975).
30) J. Kelleher, T. Davies, C.L. Smith, B.E. Walker, and M.S. Losowsky, *Internat. J. Vit. Nutr. Res.*, **42**, 394 (1972).