Figure 9 shows the proposed model for free drug delivery. Even though micelle-containing drug as well as free drug is present in the solution, according to this model, the micelle does not take part in the transfer of solute across the hexadecane–water interface and only the free drug is involved in the rate-determining step.

It should be stressed, however, that the limited data presented in Table II cannot exclude the possibility that some micelle transport may have contributed to the interphase transfer of the sterols. More extensive studies are desirable with regard to this question.

Since the present findings with the sodium taurocholate–lecithin system are very similar to those obtained with the polysorbate 80 system, the likelihood that an interfacial barrier-controlled process governs sterol absorption in rats (5) has been strengthened.

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Absorption Kinetics of Aspirin in Man following Oral Administration of an Aqueous Solution

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Abstract □ The absorption of aspirin was studied in four male subjects following an oral solution of 650 mg. The absorption process appeared to follow first-order kinetics, with a half-life ranging from 4.5 to 16.0 min. between subjects. Comparison of the area under the aspirin plasma concentration–time curve following intravenous and oral routes indicated that only 68% of the dose reached the peripheral circulation intact. A two-compartment model for both aspirin and its metabolite, salicylic acid, involving a constant fractional hydrolysis of aspirin during absorption, satisfactorily described both the aspirin and resultant salicylic acid plasma data. Methods used to calculate aspirin absorption kinetics are discussed.

Keyphrases □ Aspirin, oral—absorption kinetics, aqueous solution, man □ Absorption kinetics—aspirin, oral aqueous solution, man □ Pharmacokinetics, aspirin, oral aqueous solution—absorption kinetics, calculations, half-life, plasma concentration–time curves, two-compartment model □ Half-life—orally administered aspirin, first-order kinetics, man

The clinical importance of aspirin as a weak analgesic has led to numerous studies concerning the absorption of this drug in man (1–8). Several of these studies confirmed that, although aspirin is known to be rapidly hydrolyzed to salicylic acid *in vivo*, intact drug is absorbed and blood levels of aspirin can be demonstrated up to 1 hr. following an oral dose of the drug (1–8). Using a specific assay, Rowland and Riegelman (9) examined the kinetics of distribution and metabolism of aspirin in man following intravenous administration as its *N*-methylglucamine salt (10). The decay was biexponential with half-lives of 4 and 15 min. for the initial and final phases, respectively. A two-compartment model was the minimum that could be proposed which fitted both the observed aspirin and resulting salicylic acid plasma level data.

The present study was undertaken to examine both the absorption kinetics of aspirin and the availability or amount of unchanged drug reaching the peripheral circulation since, together with elimination, they influence the amount of aspirin in the body at any time. This drug was given in solution to obviate the effects of varying dissolution rates from tablets (11). A preliminary communication of these findings was published previously (12).

EXPERIMENTAL

Human Studies—Four male subjects were used in whom the pharmacokinetics of aspirin and salicylic acid following intravenous administration had been determined previously. Each subject ingested (within 15 sec.) 650 mg. aspirin dissolved in 250 ml. water, prepared just prior to administration. They remained seated for at least 2 hr. following the dose. Blood samples (5 ml.) were drawn from the antecubital vein usually at 0, 3, 6, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 240, 360, and 480 min. following aspirin administration. In all but one, a similar study was conducted following oral administration of 500 mg. salicylic acid in 250 ml. water. On another occasion, two subjects received intravenous logarithmic infusions of 650 mg. aspirin using an infusion pump (Harvard). The logarithmic infusion was achieved by lowering the rate of infusion at constant intervals. The duration of this interval determined the half-life. Plasma samples were assayed for aspirin using GLC, and salicylic acid was determined fluorometrically (9).

Everted Gut Studies—New Zealand white rabbits, weighing 3 kg., were used. Animals were killed with intraperitoneal thiopental, and various parts of the GI tract were removed immediately. Approximately an equal weight of each tissue (4 g.) was everted, filled with 8 ml. Krebs-Ringer solution, and placed into a 125-ml.

Table I—Half-Lives and Areas under the Aspirin Concentration–Time Curves after Intravenous and Oral Administration of 650 mg. Aspirin

Subject[a]	Age, years	Weight, kg.	Route	Half-Life, min. ($t_{1/2\beta}$)	Area, (mcg./ml.) × min.	Ratio of Areas × 100
A	28	69	Intravenous	14.5	948	72
			Oral	15.0	680	
B	28	68	Intravenous	13.7	910	69
			Oral[b]	14.0	630	
C	45	73	Intravenous	14.5	1000	66
			Oral	19.0	655	
D	52	89	Intravenous	14.0	960	65
			Oral	20.5	620	

[a] The subjects in the present study were the same as those in *Reference 10* and are listed in the same alphabetical order. With the exception of Subject C, they correspond to the subjects listed in Table I of *Reference 12*. [b] Trial 2 (Fig. 6). The oral study for Subject B in *Reference 12* corresponds to Trial 1 in Fig. 6 of the present paper.

conical flask containing 67.5 ml. Krebs-Ringer solution at 37°. Both serosal and mucosal solutions were aerated with 5% CO_2 in oxygen. To the mucosal solution was added 7.5 ml. of freshly prepared 100 mcg. aspirin/ml. solution, and samples were taken for analysis immediately and at various times for 2 hr. Samples were diluted with phosphate buffer (pH 7.0, 0.1 *M*) and salicylic acid was determined fluorometrically, while aspirin was calculated as the increase in the salicylic acid upon hydrolysis of the sample at 100° for 1 hr. Samples taken from control experiments in which no aspirin was added exhibited negligible fluorescence under the assay conditions.

In experiments with the stomach, the rabbit was fasted overnight and anesthetized. Then the stomach was cut at both ends, keeping blood vessels intact, and the contents of the stomach were removed by washing. The pyloric sphincter was then ligated and the stomach was removed, filled with 50 ml. Krebs-Ringer at 37°, and immersed in 200 ml. of Krebs-Ringer solution. Freshly prepared aspirin solution (10 ml., 100 mcg./ml.) was pipeted into the stomach, and samples were taken as in the intestinal experiments. All measurements were corrected for the hydrolysis of aspirin alone in Krebs-Ringer solution.

Hydrolysis of Aspirin in Various Fluids—Human gastric and duodenal fluids were aspirated from two volunteers. To 9 ml. of each fluid and Krebs-Ringer, at 37°, was added 1 ml. aspirin solution (100 mcg./ml.). Samples were taken at various times and aspirin was analyzed by GLC (9).

Determination of Absorption Rate—The amount of drug absorbed at various times was calculated by the method of Loo and Riegelman (13) using the aspirin plasma data. The percent of the dose absorbed is given by:

$$\frac{A_t}{A_\infty} = \frac{C_p + k_{13}\int_0^t C_p\,dt + C_T}{k_{13}\int_0^\infty C_p\,dt} \qquad \text{(Eq. 1)}$$

where A_t and A_∞ are the amounts of drug absorbed up to time t and infinity, respectively; C_p and C_T are the plasma and tissue (expressed relative to the plasma) concentrations, respectively; and k_{13} is the elimination rate constant[1] while $\int_0^t C_p\,dt$ and $\int_0^\infty C_p\,dt$ are the corresponding areas under the plasma level–time curve up to time t and infinity, respectively. As in the Wagner–Nelson (15) method, the function reaches an asymptotic value when absorption has ceased.

RESULTS AND DISCUSSION

Plasma Level Data—Aspirin plasma levels following the ingestion of 650 mg. aspirin (equivalent to two 5-gr. tablets) were similar in all subjects (Fig. 1). Levels of aspirin rose sharply, reaching a maximum (23 and 10 mcg. aspirin/ml. plasma) at 10 and 25 min., respectively, after administration. These levels then declined rapidly, with only small amounts remaining after 2 hr. Although the half-life for the decline phase was short, 14–20.5 min., it was always longer than the disposition half-life of aspirin previously determined from intravenous studies (Table I) and was due to continued absorption of aspirin during the decline phase.

Associated with the hydrolysis of aspirin, salicylic acid levels rose rapidly and eventually exceeded those of aspirin because of slower elimination rather than differences in distribution (10). Furthermore, salicylic acid levels reached a maximum subsequent to those of aspirin, which is as expected from the precursor–product relationship.

Influence of Route of Administration on Availability of Aspirin—The mean area under the plasma aspirin–time curve following the oral dose of 650 mg. aspirin was only 68% of that obtained following intravenous administration (Table I). Since area is a measure of the dose that reaches the sampling site, this would indicate that 32% of ingested aspirin does not reach the peripheral circulation after an oral dose. Incomplete absorption was excluded as a cause, since the area under the metabolite curve[2] was the same following either route of administration (Table II and Fig. 2). Consequently, hydrolysis of aspirin must have occurred either in the intestinal fluids, across the GI wall, or during the first passage of drug through the liver. Esterase activity in the intestinal fluids was negligible. The mean half-lives of aspirin at 37° in the samples of gastric and duodenal juices examined were 16 and 17 hr., respectively, which

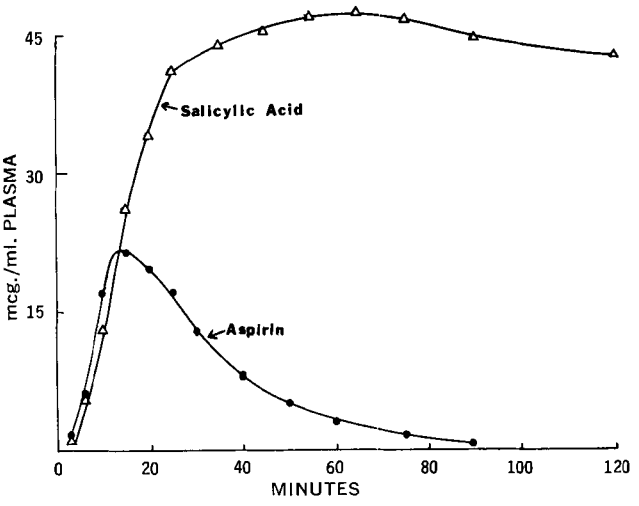


Figure 1—*Aspirin* (●) *and salicylic acid* (△) *plasma levels following oral solution of 650 mg. aspirin, Subject B.*

[1] The constant k_{13} is the elimination rate constant in a two-compartment model and should not be confused with the disposition rate constant, β, which is usually the rate constant determined from the decline portion of the oral plasma level curve (14).

[2] The considerations in the determination and comparison of the salicylic acid plasma areas are the same as those made in *Reference 10*.

Table II—Comparison of Area under Salicylic Acid Plasma Concentration–Time Curve following Intravenous and Oral Aspirin (650 mg.) and Salicylic Acid (500 mg.)

Subject	Area [(mcg./ml.) × min.] following Intravenous Aspirin	Oral Aspirin	Intravenous Salicylic Acid	Oral Salicylic Acid
A	22,000 (107[a])	20,300 (99)	20,600 (100)	20,500 (100)
B	20,300 (101)	20,500 (101)	20,100 (100)	22,700 (113)
C	21,700 (101)	22,700 (106)	21,400 (100)	—
D	14,100 (94)	15,000 (100)	15,000 (100)	14,500 (97)

[a] Figures in parentheses are the percentage of the area expressed relative to that following intravenous salicylic acid for each subject.

did not differ appreciably from the 15.5 hr. observed in Krebs-Ringer bicarbonate solution.

Little attention has been paid to the GI tract as a source of aspirin hydrolysis, although Levy *et al.* (16, 17) demonstrated the presence of esterase in hamster and rat small intestines. In the present study, all sections of the rabbit GI tract were found capable of hydrolyzing aspirin. However, the esterase activity varied, being maximal in the duodenum and minimal in the stomach and colon (Fig. 3). Even though it is realized that these results cannot be directly extrapolated to man, nonspecific esterases have been found along the entire human GI tract (18), and it would seem likely that such enzymes are responsible for some loss of aspirin during absorption.

Unlike intravenous administration, all ingested drug must pass through the liver, *via* the hepatic portal vein, before entering the general circulation. As blood samples were withdrawn from a peripheral vein, a difference in area measurements following these routes is expected for drugs having a sufficiently high hepatic clearance. With aspirin, this alone can account for the observed results as the following calculation clearly demonstrates. The apparent partition coefficient of aspirin between plasma and blood cells was found to be 2.2 and corresponds to a plasma-to-whole blood concentration ratio of 0.8 (hematocrit 0.45). The average total body plasma clearance of aspirin is 650 ml./min./70 kg. in man (10). Consequently, the total body whole blood clearance is 810 ml./min./70 kg., of which an estimated 14% (115 ml./min.) results from

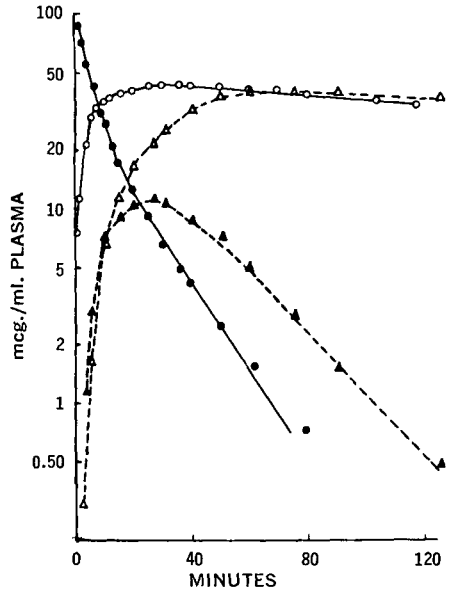


Figure 2—*Plasma aspirin and salicylate levels following oral and intravenous administration of 650 mg. aspirin, Subject C. Key: ●, intravenous aspirin; ▲, oral aspirin; ○, salicylic acid following intravenous aspirin; and △, salicylic acid following oral aspirin.*

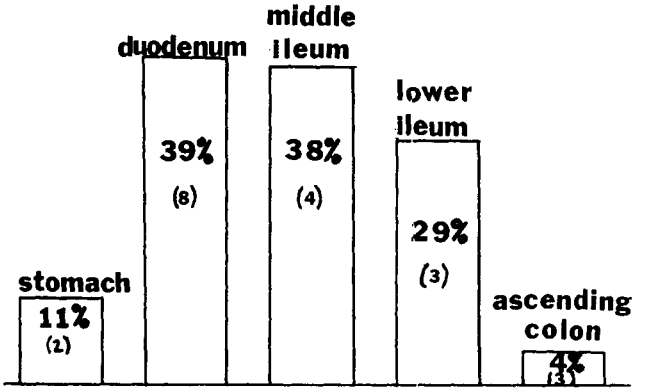


Figure 3—*Block diagram showing the average percent of aspirin hydrolyzed within 1 hr. in the rabbit's stomach and various parts of everted GI tract. In parentheses are the numbers of experiments run with each tissue.*

hydrolysis in whole blood. The latter figure was derived from the product of the *in vitro* hydrolysis rate constant of aspirin in whole human blood at 37° (K = 0.023 min.$^{-1}$, *Reference 10*) and the total blood volume. If it is assumed that the remainder (695 ml./min.) is due to hepatic metabolism, then since the blood flow through this organ is approximately 1.5 l./min. (19), *i.e.*, 25% of the cardiac output, as much as 46% of the oral aspirin could be hydrolyzed during its first passage through the liver. For salicylic acid, on the other hand, area measurements following intravenous and oral salicylic acid are similar (Table II). While this result is expected for this drug, which has a low hepatic clearance (40 ml./min., based on data given in *Reference 10* and assuming hepatic metabolism is the only route of elimination), it also implies that no appreciable metabolism of salicylic acid occurs upon transit through the gut wall.

More quantitative information regarding the relative contribution of gut esterases and liver to the loss of oral aspirin was obtained in dogs by Harris and Riegelman (20) who, on separate occasions, administered this drug by vena cava infusion, by hepatic portal vein infusion, and orally by stomach tube. In a typical experiment, these workers found that the relative areas under the plasma aspirin–time curves were 100, 59, and 46%, respectively. Evidently, in the dog at least and perhaps in man, both gut wall and liver are important sites for the elimination of oral aspirin.

Aspirin Absorption Kinetics—Prior to calculating the absorption kinetics following oral aspirin, the method of Loo and Riegelman (13), based upon the two-compartment open model, was tested by analyzing the plasma aspirin data following known logarithmic infusions ($t_{1/2}$ = 6.0 and 10.0 min.) of 650 mg. aspirin to two subjects. The calculated and known infusion (absorption) rate data were in excellent accord (13). In addition, equal areas under the aspirin plasma curve were obtained from the bolus and infusion

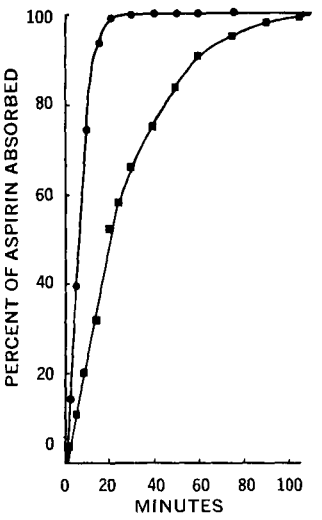


Figure 4—*Percent of aspirin absorbed* versus *time following ingestion of an oral solution of 650 mg. aspirin. Key: ●, Subject B; and ■, Subject D.*

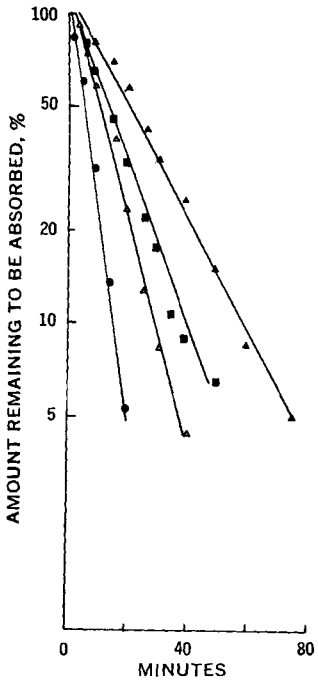


Figure 5—*Percent of aspirin remaining to be absorbed following oral administration of an aqueous solution of 650 mg. aspirin. Key: △, Subject A; ●, Subject B; ▲, Subject C; and ■, Subject D.*

studies. This agreement suggests that elimination and distribution rate constants of each subject, previously calculated from the bolus data, did not change substantially during the several months of this study and that the parameters defining the aspirin model are independent of the rate of intravenous administration. While it is conceivable that saturation of metabolic sites or a change in protein binding could occur immediately following the intravenous bolus, with a subsequent change in kinetics, their effects were not apparent in the present experiments. Although input following the oral route cannot be directly compared to that involving intravenous infusion, the present analysis would indicate that the Loo–Riegelman method should give reasonable estimates of the absorption kinetics of this drug. Also, by assuming a constant fractional hydrolysis of aspirin during absorption and transit to the sampling site, this method is still applicable since absorption calculations are expressed relative to an asymptotic value (A_∞/V_p) rather than the administered dose.

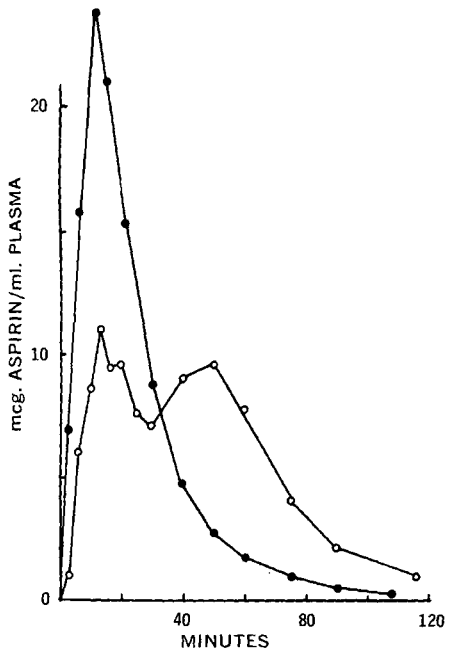
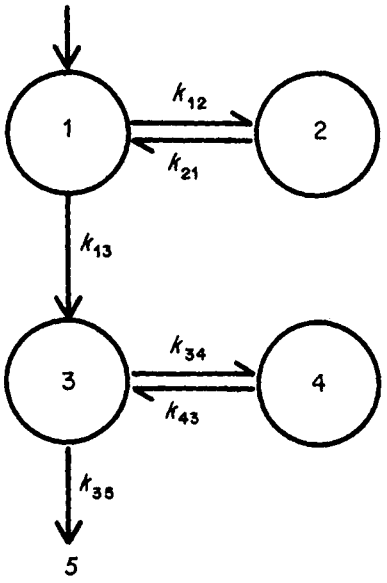


Figure 6—*Plasma aspirin levels following 650 mg. aspirin in solution on two separate occasions, Subject B. Key: ○, first trial; and ●, second trial.*



Scheme I—Diagram describing the pharmacokinetics of aspirin and salicylic acid following 650 mg. i.v. aspirin

The calculated absorption data are graphically displayed in Fig. 4; from the semilogarithmic plot of the percent remaining to be absorbed (Fig. 5), the data suggest that this process can be described by first-order kinetics with a lag period of approximately 2 min. However, it is doubtful whether this is true under all circumstances, since esterases present in the rat intestine are capable of saturation (17) and the same is probably true with those in the human GI tract. Dose-dependent absorption kinetics, as measured from the peripheral circulation, would then be expected. With low concentrations and absorption rates, the percent hydrolyzed during absorption will be greatest. As the concentration in the intestinal fluid increases, enzyme saturation may occur for part of the absorption process, and the absorption kinetics, as observed from the sampling site, will appear complex. At still higher concentrations, with saturation of the enzyme for the majority of the absorption process, the percent loss during absorption will be smallest; if it is negligible, then the observed kinetics will correspond to the loss of drug from the luminal fluid. Even this reasonably complex picture will be further complicated by variable esterase activity along the intestinal tract.

Even though the drug was given in solution, a wide variation existed in the absorption half-life of aspirin. These values ranged almost fourfold, being 4.5, 8.5, 11.5, and 16.0 min. in Subjects B, A, C, and D, respectively. Numerous reasons can be advanced for these findings. All subjects were seated and generally relaxed during the first 2 hr. of the study. Kuna (21) previously found that the gastric contents approach neutrality in a considerable number of reclining volunteers. Accordingly, since the absorption of salicylates is pH dependent (22), being slowest in alkali medium, differences may be expected. Furthermore, even though aspirin is an acid (pKa 3.5), salicylates are more rapidly absorbed in the duodenum due to the enormous increase in surface area, so that differences in stomach emptying time could affect absorption rates. Other possible factors include gastric blood flow, amount of fluid in the stomach, rate of secretion of fluids into GI tract, and degree of intestinal motility.

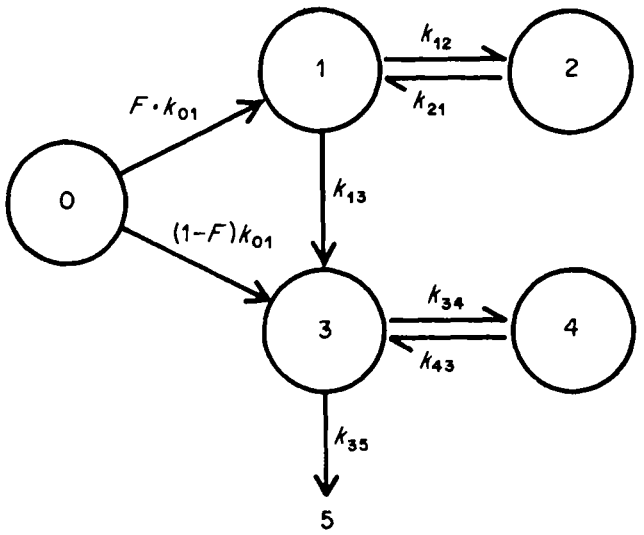
During preliminary studies, one subject was nervous and became faint while the 10-min. blood sample was being taken. Soon afterward the subject sufficiently recovered, and the study was completed. Subsequent analysis, however, showed that absorption had stopped at 10 min.; the plasma aspirin levels fell and only began to rise again after 20 min. (Fig. 6). This reduction in the rate of absorption is probably due to decreased motility of, and circulation to, the GI tract. One is prompted to ask how frequently this occurs in absorption studies where blood samples are drawn and whether "normal" volunteers in such studies exhibit drug absorption kinetics comparable to those of a patient taking the drug for therapeutic purposes.

Assessment of Model to Describe Oral Aspirin Data—Previous examination of the aspirin and salicylic acid plasma levels following

intravenous administration of aspirin led to a kinetic model in which an open two-compartment system existed for each drug and the loss of aspirin was exclusively by hydrolysis to salicylic acid in the central compartment (10, 23). This model is depicted in Scheme I, where k_{xy} is the transfer rate constant from compartment x to y. The rate constants (k_{34}, k_{43}, and k_{35}) associated with salicylic acid disposition were evaluated by administration of intravenous salicylic acid on a separate occasion.

A simple model (Scheme II) is now proposed to describe the absorption process and account for both the resultant aspirin and salicylic acid plasma levels. In this model, it is assumed that on passage of aspirin through the gut wall and liver, a certain constant fraction (F) passes through intact, that the remainder ($1 - F$) is hydrolyzed to salicylic acid, and that aspirin is absorbed by a first-order process (rate constant k_{01}). Before proceeding, a few comments about the model are appropriate. First, the availability (F) determined by the ratio of areas under the plasma aspirin curve following oral and intravenous administration is an average value for the fraction of drug cleared during absorption. In the early moments, extraction by the liver (and gut wall) is high since the drug also distributes into these tissues. Later, when distribution equilibrium is achieved, clearance by these tissues approaches a lower constant value. Second, in compartmental analysis, measurements are usually made with respect to a reference region, *e.g.*, peripheral vein blood, which is part of the central compartment. If an eliminating organ such as the liver exists between the site of administration and the sampling site, then some drug may be eliminated before entering the central compartment. For example, while the rate of presentation of aspirin to the reference region is limited by its GI absorption, aspirin passing across the gut wall and liver can be hydrolyzed to salicylic acid before entering the central compartment (Compartment 1). This model is represented in Scheme II, where Compartment 0 contains drug which has not reached the sampling site. In addition, once the salicylic acid formed during the absorption process appears in the sampled peripheral vein, it likewise is assumed to distribute instantaneously throughout its central compartment (Compartment 3). Furthermore, the rate of presentation of salicylic acid derived during aspirin absorption is the product of ($1 - F$) and the absorption rate of aspirin.

The model depicted in Scheme II was examined using the plasma data from each subject and a TR 48 analog computer[3]. All data were fractionalized in the same manner previously described (10). For each subject, appropriate rate constants were those obtained in the intravenous studies, k_{01} was calculated using the absorption data (Fig. 5), and F values were taken from Table I (ratio of aspirin areas following oral and intravenous administration). Time was defined by actual time minus lag time determined



Scheme II- Open two-compartment model describing the pharmacokinetics of aspirin and salicylic acid following 650 mg. oral aspirin solution

[3] See *Appendix* for analog computer diagram.

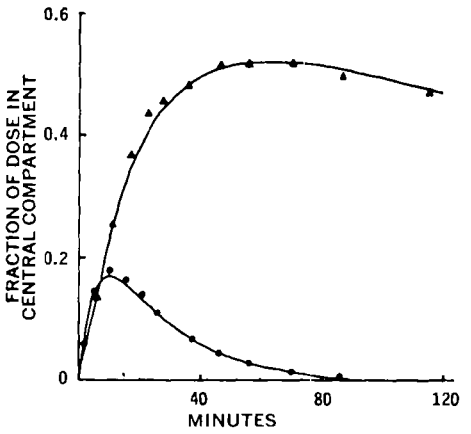


Figure 7—*Observed and predicted values for the fraction of the dose as aspirin and salicylic acid in their respective central compartment following an oral solution of 650 mg. aspirin, assuming the data are described by the model given in Scheme II. Key: ●, experimental aspirin; ▲, experimental salicylic acid; and ——, predicted analog computer curves, Subject A.*

from Fig. 5. In this study, a good fit between observed and predicted values was found in all subjects (*e.g.*, Fig. 7), demonstrating that the proposed model was sufficient to describe the data. It would also appear reasonable that rapid mixing of the salicylic acid produced during aspirin absorption does occur, as no appreciable discrepancy was noted with the earlier salicylic acid levels. However, even though a rate constant has been assigned to salicylic acid elimination, it is known to undergo dose-dependent kinetics (24, 25), and the present model for salicylic acid only applies to the dose (500 mg.) used in this study.

Comparison of Methods Used to Assess Absorption Kinetics of Aspirin—Analysis of the plasma aspirin data for the absorption rate by the method of Wagner and Nelson (15) gave faster rates than those already calculated. Loo and Riegelman (13) discussed this point in some depth, indicating that the error arises from the net effect of two factors (13). One is that the method measures an absorption–distribution constant rather than absorption alone. The other occurs because absorption continues well past peak plasma aspirin levels so that a longer half-life is observed than the disposition rate constant recorded during intravenous studies (Table I).

Most recent analyses of the absorption kinetics of aspirin, both from solution and dosage formulations, have been determined using the Wagner–Nelson method and total blood or plasma salicylate (11) (Eq. A8). The method assumes that the body acts as a single compartment and that total salicylate levels reflect the aspirin absorbed (26). Since aspirin, salicylic acid, and, consequently, total salicylate data were available in the present

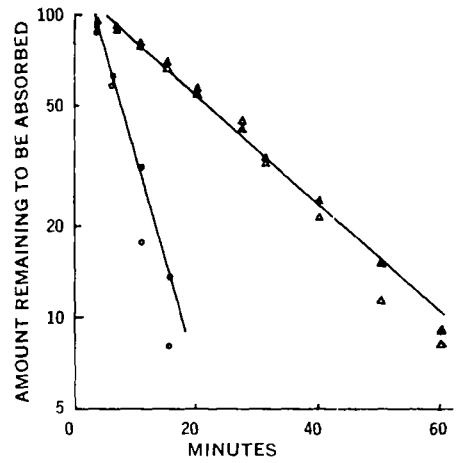
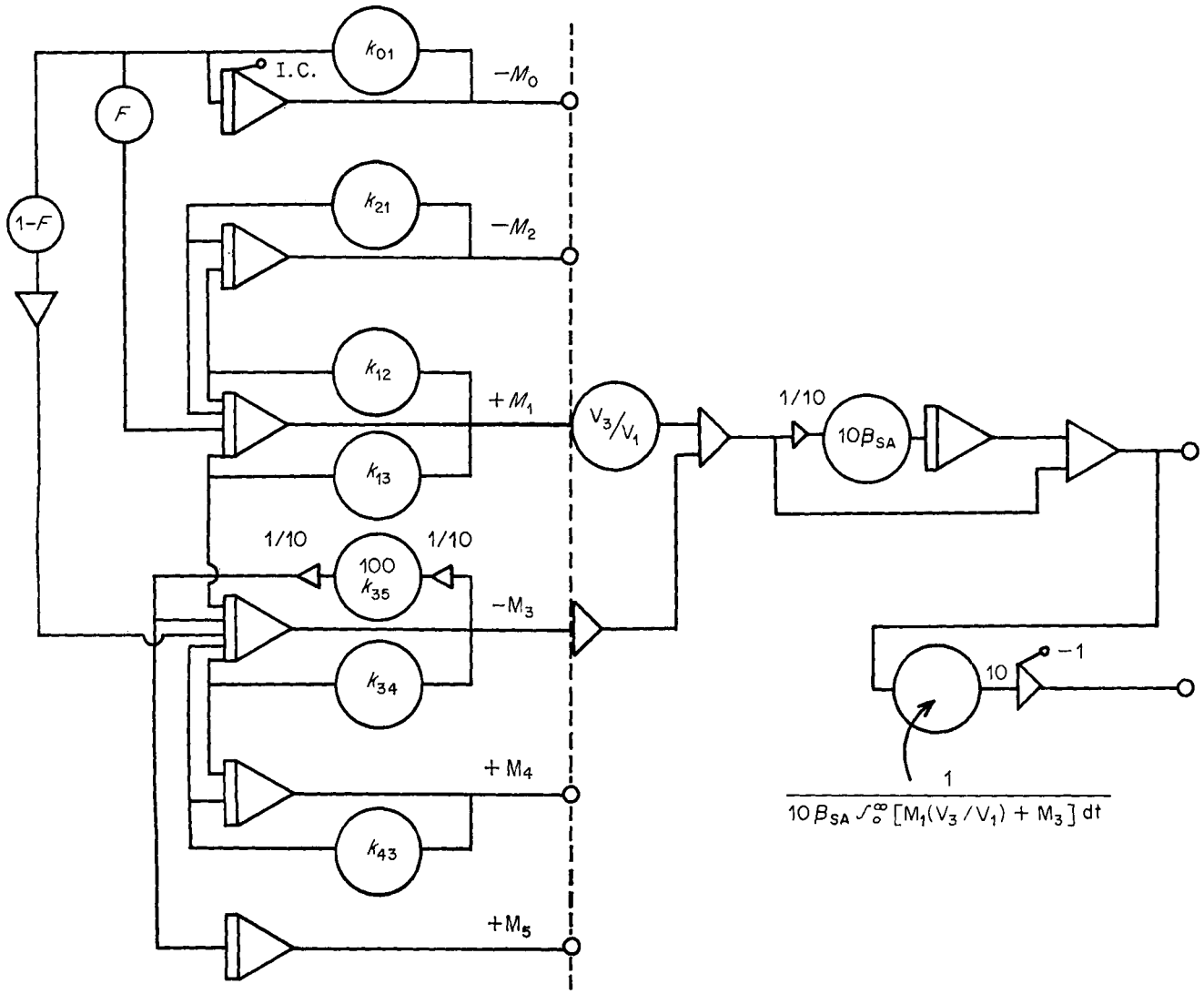


Figure 8—*Percent aspirin remaining to be absorbed based on Eqs. 1 and A8. Key: ●, Eq. 1, Subject B; ○, Eq. A8, Subject B; ▲, Eq. 1, Subject C; and △, Eq. A8, Subject C.*



Scheme III—Analog computer diagram. Portion left of the dashed line refers to Scheme II, while the entire program evaluates Eq. A8

study, the total salicylate method was compared with the Loo–Riegelman method which only uses plasma aspirin data. Figure 8 shows that, in general, the two methods are in good agreement. Such a close correspondence is achieved because essentially the entire total salicylate curve can be described by a single exponential term following the intravenous aspirin bolus. That is, owing to the rapid hydrolysis of aspirin and slow elimination of salicylic acid, the total salicylate values exhibit a very shallow distribution phase. Accordingly, the absorption–distribution rate constant, determined using the Wagner–Nelson method, approaches the absorption rate constant, and there will only be an appreciable error when absorption is very rapid.

The present study bears this out since both methods of analysis gave very similar curves except with Subject B, when half-lives of

Table III—Influence of Distribution (V_3/V_1) and Fraction of Aspirin Absorbed Intact (F) upon the Calculated Absorption Half-Life[a] Using Total Salicylate Data and Wagner–Nelson Method

	V_3/V_1	True Absorption Half-Life, 5 min. (k_{01} = 0.138) Calculated Half-Life	True Absorption Half-Life, 10 min. (k_{01} = 0.069) Calculated Half-Life	True Absorption Half-Life, 20 min. (k_{01} = 0.035) Calculated Half-Life
$F = 0$	1.0	3.0	8.0	18
	0.85	3.0	8.0	18
	0.50	3.0	8.0	18
$F = 0.65$	1.0	3.7	8.5	18.5
	0.85	4.8	9.5	19.2
	0.50	6.7	12.0	20.8
$F = 1$	1.0	4.0	8.5	18.5
	0.85	5.0	10.0	20.0
	0.50	9.3	14.0	21.0

[a] The analog computer was used to simulate the data. For each set of variables (k_{01}, F, and V_3/V_1), the asymptotic value $\beta_{SA}\int_0^\infty [M_1(V_3/V_1) + M_3]\,dt$ was obtained. A log percent remaining to be absorbed *versus* time plot was then constructed, and the half-life was determined from the portion describing the first 90% of this graph.

3.2 and 4.5 min. were determined by the Wagner–Nelson and Loo Riegelman methods, respectively. The difference between these methods was further examined using the analog computer, with a model that allowed the absorption rate constant (k_{01}), fraction of aspirin hydrolysis during absorption ($1 - F$), and ratio of volume constants (V_3/V_1) to be independently varied (*Appendix* and Scheme III). The latter was considered since total plasma salicylate is the sum of aspirin and salicylic acid and, therefore, is affected by the relative distribution of these species. As anticipated, using the experimentally determined values of $F = 0.65$ (Table I) and $V_3/V_1 = 0.85$ (10), the Wagner–Nelson method gave a good approximation to the true absorption half-life when it was 5.0 min. or greater (Table III). If all of the aspirin is hydrolyzed before entering the general circulation ($F = 0$), then one effectively measures an absorption–distribution rate constant for salicylic acid that will be greater than the true rate constant. Similarly, decreasing V_3/V_1 has the effect of lowering the apparent absorption rate constant (for conditions other than $F = 0$) by decreasing the total salicylate value at early times without affecting the asymptotic value, which is relatively insensitive to aspirin levels.

In general, therefore, analysis of total salicylate data by the Wagner–Nelson method gives an absorption rate that is consistent with the true value. However, this method allows no statement to be made regarding the proportion of the ingested dose reaching the peripheral circulation as aspirin.

APPENDIX

The mass equations describing Scheme II, for oral absorption of aspirin, are:

$$\dot{M}_0 = -k_{01} \cdot M_0 \qquad \text{(Eq. A1)}$$

$$-\dot{M}_1 = -F \cdot k_{01} \cdot M_0 + k_{12} \cdot M_1 + k_{13} \cdot M_1 - k_{21} \cdot M_2 \qquad \text{(Eq. A2)}$$

$$\dot{M}_2 = k_{12} \cdot M_1 - k_{21} \cdot M_2 \qquad \text{(Eq. A3)}$$

$$\dot{M}_3 = (1 - F) \cdot k_{01} \cdot M_0 + k_{13} \cdot M_1 - k_{34} \cdot M_3 - k_{35} \cdot M_3 + k_{43} \cdot M_4 \qquad \text{(Eq. A4)}$$

$$-\dot{M}_4 = -k_{34} \cdot M_3 + k_{43} \cdot M_4 \qquad \text{(Eq. A5)}$$

$$-\dot{M}_5 = -k_{35} \cdot M_3 \qquad \text{(Eq. A6)}$$

$$\text{dose} = M_0 + M_1 + M_2 + M_3 + M_4 + M_5 \qquad \text{(Eq. A7)}$$

where M_x is the amount of drug in Compartment x. The analog computer program for this scheme is shown in Scheme III.

The Wagner–Nelson equation for absorption, based on total salicylate data, is given by:

$$\frac{A_t}{A_\infty} = \frac{(C_p^{ASA} + C_p^{SA}) + \beta_{SA} \int_0^t (C_p^{ASA} + C_p^{SA})\, dt}{\beta_{SA} \int_0^\infty (C_p^{ASA} + C_p^{SA})\, dt} = \frac{[M_1(V_3/V_1) + M_3] + \beta_{SA} \int_0^t [M_1(V_3/V_1) + M_3]\, dt}{\beta_{SA} \int_0^\infty [M_1(V_3/V_1) + M_3]\, dt} \qquad \text{(Eq. A8)}$$

where C_p^{ASA} and C_p^{SA} are the respective plasma levels of aspirin and salicylic acid, V_1 and V_3 are the corresponding volumes of the central compartment of each species, and β_{SA} is the disposition (elimination) rate constant for salicylic acid. (Strictly speaking, this rate constant should be that for total salicylate, but since $\beta_{ASA} \gg \beta_{SA}$, it may be approximated to β_{SA}.) The analog computer program for Eq. A8 is shown in Scheme III, and the function $1 - A_t/A_\infty$ *versus* time is plotted on an *X-Y* recorder.

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