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# CONTROLLED ENTRY OF ORALLY ADMINISTERED DRUGS: PHYSIOLOGICAL CONSIDERATIONS

Alan F. Hofmann, M.D.
Jeffrey H. Pressman, M.D.
Charles F. Code, M.D.
Division of Gastroenterology
Department of Medicine
University of California at San Diego

Kathryn F. Witztum, M.D.
Division of Nuclear Medicine
Department of Radiology
University of California at San Diego

Abstract. Physiological considerations bearing on the controlled entry into the systemic circulation of orally administered drugs in healthy man are reviewed. The most desirable site for drug absorption is the sterile portion of the small intestine, so that the time "window" available for absorption is not greater than the minimum small intestinal residence time in this segment. This appears to vary widely between individuals. Methodology for sampling intestinal content and for defining the fraction absorbed and the physical state of an administered drug are summarized. Small intestinal transit and gastric emptying rates are now estimated in man by imaging techniques using $Tc^{99m}$ labeled sulfur colloids. Small intestinal transit may also be estimated non-invasively by measuring breath $H_2$ after administration of a meal containing a non-absorbable disaccharide such as lactulose, but the validity of such a method is uncertain because of the acceleration of intestinal transit by lactulose. The major determinants of small intestinal transit in the fasting state is the interdigestive motor complex. During digestion, complex neurohumoral factors influence transit. Literature values for small intestinal transit are tabulated. The biochemical and physical features of the micro-environment of the stomach and small intestine during the fasting state and digestive state are reviewed. First-pass considerations are outlined, and the need for developing physiological pharmacokinetic models stressed. Available data suggest that 2-3 hours is the maximum time available for the absorption of any drug in the sterile region of the small intestine. Therefore, future therapeutic efforts aimed at slowing absorption should probably be aimed at



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slowing gastric emptying, unless passage of drug into the colon is judged acceptable. For rational design of controlled entry drugs, greater cooperation between the gastroenterologist and the pharmaceutical scientist appears needed.

The purpose of this article is to review aspects of human gastrointestinal physiology that are relevant to the controlled entry into the systemic circulation of orally administered drugs. Most of the paper will consider the events influencing translocation of drugs to and across the enterocyte into portal blood; a brief portion will consider the role of hepatic uptake, i.e., first pass clearance.

Some Assumptions:

The desirable site of absorption of orally administered drugs is the proximal and mid small intestine. The stomach is unlikely to be an important absorptive route because of its low surface area and its impermeability to small hydrophilic molecules. The colon not only has a small absorptive area but also has a lumen full of bacteria. The small intestine is essentially sterile until the distal part of the ileum, at which point bacteria begin to increase in number and variety.[1,2,3] If drugs are not completely absorbed prior to encountering bacteria, they may be biotransformed by bacteria and the biotransformation products absorbed. In principle, this is undesirable since the pattern of bacterial biotransformation may vary widely from individual to individual and because neither the efficacy nor the safety of even the major bacterial products are usually defined in preclinical testing. Since in man the length of the small intestine

is probably 300-400 cm,[4] a length of about 180-350 cm is available as a bacteria-free absorptive site. Therefore, every drug must be formulated in such a manner that it is largely absorbed in this length of intestine.

If drugs must be absorbed during transit in the sterile portion of the small intestine, the minimum time allowable for such absorption to occur is the shortest time required for transit from the duodenum to the bacteria-rich portion of the ileum, which we shall term the distal ileum.

Two aspects of small intestinal transit must be considered. The first is that it is desirable and indeed necessary to distinguish between events occurring during the interdigestive state and the digestive state (digestion and absorption of meals). The second aspect is that it seems necessary to consider not only the mean transit time, but also confidence limits for transit time. That is, if a drug is designed such that it does not dissolve completely until 180 minutes after ingestion, it will not be fully absorbed in the sterile small intestine in an individual whose small intestinal transit time (SITT) is 90 minutes. The simplest arbitrary solution is to attempt to find a figure for "$SITT_{95}$", i.e., the small intestinal transit time which is equal to or greater than that of 95% of healthy individuals. For example, Northfield's group[5] gave a figure of about 220 minutes for a mean small intestinal transit time of a solid meal in 15 healthy volunteers. The standard deviation was about 70 minutes meaning that a $SITT_{95}$ would be only 80 minutes!

This problem is further confounded by the possible between- and within- subject variability in the portion of ileum colonized by bacteria.

At present, drugs, whether present as a particulate dispersion or as a micellar or molecular solution, are considered to be propelled along the small intestine at the same net propulsive rate as food particles. This may not be correct, but no experimental data are available. Wilkinson[6] has compared the time course of fecal excretion of the non-absorbable water soluble polymer, polyethylene glycol (PEG), having a molecular weight of about 3600 (PEG 4000) with that of the insoluble and dense (sp. gr. 5.2) pigment, chromium sesquioxide. PEG was excreted considerably more rapidly. However, it seems likely to us that the separation occurred in the stomach and the colon, rather than the small intestine. Bechgaard and Ladefoged reported that pellets of density 1.6 had a much slower transit time (25 hrs) than pellets of density 1.0 (7 hrs) in a study using ileostomy patients. However, the pellets were quite large; recovery was incomplete; and the possibility of delayed or incomplete gastric emptying makes the results very difficult to interpret. Much more experimental work is needed in this area.

For most controlled delivery formulations, the design is to make dissolution rate-limiting. In general, neither diffusion through the unstirred layer nor membrane permeation are considered to be rate limiting in the kinetics of absorption.

Methodology for Defining the Relevant Physiology in Man:

In man, small intestinal transit has been estimated by examining the time required for a bolus of barium sulfate to enter the cecum using fluoroscopy or sequential x-ray photographs. This so-called "barium meal" was probably not a true meal, in that it did not initiate the usual sequence of neuro-humoral events that regulate propulsion of a a physiological meal; and results obtained using the classical "barium meal" are usually considered to have little bearing on the transit time of a meal under physiological conditions or a group of molecules during the fasting-state.[8] Subsequently, attempts were made to develop more "physiological" contrast material, and small intestinal transit was estimated in this way.[9] Results of a number of older studies which estimated transit time by passage of barium containing meals are summarized in Table 1.

More recently, in a series of important papers, Lagerlof and his colleagues used PEG 4,000 in a liquid test meal and direct intestinal sampling to measure both nutrient absorption and small intestinal transit in man.[10,11] This work, which was summarized in a thoughtful and readable monograph,[12] illus-trated the range of transit times that one observed with the marker. These workers found that the early part of the meal moved rapidly to the distal part of the intestine, whereas subsequent parts of the meal moved more slowly along the intestine. Single measurements of small intestinal transit have also been made in studies from the Mayo group using aspiration at the ileo-cecal valve.[13]

Table 1

ESOPHAGO-GASTRO-DUODENAL-JEJUNAL-ILEAL (MOUTH TO CECUM) TRANSIT TIME IN NORMAL MAN

| Author & Reference | Year | Interval Measured | Method | Meal | # Studied | Mean (min) | S.D. (min) | Range (min) | Validation |
|---|---|---|---|---|---|---|---|---|---|
| Manville & Ane (84) | 1932 | mouth to cecum | radiol. | barium/ protein | 6 | 138 | | | |
| | | | | barium/ cho | 5 | 162 | | | |
| | | | | barium/ fat | 6 | 225 | | | |
| Kim (85) | 1968 | mouth to cecum | radiol. | barium | 315 | 84 | | 15-300 | |
| Bond & Levitt (21) | 1975 | mouth to cecum | breath hydrogen PEG | 10 g lactulose in 100 ml $H_2O$ | 40 | 72 | | 25-118 | PEG added to meal & collected through polyetheylene tube. First appearance of PEG correlated well with transit measured by breath hydrogen (r=0.97) |
| | | | | 5 g lactulose in 100 ml $H_2O$ | 9 | 128 | 57 | | |
| | | | | 10 g lactulose in 100 ml $H_2O$ | 9 | 94 | 45 | | |
| | | | | 20 g lactulose in 100 ml $H_2O$ | 9 | 40 | 24 | | |

## ESOPHAGO-DUODENAL-JEJUNAL-ILEAL TRANSIT IN NORMAL MAN

| Author & Reference | Year | Interval Measured | Method | Meal | # Studied | Mean (min) | S.D. (min) | Range (min) | Validation |
|---|---|---|---|---|---|---|---|---|---|
| Read et al. (20) | 1980 | mouth to cecum | breath hydrogen $Tc^{99m}$ | mixed | 14 | 234+ 378* | 90+ 90* | 90-444+ 208-654* | $Tm^{99}$ sulfur colloid incorporated into mashed potatoes demonstrated good correlation with breath $H_2$ "secondary rise". |
| | | | | mixed | 6 | 261+ 412* | 31+ 88* | | |
| | | | | mixed + 10 g lactulose | 6 | 226+ 359* | 76+ 83* | | |
| | | | | mixed + 20 g lactulose | 6 | 185+ 322* | 50+ 71* | | |
| | | | | mixed + 40 g lactulose | 6 | 131+ 300* | 32+ 95* | | |
| | | | | 10 g lactulose in 400 ml $H_2O$ | 11 | 48+ | 15+ | | |
| Corbett et al. (22) | 1981 | mouth to cecum | breath hydrogen | 10 g lactulose in 100 ml $H_2O$ | 20 | 93 | 30 | 40-130 | |

(continued)

Table 1 (cont.)

ESOPHAGO-GASTRO-DUODENAL-JEJUNAL-ILEAL TRANSIT IN NORMAL MAN

| Author & Reference | Year | Interval Measured | Method | Meal | # Studied | Mean (min) | S.D. (min) | Range (min) | Validation |
|---|---|---|---|---|---|---|---|---|---|
| Read et al. (86) | 1982 | mouth to cecum | breath hydrogen | mixed | 11 | 270+,§<br>408+,§ | | | |
| | | | | mixed with all components doubled, except non-absorbable cholesterol | 11 | 294+,§<br>440+,§ | | | |
| | | | | mixed with 25 ml corn oil | 8 | 250+,§<br>370+,§ | | | |
| | | | | mixed without oil | 8 | 260+,§<br>340*,§ | | | |
| Kupfer et al. (5) | 1982 | mouth to cecum | breath hydrogen | mixed | 15 | 223 | 66 | | |

+time from ingestion to "secondary rise" in breath hydrogen.
*time from ingestion to peak rise in breath hydrogen.
§data estimated from graphs.

In the past five years, aggregates of colloidal size (sulfur colloid),[14] resin particles containing chelating groups,[15] or simple chelating molecules[16] tagged with the pure gamma emittor $Tc^{99m}$ have become available. The nuclide $Tc^{99m}$ has excellent imaging properties, and an extremely convenient physical half life ($T_{\frac{1}{2}}$ of 6 hours). When used together with a large field of view camera and computer analysis of digitized data, an accurate and reproducible estimate of gastric empyting can be made.[17] This technique is now being extended to the measurement of small intestinal transit in health and disease.[20]

Small intestinal transit may also be estimated indirectly by using a probe molecule that is not absorbed, but whose bacterial degradation gives rise to a signal. The initial application of this technique featured the administration of lactulose, a non-absorbable disaccharide, which is converted to hydrogen by anaerobic colonic bacteria.[21] The hydrogen, in turn, is partly absorbed and excreted in breath in which it is easily measured by gas chromatography or by an electro-chemical detector.[22] The appearance time of $H_2$ in breath correlates satisfactorily with the passage of lactulose into the cecum, as assessed independently by direct sampling of distal ileal contents using a naso-intestinal tube.[21]

There are several problems with the lactulose-$H_2$ method, as described by Bond and Levitt. First, at least 10 g of lactulose must be used to generate an unequivocal $H_2$ signal, and the response is quite variable within and between subjects.[23] This

amount of lactulose is a strong osmotic stimulus which accelerates intestinal propulsion, accelerating the transit through the small intestine. Second, a rare individual lacks the colonic flora responsible for converting lactulose to hydrogen.[24] Further, if individuals ingest a high fiber diet, then they may have a high baseline production of $H_2$, preventing detection of a discernible rise in breath $H_2$ excretion.[25]

Recently, our laboratory began to explore the feasability of measuring small intestinal transit using $^{14}C$-lactulose (generously provided by Phillips-Duphar in the Netherlands), and measuring $^{14}CO_2$ in breath.[26] Since only a negligible mass of carrier lactulose is required, it is apparent that the problem of the lactulose load accelerating intestinal transit is obviated. On the other hand, it is not at all clear where the site of bacterial degradation of $^{14}C$-lactulose occurs, i.e., it could be either in the distal ileum or colon. It is also not known in what form the radioactivity is absorbed, i.e., how many chemical steps there are between the degradation of lactulose and the appearance of $^{14}CO_2$ in breath.

It is quite simple to measure $^{14}C$ radioactivity in breath by breath titration using an organic base,[27,28,29] and in principle, if the $^{14}C$ is absorbed either as $^{14}CO_2$ or as a molecule which is rapidly and predictably converted to $^{14}CO_2$, then the time course of appearance of $^{14}CO_2$ in breath should give an indication of the rate of transit of lactulose to the site of bacterial degradation. In early experiments, we attempted to validate the use of $^{14}C$-lactulose by comparing the time course of $^{14}CO_2$ excretion

with that of $H_2$. Results were only in fair agreement ($r \approx 0.8$). We are now carrying out further validation experiments in which the time course of $^{14}CO_2$ appearance is compared with the time required for a $Tc^{99m}$ labeled bolus to reach the cecum, as assessed by the gamma camera computer system.

A major problem with any non-invasive method is that it gives only a single value for transit time. Transit time in fact must be a distribution of individual transit times and, as any curve, must have a shape requiring at least two parameters for description.

To assess events in the proximal small intestine, for example, the time course of passage of a meal marker, direct sampling by intubation is desirable. In all intubation experiments, it is desirable to have a non-absorbable reference marker, such as PEG 4000, so that results are not influenced by water absorption or secretion.[30] The traditional marker, PEG 4000, may now be purchased in radioactive form labeled with either $^{14}C$ or $^{3}H$. PEG may also be determined turbidometrically if its concentration is sufficiently high.[31] Recently, water soluble polymeric dyes have been synthesized[32] and appear promising for use as non-absorbable reference markers.[33] A number of low molecular weight substances have also been used as reference markers.[34,35]

If one ingests a solution of drug containing PEG, or other suitable markers, then the ratio of drug to PEG in the aspirate compared to that of the ingestate indicates the fraction of the drug that has been absorbed from the sample of intestinal content

that was aspirated. If multiple sites along the small intestine are sampled, one may obtain a profile of intestinal absorption.[36,37,38] A superior technique, developed by Soergel,[39] is to infuse the marker at a defined rate into the proximal small intestine. One then samples distally at one or more loci. From the flux of the test substance past the sampling site, information is obtained on the rate and time course of absorption.

A variant on this technique to measure rates of absorption is a steady state segmental perfusion technique, developed by Fordtran (summarized in 40); the assumptions involved have been treated in a theoretical article.[41] Levitt and Bond[42] have, however, questioned the validity of conclusions derived from absorption studies based on marker concentration, when such experiments are carried out under non-steady state conditions. Further, when such studies are used to estimate rates of absorption, true membrane permeation coefficients cannot be calculated easily because of the presence of an unstirred water layer.

Most intubation experiments rely on siphonage to obtain samples. A number of studies have shown that < 20% of the luminal contents passing a sampling site are removed by siphonage.[43] In principle, one would like to sample less than 20% of small intestinal content so that the sampling procedure will not disturb the usual fluid dynamics.

In analysis of small intestinal content, it is often desirable to define the physical state of the test substance,

i.e. whether it is completely in solution or what fraction is present in the particulate phase of small intestinal content. The insoluble phase may be separated by centrifugation or filtration.[cf. 44,45] It is assumed that the sample of small intestinal content by aspiration is a valid sample, i.e., that neither the liquid nor the particulate phase is preferentially aspirated. The validity of this assumption is not known.

Luminal sampling techniques have great power, and in our judgment, have been insufficiently exploited by pharmaceutical scientists. There are some problems, however. First, multi-lumen tubes must usually be constructed by the investigator, as they are not available commercially. Second, correct placement of the tube in the stomach such that it rapidly passes into the duodenum requires fluoroscopy, which means that x-ray facilities must be available and the subject be exposed to radiation. X-ray documentation of the sampling site is desirable. This in turn means clearance by both the Institutional Review Board and the Radiation Safety Committee. It is also necessary to have available a cooperative radiologist at hand. In addition, tubes, whether passed by nose or by mouth, are often quite uncomfortable to human volunteers. On the other hand, there is an extensive body of literature based on this methodology. An indwelling tube may be left in place in the small intestinal lumen in a subject for a period of at least a week without difficulty.

In general the tradition of the pharmaceutical scientist has been to administer compounds by mouth, to assume that the com-

pound behaves identically in the small intestine in vivo as in a beaker (in vitro), and to infer the rate of absorption from the time course of the concentration of the drug in peripheral blood. Such a procedure is invariably risky and may give rise to erroneous conclusions.

Determinants of Small Intestinal Transit Time in Health:

A major step in understanding the motor action of the small bowel has been the recognition, in recent years, of the decisive difference between the patterns of the fasted and fed state. These have been more accurately designated interdigestive and digestive because it has been found that the digestive pattern persists and the interdigestive pattern does not start until the ingested meal is digested and absorbed. All of the factors which prolong the period of digestion, for example, the addition of fat to the diet, also prolong the motility pattern of the digestive period.

The interdigestive pattern in man and most mammals displays cycles composed of four consecutive phases of motility.[46-49] The cycles repeat until the next meal is eaten. They start simultaneously in the stomach and duodenum and migrate distally.

The first phase is a period of rest of about 30-40 min when the stomach and small bowel show no motor activity. In the small bowel, during phase II, segmental contractions or mixing contractions occur with increasing frequency and intensity over a period of some 30-40 min to end in a cresendo of some 60-90 contractions of maximum strength. They are no longer segmental or fixed in

position but are circular and migrate distally. The distance of their individual distal travel is limited--about 80-90 cm in the uppermost small bowel diminishing to 20 cm or less in the most distal ileum. They comprise a band or length of bowel over which peristaltic contractions pass. The band starts in the duodenum and migrates slowly distally requiring about 90-120 min to reach the terminal ileum. As these activity waves sweep everything in the small bowel before them; they are termed the interdigestive intestinal housekeeper.[49] After they pass a point in the bowel, phase IV occurs, during which the contractions, peristaltic and segmental, quickly diminish in frequency and intensity and soon disappear completely to usher in phase I again, the period of rest.

As Phase III--the activity front or housekeeper--dies out in the terminal ileum, it starts again in the stomach and duodenum; and the entire cycle of sequential phases recurs in the duodenum and migrates again to the terminal ileum, one entire cycle requiring 90-120 min. And this recycling continues until a meal is eaten. The hormonal control of interdigestive motility is under active investigation.[cf.50] The large bowel does not participate in this cyclical sequence of motor events.

The stomach displays Phase I, during quiescence, Phase II which displays a digestive or mixing type of gastric peristalsis, and Phase III with some 15-20 housekeeper peristaltic contractions. These are special contractions seen in the normal stomach only during Phase III of the interdigestive motor complex. They

create a solid diaphragm across the stomach as they sweep distally all the way to the pylorus. They force everything before them out of the stomach; they are the gastric housekeeper.

The ingestion of a small meal, 50 g of meat or 100 ml of milk, will interrupt the sequence of the interdigestive pattern of motility and establish the digestive pattern whose purpose is to mix, rather than to propel. Larger meals, larger in volume and nutritional content, will prolong the interval between housekeeper episodes.

The major action of digestive gastric peristalsis is to mix and emulsify the contents. In the stomach, each gastric digestive peristaltic sweep ends with contraction of the terminal antrum, which closes the pylorus and retropels most of the contents ahead of the peristaltic contraction back into the gastric antrum and corpus. The action is that of a jet emulsifier. Whenever the gastric pressure exceeds that in the duodenum, liquids will leak out into the duodenum; this occurs when the pylorus is relaxed between terminal antral contractions. Solid particles are retained, however. The stomach fails to recognize a solid particle when it is less than 1-2 mm in diameter. Such particles are processed as a liquid.[51]

Compliant particles pass more readily then solids. Few, if any, solid particles of 5 mm or more in diameter will leave the stomach during digestion. They are all swept out of the stomach by the gastric housekeeper peristaltic contractions of the first interdigestive housekeeper sequence occurring after their

ingestion. They will then be swept through the small bowel by the Phase III or housekeeper peristaltic sequence and will require about 90-120 min to travel from the duodenum to the colon.

The motility of the small bowel during digestion is composed almost exclusively of segmental contractions. The predominant effect of these contractions is to mix the contents. Distal propulsion also occurs, but its exact mechanism has not been documented. Peristaltic contractions are seldom, if ever, seen during digestion in health in the jejunum and ileum. Liquids are spread out over the entire small bowel quite quickly (pylorus to terminal ileum), but by what mechanism or at what rate solid particles of more than 1 mm are transported distally is not known. Like the stomach, the small bowel requires an interdigestive housekeeper to clean it of solids more than 1 or 2 mm in diameter.

Thus, it can be appreciated that whether a medication is absorbed from the intestine or passes into the colon, and where it may reside at different times in its passage, will depend upon whether it is taken as a solid or a liquid and whether it is taken in the digestive or interdigestive period. If a medication is taken as a solid particle of more than 2 mm in diameter, its fate will depend on how long it can withstand the action of acid and neutral digestive juices. If it withstands the effects of acid digestion, it will remain in the stomach, whether it is taken with a meal or not, until the first gastric interdigestive

housekeeper occurs. It will then pass down the small intestine to the cecum in the next 90-120 min. It would appear in stool sometime in the next 24 hrs.

If a medication is taken as a solution of 100 ml or more, it will pass most quickly into the small bowel and be absorbed there. Isotonic saline (non-nutrient) solutions leave the stomach quickest and are absorbed the fastest. If a medication is ingested with nutrients, its gastric emptying will be delayed, as will its passage along the small bowel.

Quantitative determinations of the effects of these influences on drug absorption are in short supply. Application of the newer techniques are providing the most useful information. For example, Northfield's group[5] has published data based on the appearance of breath $H_2$ after a meal containing baked beans,[5] and Read and his colleagues have published limited data on transit in healthy volunteers ingesting a lactulose containing meal.[20] (These data are also summarized in Table I). It is clear that the data base is far too scanty to permit any definition of confidence levels which are necessary to define a value for $SITT_{95}$. The wide range in published data for transit times are illustrated in Figure 1.

Esophageal transit: Rapid esophageal transit has always been assumed to occur in healthy subjects and to be independent of position, since studies by Ingelfinger's group had shown that an individual could drink water quite well while standing on his head.[52] Very recently this assumption has been called into question. Subjects were given a capsule containing $Tm^{99}$ which

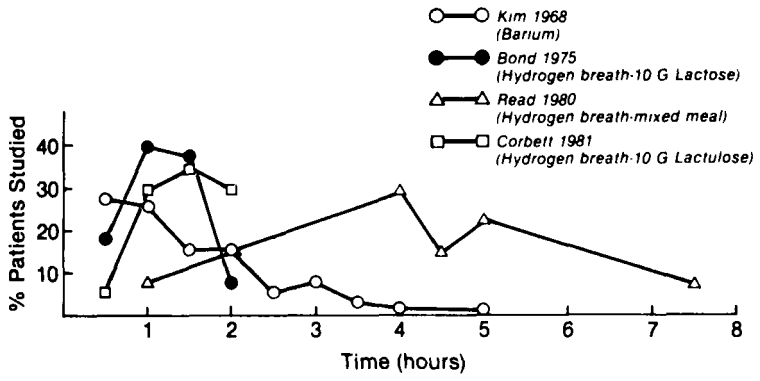


Figure 1. Published data for mouth to cecum transit time in healthy volunteers. The type of meal administered is shown.

was ingested with a single swallow of water. In a number of subjects, the capsule remained at the gastro-esophageal junction for a period of 15 to 30 minutes,[53] confirming older work with radiopaque capsules.[54] These studies are not entirely satisfactory because it is not at all clear that the gelatin capsules were similar to those employed for most drug formulations and because soft gelatin capsules when moistened may develop adhesive properties. Obviously further studies are indicated.

Gastric emptying: As discussed above, the availability of $Tc^{99m}$ or other gamma-ray emitting isotopes, the gamma camera, and digitized data which can be analyzed using computer techniques has meant that non-invasive quantitation of gastric empyting is now relatively easy to carry out. A number of studies have appeared recently[17,18,19,55-57] which support older studies[58,59] indicating that gastric emptying is essentially mono-exponential with a $T_{\frac{1}{2}}$ depending on meal content, especially fat and osmolality.

Environment of Ingested Drugs:

Ingested drugs pass through two environments--the gastric environment and the small intestinal environment. In all probability, the gastric environment differs during the fasting state from that occurring during the digestive state, whereas small intestinal content is quite similar, at least qualitatively.

During the fasting state, gastric secretion enters the stomach and is not buffered. Thus, the chemical environment for a drug ingested during the fasting state is simply 0.15 M HCl (containing pepsin). The pH could be increased considerably by pre-treating the subject with an anti-secretory drug such as cimetidine, but it is doubtful whether $H_2$ blockers will ever be used solely to influence the absorption of drugs.

Gastric content is much more alkaline during a meal because of the buffering capacity of food. Limited studies suggest that gastric pH will usually be 3-5 during digestion of a meal and fall only at the end of the meal.[60,61,62]

In the duodenum, the pH increases abruptly--to about 6--as bicarbonate secreted by the pancreas and the duodenal mucosa neutralizes the acidic gastric contents.[30,38,39] Small intestinal content is rich in pancreatic enzymes such as esterase, lipase, amylase, proteases, and nucleases.

Bile contains mixed micelles of bile salts and lecithin. In the small intestine, the lecithin is hydrolyzed to lysolecithin and fatty acid by the pancreatic phospholipase. During digestion, the micelle has its lecithin replaced largely by fatty acid

and monoglyceride which are produced by the action of pancreatic lipase on ingested triglyceride.[63,64] There may be a liquid crystalline phase of calcium-fatty acid soap if dietary calcium is sufficiently high.[64] In most instances, however, calcium salts do not form probably because the activity of ionized calcium is decreased greatly by non-specific electrostatic binding to the mixed micelles present in small intestinal content. (A notable exception to this generalization is dietary oxalate which remains insoluble as the calcium salt.[65])

Any lipophilic or amphipathic molecule, including any drug molecule, will be partitioned between the micellar phase and the molecular phase. The effect of micelles is to diminish the activity of the monomer. However, for insoluble monomers, the micelle provides a mechanism of solubilization such that the molecular phase can be kept saturated with monomer.[66] For fatty acids, the diffusive flux through the boundary layer is greatly accelerated because both micelles and molecules can diffuse. The end result of micellar solubilization is to increase the concentration of fatty acid in solution by about three orders of magnitude and to increase diffusion through the unstirred layer by a factor somewhat greater than 10.[67]

For insoluble molecules which enter the small intestine, the problem is dissolution which transfers molecules from an insoluble phase to a dispersed, molecular phase. The surface activity of small intestinal content is presumably quite high--with a surface tension of less than 5 dynes/cm.[cf.68] Experimental measurements are needed. Bile salts are not particularly surface

active,[69] but the combination of bile salts and partially ionized fatty acids, at least in vitro, is associated with a striking lowering of oil/water interfacial tension.[68]

It has been proposed that a major function of bile salts is to keep reactive surfaces such as the oil/water interface "unfouled" during digestion.[70] Presumably this "detergent" effect should also apply to any solid/liquid interface that is also present, including the membrane of the enterocyte.

Despite the extraordinary variety of substances that are ingested, the intestinal mucosa stays remarkably clean; and enterocyte storage diseases are unknown. The reason for the remarkable surface "sanctity" has not been the subject of any serious study, to our knowledge. The simplest answer is that the villus tip cells have extremely rapid turnover,[71] so that even if they do adsorb substances that are not translocated, they rather quickly slough into the intestinal lumen. The villous tip cells are thus a functional, but disposable, surface.

The small intestinal surface also remains free of bacteria. It is thought that the immunoglobulin A[72] or possibly mucous constituents[73] which are secreted by the enterocyte actually agglutinate bacteria. However, certain bacteria do possess external proteins (adhesions) which permit them to invade the mucosal surface.[74] Whether elucidation of the biochemical mechanism of this mucosal penetration will bear on capsule coatings is not clear.

It is beyond the scope of this presentation to discuss the role of enterocyte uptake. Suffice it to say that the design of

most drugs is based on the paradigm that the absorptive surface of the small intestine is a vast flood plain of octanol (for review, see 75). Drugs have not been designed to take advantage of the extraordinarily active catalytic surface of the jejunum, although drugs have been designed to prevent inactivation by surface enzymes, e.g. the purpose of the 15-methyl groups on certain prostaglandin analogues is to prevent inactivation of the prostaglandin by the dehydrogenase on the surface of the enterocyte. Current concepts of tissue uptake are generally modeled on octanol-water distribution ratios and neglect adsorption effects such as might occur with drugs that are surface active.[76] On the other hand, wet octanol is a structured phase because of the hydrogen bonding between water molecules and the primary alcoholic groups, and the structure of octanol saturated with water may well simulate that present in the lipid membrane of the enterocyte. It would be of interest to compare the partition of drugs between liposomes and water with that between octanol and water to see which distribution ratio is a better predictor of absorption from the small intestine.

In a sense dietary fat may be a good model for a controlled release drug. The bioavailability of dietary triglyceride is nearly 100% in amounts up to 600 g/day. This complete absorption probably results from the combination of multiple factors: controlled gastric emptying, a great excess of pancreatic lipase and bile salts, and a great excess of absorptive surface. When micellar solubilization of fatty acid is deficient because of a relative shortage of bile salts, fat digestion is sub-optimal and

fat absorption occurs over a greater length of small intestine.[77] This "anatomical reserve" must also be quite important in drug absorption, as will be discussed subsequently by Dr. Norman Ho.

First pass effects: Two kinds of first pass effects are to be considered: biotransformation by the enterocyte and hepatic uptake with or without biotransformation. Although biotransformation of drugs by the enterocyte is well documented,[78] it must be quite uncommon. It seems likely that the first-pass hepatic uptake of any drug biotransformation product is never complete. If so, the absence of biotransformation products in peripheral blood after oral ingestion of a drug permits exclusion of significant enteric biotransformation.

First-pass hepatic effects may exceed 90%, and if present, must be quantitated to develop a valid pharmacokinetic model for the drug's metabolism. The presence of significant first pass effects can be tested for by comparing the $AUC_{iv}$ with that of the $AUC_{oral}$.[79] However, only if either an independent assessment is made of first-pass uptake or of bioavailability (by direct intestinal sampling) can an adequate pharmacokinetic model be made. We have recently reported the application of this technique in defining the bioavailability of chenodeoxycholic acid.[80]

Finally, it seems to us that future pharmacokinetic models for drugs with first-pass effects should be of the type that are physiological pharmacokinetic models.[81,82] Such models give a much better and simpler description of drug metabolism, and are much easier for the prescribing physician to understand. We

believe the time has passed to describe drug distribution by compartments that have only mathematical meaning.

During the past five years, our own laboratory, in collaboration with the University of Torino and The Polytechnic Institute of Torino, has developed a physiological pharmacokinetic model for the description of the enterohepatic circulation and metabolism of bile acids that should be generally applicable to any drug that has an enterohepatic circulation.[83] The model is based on some nine spaces, each of which has an anatomic meaning and each of which contains compartments that correspond to individual chemical species. The compartments are connected by linear transfer coefficients, and these transfer coefficients are categorized functionally, i.e., they correspond to flow, transport, or biotransformation. The model also has time-dependent features, so that fluxes change during digestion.

The model is mentioned only to note that a major problem in developing the model was the inadequacy of information on intestinal transit. Such information may be essential for a complete pharmacokinetic description of the metabolism of any compound having an enterohepatic circulation.

Conclusions. Small intestinal transit, as viewed by the gastroenterologist, seems too rapid to permit design of drugs that will give controlled entry from a sterile environment for more than 3 hours in 95% of the population. It may be that information on small intestinal transit, limited as it is, cannot be applied directly to drug transit, but this seems unlikely.

Gastric emptying may play a more important effect than is realized, but delayed gastric emptying will increase the timed release, only if there is intra-gastric dispersion. Finally, it must be remembered that the bacterial flora begin to increase greatly in number and variety as one approaches the distal small intestine. Any approach to controlled oral delivery which is based on the kinetics of dissolution per se runs the risk of exposing unabsorbed drug to bacteria in the small intestine. Whether this exposure is important pharmacologically depends on whether bacteria alter the drug and the fate of the bacterial biotransformation products.

It should also be noted that this entire paper has dealt only with the situation in health. If intestinal transit is more rapid, as is claimed to occur in patients with irritable bowel syndrome,[22] then the time window (or transit window) for controlled entry would be still briefer.

The need is to sample intestinal content in order to define the influence of drug formulation on transit, dispersion, dissolution, absorption, and bacterial biotransformation. The techniques used by investigative gastroenterologists are so simple in principle that they can readily be adapted by the pharmaceutical scientist. In our judgment, there is a need for much greater collaboration between medicine and pharmacy, both of whom have the common aim of bringing rational and effective therapy with predictable absorption, distribution, and metabolism to patients with disease.

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