DRUG ABSORPTION

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In recent years the research of drug absorption in the gastrointestinal tract by physico-chemical methods (e.g. measurements of pk values, charge distribution, polarity, water and lipid solubility, molecular size, and corpuscular size) revealed few new aspects for the absorption of drugs in the organism. According to the conventional theory, drug absorption is in most cases a physical process; the drug is absorbed by diffusion. The theory states that the epithelium of the gastrointestinal tract is permeable for a lipid-soluble drug. A drug with an acidic or basic group passes the lipid barrier un-ionized. However, some experiments seem to indicate that lipid-soluble material is not the only material that can permeate a lipid membrane. Salicylic acid, which is fully dissociated under physiological conditions, and even quaternary bases, are absorbed in minute amounts. Also the theory must be revised (1) that only hydrophilic and lipid-insoluble substances and ions of organic bases or acids pass the membrane through water pores. It is possible that the electrolytes diffuse through water channels via the epithelium of the intestine. The water channel is less permeable (2) and special transport mechanisms seem to play a more important role than was realized until recently.

lein (4), and 2-pyridine aldoxime methiodide (5). Two facts have become important for the analysis of special transport mechanisms: sodium as the driving force for the uphill or active transport of organic chemicals, and the inhibition of absorption of sugars, amino acids, uracil, and the taurocholic acid by cardiac steroids and other substances which inhibit the sodium transport. For numerous references to the literature, mainly on the inhibition of glucose and amino acid absorption (by cyanide, dinitrophenol, malonate, fluoracetate, atabrine, arsenate, copper, acid, etc.), see Wilson (6), Wiseman (7), and Crane (8). Experiments done by Lauterbach (9), who used the isolated perfused small intestine of the rat according to the method of Fisher & Parsons (10), have shown that enteral transport system in this case is resistant for glycosides. In rats the absorption of sodium is not influenced by convallatoxin; in guinea-pigs the absorption of sodium is inhibited.

Intestinal Absorption of Digitalis

Based on experiments done in rats with tritium labeled digitoxin, ouabain, digoxin, and peruvosid, Forth, Furukawa & Rummel (11–14) state that polar and nonpolar glycosides permeate the intestine mainly by diffusion. However, experiments done by Lauterbach (9) using the perfused intestine of the rat have shown that the rate of absorption decreases asymptotically and approaches a finite value by increasing the glycoside concentration in the mucosal perfusion fluid.

$$\left[\text{Rate of absorption} = \frac{\text{absorbed mole of cardenolid/cm of intestine} \cdot h}{\text{mole of cardenolid/ml perfusion fluid}} \cdot 100\right]$$

Division of the two rates of absorption which are derived from the perfusion with $25 \cdot 10^{-9}$ and $100 \cdot 10^{-9}$ moles of cardenolid/ml perfusion fluid respectively gives a value that approaches unity. The author concluded from this finding and from experiments done with increasing doses of convallatoxol, ouabain, and strophanthidin that were administered in the mucosal perfusion fluid, that the absorption of cardiac glycosides cannot be explained by diffusion alone (15–20), in contrast to the corticosteroids (21) and other drugs (22).

In regard to the absorption, Lauterbach & Vogel (23) described two forms of glycosides: one in which the enteral effective amount corresponds to the enteral applied dose (e.g. digoxin) and one in which the enteral effective amount differs from the enteral applied dose. Experiments were done with cats. The cats received under constant conditions intraduodenal increasing amounts of four glycosides. With increasing enteral amounts of convallatoxin and ouabain the enteral efficacy rises at first sharply, reaches a plateau and then increases again (see Figure 1). The experiments indicate that polar glycosides permeate the intestine by two mechanisms: an active transport, and diffusion. The plateau could be due to a saturation effect of the transport system. At higher concentration, absorption is also by diffusion. The rate of enteral absorption for cardiac glycosides is therefore not a fixed value and must be determined for a definite dose and concentration ratio respectively. Therefore two points similar to pyrimidine (24) must be considered: (*a*) absorption by diffusion; (*b*) absorption by an active transport carrier.

Recently Lauterbach (25) found that the enteral transport mechanism for cardiac steroids is in fact a secretion mechanism that eliminates digoxin and convallatoxol from the blood into the lumen of the intestine. The author infers from the findings of the dose dependence on the enteral rate of absorption, as well as from the results regarding the uptake of digitoxin and ouabain into the isolated mucosa of the guinea-pig, that transport mecha-

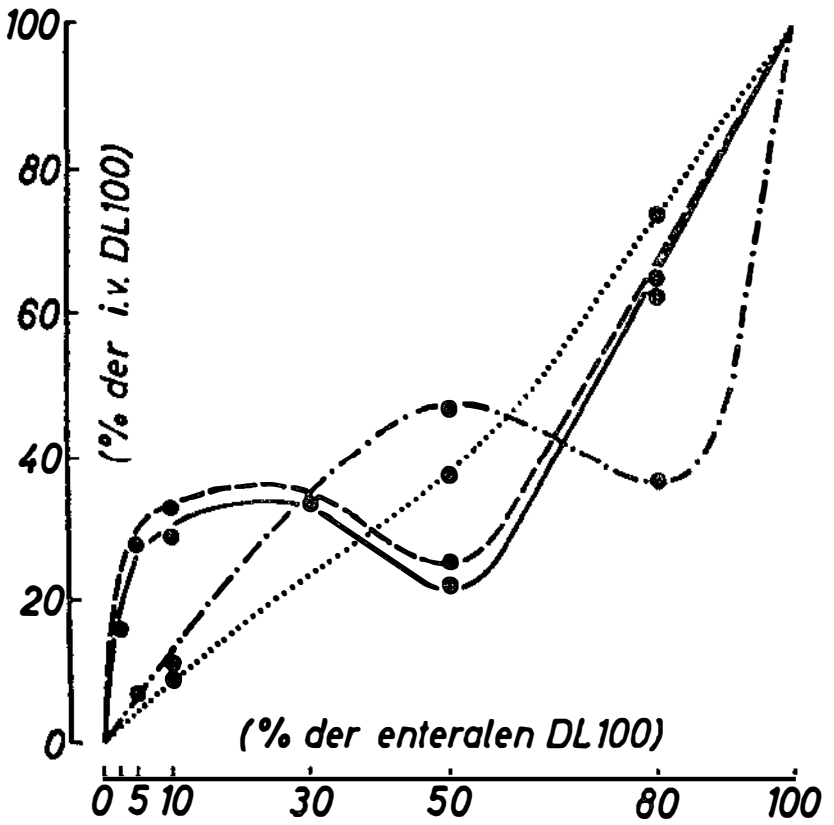

FIG. 1. Plot of enteral effective dose in % of intravenous LD_{100}) against the enteral infused dose (in % of enteral LD_{100}). ..... digoxin, -.-.-. ouabain, ------- desacetyllanatosid C, ———————— convallatoxin. (From Lauterbach, F., Vogel, G. 1968. *Arch. Pharmakol. Exp. Pathol.* 259:248).

nisms are also involved in the enteral absorption of glycosides. It is not known whether these transport mechanisms facilitate the secretion (26).

REQUIREMENT AND ENTERAL ABSORPTION OF IRON

When substances are absorbed they first leave the intestinal lumen and enter the epithelial cells. After transfer across the cells, a process that may involve various stages, they leave the other side of the cell and enter the fluid of the lamina propria, and from this they enter the blood capillaries or lymph capillaries to be carried away from the intestine. The amount and rate of absorption is therefore dependent on the function of the intestinal cell. In general, by oral application the amount of absorption is dependent on the dose. However, in special instances absorption is regulated by the

requirement of the organism. The problem of feed-back demonstrated on iron metabolism can show this. Could the organism protect itself against an excess of iron? In the search for factors that regulate iron metabolism in the organism the regulation of iron absorption was attributed to the cells of the mucosa. It was shown that the amount of absorption is proportional to the saturation of iron in the cell of the mucosa. Recently gastroferrin, a protein of the gastric juice that complexes with iron, was also considered as a regulating factor in iron metabolism. Forth & Rummel (*27*) investigated the influence of gastric juice on the utilization of iron and found no difference in the rate of absorption in normal and anemic rats when iron was administered to the gastric juice. The experiments were done on tied loops of the upper jejunum and ileum. The authors concluded that the amount of

TABLE 1. ONE-HOUR EXPERIMENTS DONE ON RATS

Metals	Cr		Mn		Fe		Co	
Offered as	^{51}Cr-$CrCl_3$		^{54}Mn-$MnCl_2$		^{59}Fe-$FeCl_3$		^{60}Co-$CoCl_2$	
	I	II	I	II	I	II	I	II
	5.1	7.3	1.8	1.0[a]	5.2	0.7[a]	32.9	2.6[a]
	± 1.7	± 4.5	±0.7	±0.3	±2.3	±0.5	±15.1	± 1.1
Metals	**Cu**		**Zn**		**Hg**		**Tl**	
Offered as	^{64}Cu-$CuSO_4$		^{65}Zn-$ZnCl_2$		^{203}Hg-$HgCl_2$		^{204}Tl-Tl_2SO_4	
	I	II	I	II	I	II	I	II
	14.9	11.4	6.9	8.4	0.7	0.5	81.4	64.4[a]
	±11.5	± 4.2	±3.0	±3.7	±0.2	±0.1	± 6.7	± 7.0
Metals	**Sn**		**Pb**		**Sb**			
Offered as	^{113}Sn-$SnCl_2$		^{210}Pb-Pb-Acetat		^{125}Sb-$SbCl_3$			
	I	II	I	II	I	II		
	0.5	0.4	6.9	6.2	7.4	2.3[a]		
	± 0.3	±0.2	±1.9	±2.0	±2.6	±4.8		

[a] $= p < 0.05$ gegen I.

I: Tied loops of jejunum in situ.

II: Segments of the ileum in vivo.

The numbers are mean values taken from 5–15 experiments. The values represent the absorbed amount in % of administered metal salts. (From Leopold, G., Furukawa, E., Forth, W., Rummel, W. 1969. *Arch. Pharmakol. Exp. Pathol.* 263:275)

gastroferrin in the gastric juice has no influence in regulating the absorption of iron. The influence of various ligands on the absorption of iron was thoroughly investigated by Rummel & Forth (28–30). Ligands forming

neutral or charged complexes show different modes of action in the absorption of iron. Only lipophilic complexes facilitate the absorption of iron. Forth et al (30) investigated the process by which rats can utilize complex bonded iron. They measured the retention of metallic and complex bonded Fe^{59} six days after the iron was applied to normal and anemic rats by a stomach tube. When iron salts were offered to anemic rats—calculated by 100 g body weight—the rats assimilated five times more iron than normal ones. However, all investigated complex forming compounds reduce the enhanced iron absorption in anemic rats. Addition of EDTA, citric acid, ascorbic acid, and nicotinhydroxamic acid slowed the absorption of iron in anemic rats by 87%, 40%, 32%, and 31% respectively. In anemic rats—calculated by 100 g body weight—the absorption of iron is higher in the presence of citric acid by 8.7%, EDTA by 6.3%, nicotinhydroxamic acid by 3.7% and ascorbic acid by 2.7% than in normal rats. Other experiments showed that the perfusion of iron through the intestinal wall of isolated jejunum segments in iron deficient rats is 5–10 times higher than in normal rats. This effect could be due to an increased permeability of the intestinal segment. In this case the permeability for iron should be enhanced in both directions from the mucosa to the serosa and vice versa. Forth & Rummel (31) examined the theory on everted sac preparations according to Wilson & Wiseman (32) and found that iron is transferred in significant quantities in iron deficient segments from the mucosa to the serosa. It is believed that the permeation in both directions follows different routes. By permeating from the mucosal perfusion fluid to the serosa, the iron contacts the microvilli and reacts with an iron binding system in the membrane or cytoplasm which is responsible for the increased absorption of iron in iron deficiency. The iron passes from the interior of the cell to the surface of the serosa. In the other direction the route is a different one. The iron passes directly via blood vessels through the intercellular hole to the surface of the mucosa without being taken up in larger quantities by the cells.

Forth et al (33) investigated the iron-binding system of the mucosa cells in vitro on everted sac preparations of normal and anemic rats. The radioactive metal salts were administered in the mucosal perfusion fluid. The binding and the permeation of iron [Fe^{59}-($FeSo_4$)], cobalt [Co^{58}-($CoCl_2$)], and copper [Cu^{64}-$CuSo_4$)] were measured. The administered part of the radioactive metal salts which passes within 2 hours from the intestinal segments of anemic rats to the serosa is for iron 10 times and for cobalt 3 times higher than in normal rats. However, for copper there is no difference. The binding of iron and cobalt in iron deficient intestinal segments is 4.0 and 3.6 times higher, respectively, than in normal segments. Contrary to this, the binding of copper in iron deficient and normal segments is the same. The experiments seem to indicate that the iron deficient mucosa cannot differentiate between iron and cobalt. It is believed that the system of active transport in the mucosa is more specific for iron, since in iron defi-

ciency, iron permeates 3 times faster than cobalt.

Recently the same research group (34) investigated in situ on tied small intestinal loops of rats the absorption of toxicologically important heavy metals. They compared these results with the results obtained from in vitro everted sac preparation.

In the jejunum the absorption of iron and cobalt is much higher (7.5 and 12.6 times respectively) than in the ileum. However, if chromium and zinc are administered, the rate of absorption in the ileum is higher than the respective rate in the jejunum. Thallium, with the highest rate of absorption, excels cobalt which comes second. Jejunum and ileum absorb thallium in almost equal quantities.

Blood Flow and Intestinal Absorption

After passing the intestinal epithelial cells, a substance is carried away by blood and lymph. The blood flow may influence the intestinal absorption in several ways: (*a*) "Mechanical," the draining effect of the blood. A diminished blood flow causes an increase of the interstitial concentration and a decrease of the concentration gradient followed by a lowered absorption rate. This mechanical factor is important for substances passing the epithelium passively by diffusion (35–37). (*b*) "Biochemical." For substances passing the mucosal barrier by active mechanism. A sufficient oxygen supply is necessary to maintain this transport. If the blood flow falls below a critical limit the active transport will stop (38–42). (*c*) "By secondary morphological alterations." A sufficiently long period with decreased blood flow, for instance, 10 minutes ischemia (42) or 20 minutes subnormal blood flow (35, 36, 43), cause changes in the structure of the intestinal epithelium followed by a decrease of absorption. But such morphological injuries do not influence the passive absorption of aniline and antipyrine (35, 36).

Theory.—The mechanical factor of blood flow, the draining effect, can be treated mathematically. The main topic of theoretical consideration may be the influence of blood flow on intestinal absorption (44–48) or the possibility of inferring the mucosal blood flow from the absorption of a substance (49, 50). From a three-compartment-model (intestinal lumen, interstitial space, streaming blood) a simple equation can be derived for the dependence of the intestinal absorption on blood flow (44, 45).

$$\phi = \frac{C_{DO} - C_{PA}}{\frac{1}{kF_D} + \frac{1}{\alpha a_1 V_B}}$$

ϕ = absorption rate, appearance in the intestinal venous blood (mol min^{-1}), C_{DO} = luminal concentration (mol ml^{-1}), C_{PA} = arterial plasma concentration (mol ml^{-1}), k = permeability coefficient of the epithelium (ml min^{-1}

cm^{-2}), F_D = mucosal surface area (cm^2), α = fraction of blood flowing through capillaries near the epithelium, a_1 = concentration ratio of blood and plasma, V_B = whole intestinal blood flow (ml min^{-1}).

The equation is valid for the following restricted condition: small intestinal segment, zero water net flux, stationary state (concentration independent of time), the substance leaving the intestinal lumen appears completely in the blood, transport through the epithelium proportional to the concentration, concentration equilibrium between the interstitial space and the plasma at the venous end of the capillary [for details see (45)]. The denominator of the equation can be interpreted as the entire resistance of the distance intestinal lumen to blood. The resistance is divided into two parts: the resistance of the distance intestinal lumen to capillary wall (first term of the denominator) = resistance of the "epithelium," and the resistance of the draining system (second term of the denominator). The reciprocal of the first term, $k F_D$, is a blood flow independent measure for the permeability of the epithelium relative to a substance.

A high permeability means a small first term of the denominator so that the second term governs the equation: the blood flow determines the absorption. The absorption rate is blood flow limited and may be used to measure the mucosal blood flow (49). The influence of blood flow on intestinal absorption diminishes with decreasing permeability of the epithelial cells (increasing first term). Finally the intestinal absorption becomes independent of blood flow (see figure).

For practical use the equation is to be adapted to the special experimental conditions (45) (single intraluminal injection or continuous perfusion). Sometimes the appearance of the substance on the serosal side is to be considered (Winne, unpublished results). The influence of blood flow on fluid absorption is more complicated since the solute as well as the water absorption and their interactions are to be considered (48). Theoretical deductions point to a fluid absorption independent of blood flow using isotonic saline solution on the luminal side. The dependence on blood flow is expected when the gut is perfused by nonisotonic saline solutions.

Methods.—For investigating the influence of blood flow on intestinal absorption it is necessary to measure simultaneously the intestinal blood flow and the intestinal absorption and to vary arbitrarily the blood flow. In absorption experiments the disappearance from the intestinal lumen is to be distinguished from the appearance in the intestinal venous blood. Differences between these two quantities are caused by an accumulation of the absorbed substances in the intestinal wall, by dropping out on the serosal side, and by transport in the lymph.

The published methods suitable for the purpose mentioned were not always developed for it. Single jejunal or ileal loops (36, 44, 49, 51–53) or the whole small intestine (54–57) from dogs (49, 51, 56, 58), cats (57),

rats (36, 44, 52–54), frogs or toads (55) are used. On principle, methods with natural arterial blood supply (36, 44, 49, 51, 57) and artificial vascular perfusion (52–56, 58; for former literature see 55) are to be distinguished. The vascular perfusions are done in situ (52, 54, 58), or in vitro, in a saline bath (56), in a wet chamber (53), or in a paraffin bath (56). The latter two methods enable one to investigate the serosal "sweat." The solution for the vascular perfusion is an artificial one (52–56) or the blood is pumped from the femoral artery to the superior mesenteric artery (58).

During artificial vascular perfusion the blood flow is arbitrarily fixed by the pump. The natural arterial blood supply can be diminished by constriction of the superior mesenteric artery (49, 51); this is not possible in very small animals. In the rat the intestinal blood flow can be varied indirectly by changing the circulating blood volume (36, 44): if the venous outflow of the intestinal loop is not reinfused and the loss of blood is compensated by an infusion of heparinized blood into the jugular vein, the intestinal blood flow can be varied by changing the venous blood infusion. A drop recorder measuring the venous outflow may serve as a control. The measurement of blood flow may be omitted if the velocity of the vascular perfusion is known, otherwise a flow (57), a drop recorder, or the weighing of the venous outflow give the desired intestinal blood flow (36, 44).

The disappearance rate follows from the concentration and volume change of the luminal fluid. The appearance rate is calculated from the arterio-venous concentration difference and the blood flow. The measurement of the concentration in the arterial blood is not necessary, if the intestinal venous blood is not reinfused. In this case the equations for the dependence of the absorption rate on blood flow are much simpler.

Dependence of intestinal absorption on blood flow.—Figure 2 shows clearly the influence of blood flow on the intestinal absorption of drugs [selected data from (35–37)]. The absorption (appearance in the intestinal venous blood) of tritiated water is nearly blood flow limited, while the absorption of ribitol is independent of blood flow. The dependence of intestinal absorption on blood flow increases with increasing absorbability and decreasing blood flow. The concentration in the intestinal venous blood is inverse to the appearance rate: the concentration decreases with increasing blood flow and the curves become steeper with decreasing absorption rate.

The appearance rate of amidopyrine, antipyrine, benzoic and salicylic acid (35, 36), ethanol (37), glucose (43, 55, 59–61), and galactose (62), as well as the disappearance rate of glucose (58, 61, 63), xylose (58), glycine (63), carbon dioxide (64), sodium (61), and water (61) decreases with decreasing blood flow. The appearance rate of iron and copper (53) and the disappearance rate of sorbose (61) are independent of blood flow. The disappearance rate of glucose begins to drop below 50% of normal blood flow. The oxygen consumption (63) and ATP content of the mucosa (65) run

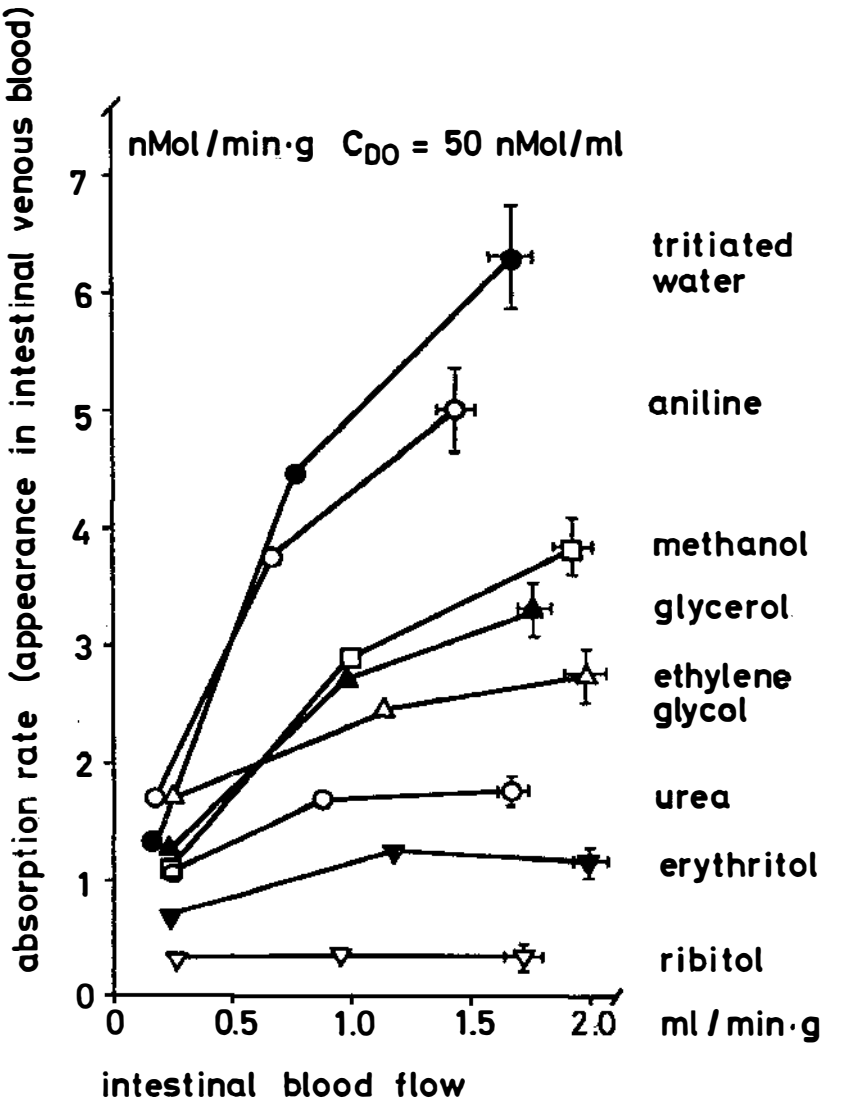

FIG. 2. Influence of blood flow on intestinal absorption (appearance in the intestinal venous blood) of several substances from the jejunum of the rat. Selected data from (35, 36, 37). 95% confidence limits.

parallel. Also during longer constriction of the superior mesenteric artery the absorption of xylose and ^{131}J-triolein is diminished (66). The fluid absorption (disappearance rate) from isotonic saline solution is independent of blood flow, while the positive and negative water net flux induced by hypo- and hypertonic saline solution decreases with decreasing blood flow (43).

Vasoactive drugs can influence the intestinal absorption by means of the blood flow. According to the results mentioned above an intravenous infusion of 5-hydroxytryptamine, norepinephrine, or vasopressin diminishes the intestinal blood flow of rats and simultaneously the appearance of tritiated water in the intestinal venous blood. An intravenous infusion of histamine causes a short rise of intestinal blood flow and the appearance rate of tritiated water (44). A subcutaneous pituitrin injection diminishes the water absorption in the dog (67).

The whole intestinal blood flow is not always a measure for the "effective mucosal blood flow" that is carrying away the absorbed substances. An intraarterial infusion of epinephrine can raise or lower the intestinal blood flow as well as the glucose disappearance rate and the oxygen consumption (68). But also an increase of blood flow and simultaneously a decrease of glucose disappearance were observed (68). An intraarterial infusion of acetylcholine decreases the glucose disappearance, while the blood flow is increased (68). Vasopressin diminishes and bradykinin raises the whole intestinal blood flow, while the ^{133}Xenon disappearance rate remains unchanged (49).

It must be considered that the blood flow pattern in the intestinal wall is changed. A vasoconstrictor excitation (69, 70), or shock (71, 72), cause the blood flow to decrease, especially in the mucosa. An intravenous infusion of isopropylnorepinephrine increases predominantly the mucosal blood flow (70, 73). It is supposed that arterio-venous anastomoses in the submucosa are opened (68) and are especially effective during high blood flow (74, 75).

The vascular structures of the intestinal villi with neighboring arteries and veins suggests that a counter current exchange may retard the absorption (49, 76). An arterio-venous shunt was proved for oxygen (75, 77). It is mainly effective during low blood flow (73, 74).

Ischemia and intestinal absorption.—During an experimental traumatic and hemorrhagic shock the glucose (78, 79) and water (79, 80) disappearance rate decreases or remains unchanged (80, 81). The fluid absorption from isotonic saline solution rises (80). The water net flux directed into the intestinal lumen induced by magnesium sulphate increases in shock (82), while the absorption of magnesium and sulphate does not change (83).

Oxygen-dependent transport mechanisms are inhibited for a longer time by too low blood flow: After 20–25 minutes subnormal blood flow (20–30%

of normal) the glucose disappearance does not increase in spite of restoring normal blood flow (43) just as the sodium and water disappearance after a period with constricted aorta (61). An ischemia inhibits the dinitrophenol response, the sodium-dependent accumulation of phenylalanine and isoleucine (39, 40, 42) measured in vitro with sufficient oxygen supply after the ischemia. But if, during the ischemia, the intestinal lumen is perfused by a solution saturated with oxygen, the accumulation is not diminished (41). The absorption capacity of the intestine is completely restored after 2–7 days (39, 40, 42). Similarly, the serosal appearance of glucose, DL-alanine, D-leucine, L-leucine, and L-glutamic acid measured in vitro is diminished after a traumatic shock or an ischemia lasting 1–2 hours. The appearance of sorbose and fructose is unchanged (38). Perfusion of the intestine during the shock by a solution containing oxygen prevents the drop of the glucose absorption (38).

Lymph flow and intestinal absorption of drugs.—The transport of drugs by lymph is quantitatively unimportant, since the intestinal blood flow is 500–700 times larger than the intestinal lymph flow (57, 84, 85). Less than 2% of digitoxin, ouabain, digoxin, and peruvosid (57), p-aminosalicylic acid and tetracycline (86) appears in the intestinal lymph. The lymph concentration lies below the portal vein (57) or little above the systemic (86) blood level. Similar lymph concentrations are measured after intravenous application of the drugs. There is the impression that drugs, after passing the intestinal epithelium, arrive at a compartment that is drained by blood and lymph. Because of the large blood volume draining this compartment, the drug is almost completely carried away by blood. The intestinal application of tripalmitin doubles the lymph flow and increases the lymph and blood concentration of tetracycline; the lymph concentration of p-aminosalicylic acid remains unchanged (86). An emulsion of olive oil does not enhance the intestinal absorption of digitoxin (57).

Passage-Time and Intestinal Absorption

The physiological and biochemical conditions between man and animal vary; they can even vary within families of animals, e.g. rats and guinea-pigs. Therefore any final judgment on the amount of drug absorption in man has always to be taken "cum grano salis," if the experiments are done on laboratory animals. Absorption will be influenced by dose, concentration of the orally applicated substances, the route of permeation, the size of the surface that binds the drug, and last but not least by the function of the gastrointestinal tract. If an orally applied drug is partially or not at all absorbed by the stomach then the passage-time, which can be influenced by physical and chemical means, becomes important. Experiments done on rats and dogs by Görisch & Hüttl (87) showed that cold solutions pass more quickly into the small intestinal lumen than warm ones. A cold aqueous so-

lution of neostigmine hydrobromide is significantly more toxic in the organism than a comparable warm solution. It is well known that acids in nutrition delay gastric emptying. This acid effect was verified by HCl and recently for organic acids (Hunt & Knox 88). It is known that drugs can increase or diminish the passage-time. In some cases it was observed that substances can obstruct the enteral absorption of orally administered drugs by relaxing the smooth muscles in the intestinal tract. Here is a wide field for pharmacological research in the future.

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