Progress report

The circulation of the small bowel mucosa

Absorption, secretion and motility, the three major functions of the small intestine, are localized in different parts of the intestinal wall and have nutritional demands of different magnitudes. 'Active' absorption across the intestinal epithelium and secretion which, according to the classical concepts, occurs mainly in the crypts, are processes consuming considerable amounts of oxygen. The motility of the muscularis, on the other hand, requires comparatively little oxygen.

It is generally believed that the magnitude of the blood supply to a tissue is closely adjusted to its current demand for oxygen and that regulatory mechanisms exist which increase blood flow to an organ in situations of enhanced metabolism¹. It seems therefore reasonable to assume that blood flow is unevenly distributed within the intestinal wall. Moreover, changes in flow may only occur in a certain wall layer, eg, a vasodilatation may be restricted to the muscularis during intestinal motility.

From the discussion above it seems clear that it would be interesting to be able to study, eg, mucosal blood flow separately. However, few investigations have until recently been devoted to the study of intestinal intramural flow distribution. One aim of this article is to summarize the recent progress in this field and to discuss the relationship between villous blood flow and intestinal absorption.

Methods for Measuring Intestinal Flow Distribution

During the last two decades some attempts have been made to quantify the intestinal flow distribution in experimental animals using different tracer techniques. In the early studies water-soluble compounds, such as ⁸⁶Rb, were injected intravascularly and the amount of tracer in the different wall layers was determined and taken as a measure of flow distribution^{2,3,4,5}. Apart from the disadvantage that only one experiment could be performed on each animal, it seems unlikely that the tissue uptake of lipid-insoluble compounds is limited by flow, since only a small fraction of the total capillary surface area is available for the exchange of water-soluble compounds⁶.

In this laboratory two techniques have been developed for the study of intestinal flow distribution. In one an inert lipophilic gas, ⁸⁵Kr, dissolved in saline, was injected intraarterially as a slug^{7,8}. The disappearance of the radioactive gas from the small bowel was followed by α - and/or β -radiation detectors. The disappearance curve recorded with a scintillation detector was as expected multiexponential, reflecting the heterogeneity of flow within the intestinal tissue, and the curve could be resolved into four components. Using a number of independent techniques it was possible to demonstrate that each component mainly reflected the washout from a certain intestinal wall layer. The second method, based on the indicator-dilution principle,

utilized labelled, intravascular tracers, such as ^{32}P -labelled red cells or plasma colloids⁹. These were injected as a slug into the superior mesenteric artery and their transit through the mucosa was monitored with a β -detector placed in the gut lumen. Knowing the amount of tracer injected and the flow rate at the injection site, it was possible to determine regional plasma or red cell flow from the height of the recorded indicator-dilution curve and regional volume from the area under the curve.

Intestinal Haemodynamics

The control of the intestinal vasculature resembles in principle that of other systemic vascular circuits, ie, local and remote (nervous and hormonal) controlling mechanisms exist, and a short survey of these will be given. The quantitative data reported below were obtained in cat experiments using the inert gas wash-out technique and the indicator-dilution method described above. There is reason to believe that there is a fairly close quantitative resemblance between man and cat as regards the intestinal circulation¹⁰.

In a denervated intestinal segment of an anaesthetized cat that has been fasting for 12 to 24 hours, total intestinal blood flow amounts to 20-40 ml/min $\times$ 100 g intestinal tissue⁸. Villous plasma flow is then 20-50 ml/min $\times$ 100 g villous tissue¹¹. Since the haematocrit is fairly low in the villous vessels (about 50% of arterial) due to a plasma skimming¹², this plasma flow corresponds to a blood flow of about 30-60 ml/min $\times$ 100 g; 75-85% of total intestinal blood flow is distributed to the mucosa-submucosa¹³ and roughly one third of this flow, ie, about 20% of total flow, passes the villi¹¹. Mean transit time of plasma through the villi is 4-8 sec¹¹.

The intestinal vascular bed exhibits a 'functional' hyperaemia during digestion, splanchnic blood flow usually increasing 100-200% above control^{14,15,16,17,18,19,20,21,22}. Two mechanisms have recently been proposed to account for this vasodilatation. Fara and coworkers²³ suggested that the physiological release of secretin and cholecystokinin after a meal increases intestinal blood flow, while a local nervous vasodilatory reflex was inferred from experiments performed by Biber *et al*^{24,25}. The nervous reflex was proposed to be elicited via a mechanical stimulation of the bowel mucosa by the food. The flow distribution within the small intestine during functional hyperaemia has not been studied with any reliable method. The potential flow capacity of the cat small intestine is, however, very high indeed. Total venous outflow can be increased 8 to 10-fold from 'resting' level to flow values above 200 ml/min $\times$ 100 g by means of potent vasodilator drugs. At intense vasodilatation induced by isopropylnoradrenaline villous blood flow reaches 350 ml/min $\times$ 100 g villous tissue¹¹. In this situation more than 90% of total blood flow is diverted to the mucosa-submucosa^{8,13} and almost half of total flow is passing the villi¹¹. Mean transit time of plasma in the villi is slightly less than 1 sec at maximal dilatation¹¹.

The extrinsic nervous control of the intestinal vasculature is exerted by sympathetic vasoconstrictor fibres. No parasympathetic vasodilator outflow to the small bowel exists²⁶. Electrical stimulation of the regional vasoconstrictor fibres induces a characteristic flow response in the small intestine^{27,28}. Initially, total intestinal blood flow is drastically reduced. However, within 2 to 4 min after the onset of constrictor fibre stimulation, intestinal blood flow again increases, reaching a new steady state level only moderately

below control, the resistance increase seldom exceeding 100% above control. This 'autoregulatory escape from vasoconstrictor fibre stimulation' is not due to any fatigue of the nervous transmission, since the intestinal veins remain constricted throughout the stimulation period²⁷.

It has earlier been claimed that the sympathetic nerves cause a pronounced vasoconstriction in the mucosal vessels. However, using the indicator dilution technique described above no such change of blood flow can be demonstrated²⁹. In fact, after an initial vasoconstriction villous plasma flow seems to be, if anything, somewhat larger than control during the 'steady state phase' of vasoconstriction. A larger portion of total intestinal blood flow is then diverted to the villous vessels, while mean transit time remains at the control level²⁹. These observations suggest that the autoregulatory escape is secondary to a redistribution of intestinal intramural blood flow³⁰.

The intestinal blood flow exhibits autoregulation, ie, flow stays constant in the face of fairly large variations of arterial inflow pressure. This phenomenon is usually explained by the inherent property of vascular smooth muscle to be modulated by transmural pressure (Bayliss mechanism)³¹. According to this hypothesis an increased (decreased) transmural pressure will *per se* cause vasoconstriction (vasodilatation). Arterial inflow pressure must fall below 60-70 mm Hg until total blood flow of a denervated intestinal segment is reduced³². The autoregulatory capacity of the villous vasculature is even more pronounced, villous plasma flow being maintained at the control level even when arterial blood pressure is lowered to 30 mm Hg³². Since intestinal blood flow then is half control, an increasing portion of total flow is diverted to the villi during arterial hypotension. Mean transit time is greatly prolonged when lowering arterial inflow pressure, reaching a value of 20 to 30 sec at an arterial pressure of 30 mm Hg³².

The Relationship between Mucosal Blood Flow and Absorption Rate

Mucosal blood flow is obviously one factor of importance for the rate of intestinal absorption. As regards 'actively' transported substances blood flow not only constitutes the transport vehicle but also delivers the nutrients for epithelial cell metabolism. This complex relationship between flow and 'active' absorption is reflected by the varying results obtained by different researchers. In fact, in the hands of one and the same experimenter the absorption rate of 1-phenylalanine and 3-O-methylglucose is affected differently by flow depending on whether flow is increased from a low level or decreased from a high one^{33,34}.

Passively absorbed solutes are affected by flow in a more predictable manner. It has been demonstrated repeatedly, particularly in a series of investigations on the rat by Winne³⁵, that absorption rate for lipid-soluble compounds varies with flow while absorption for water-soluble compounds, such as urea and erythrose, are more or less independent of flow. These observations reflect the permeability characteristics of the epithelial lining of the intestinal tract, being little permeable to water-soluble compounds having a molecular weight exceeding 100³⁶, while lipid-soluble solutes easily traverse the gut epithelium. Hence, for most water-soluble substances the passage across the intestinal epithelium represents the rate-limiting absorptive step.

The detailed knowledge of the haemodynamics in the cat small intestine

prompted a study of the absorption of an inert substance, ^{85}Kr , as a model for lipid-soluble compounds^{37,38}. In agreement with the circulatory observations, the absorption rate of ^{85}Kr increases upon intestinal vasodilatation³⁷, while sympathetic vasoconstriction causes no change in ^{85}Kr absorption rate³⁸. However, when perfusion pressure is lowered by partial occlusion of the superior mesenteric artery absorption rate decreases³⁸ although villous plasma flow remains at the control level³³. This peculiar observation can only be explained by the presence of a countercurrent exchanger in the intestinal mucosa³⁰.

The Intestinal Countercurrent Exchanger

The following anatomical description presents the vascular architecture of the mucosa in cat which largely resembles that of man (see fig 1)^{39,40,41}. The submucosal layer contains a close-meshed vascular network and from this plexus arterial vessels emerge towards the mucosa, each cat villus usually being supplied by a single vessel. This arterial vessel (diameter around 20 μm) runs in the central villous core without branching and loses its muscular coat at the villous base. The permeability characteristics of this vessel, for example, the possible presence of intercellular 'pores', is not known. Close to the villous tip, the central vessel arborizes into a dense, subepithelial capillary network (fig 1). In these capillaries there seems to exist a 'pore' system with functional dimensions similar to that in skeletal muscle capillaries but with a total 'pore' area considerably higher than in the muscle capillaries¹¹. The

Fig 1 Left panel: Schematic drawing of the vascular anatomy of a cat villus. The capillary vessels of the figure denote a dense subepithelial capillary network. Note that the ascending arterial vessel and the descending capillary network and venous vessel form hairpin vascular loops. Right panel: The vascular anatomy of a human villus as depicted by Spanner⁴⁰. Black vessels denote arterial vessels, grey vessel a venous one.

capillaries collect into veins at the villous base. Each villus is also provided with a central lymphatic vessel.

It is clear from the anatomical description above and from fig 1 that the main direction of blood flow in the subepithelial capillary network must be opposite to that of the central arterial vessel. Thus, the anatomical prerequisites exist for an intestinal countercurrent exchanger. From a functional point of view it is, however, more interesting to know if the transit time of blood in the hairpin vascular loops of the villi is long enough to allow any significant diffusion of solutes across the 20 μm long intervascular distance. As indicated above, mean transit time of plasma in the villi is 4-8 sec at 'rest', about 1 sec at intense vasodilatation, and 20-30 sec at low perfusion pressure. Assuming free diffusion in water, it can be calculated that a 75% concentration equilibrium is reached across a 20 μm distance in about 0.1 sec for most 'physiological' solutes having a molecular weight less than 500-1000. Thus, diffusion across this distance is a fast process compared with the villous transit time of plasma and there may be a considerable intervascular cross-diffusion of substances, provided that a concentration gradient exists and that vascular permeability to the solute is high. The available evidence suggests that the capillary permeability to lipid-soluble solutes is large while the exchange of water-soluble substances is partially or wholly restricted⁶. It seems therefore *a priori* reasonable to assume that particularly lipid soluble solutes 'cross diffuse' rapidly from one limb to the other and, hence, are easily 'trapped' in the exchanger.

The intestinal countercurrent exchanger may be approached either from the 'luminal' side, as during intestinal absorption, or from the 'tissue' side via the blood stream as schematically illustrated in fig 2. In the 'absorptive' situation the villous exchanger may 'hinder' net blood absorption of solutes. When supplied by the blood stream, the exchanger tends to impair net blood transport into the villous tissue because of cross diffusion at the villous base. The efficiency of the intestinal countercurrent exchanger in 'hindering' net blood transport can, however, be expected to be much higher when approached from the 'luminal' side, since the linear flow rate must be much slower in the subepithelial capillaries than in the central villous vessel, where the blood volume is only about one tenth of that of the capillary network. Since volume flow is identical in the two limbs of the hairpin vascular loops, linear flow rate in the subepithelial capillaries must be approximately one tenth of that in the arterial vessels. Hence, during nine tenths of the transit times given above, plasma is located in the villous capillaries.

Returning to the observation of a decreasing ⁸⁵Kr absorption in the face of an unchanged villous blood flow, this is, according to the countercurrent hypothesis, explained by the lowering of linear rate of flow. As described above mean transit time increases three to fivefold as perfusion pressure is lowered, prolonging the time for cross diffusion in the countercurrent exchanger making the exchanger more 'efficient' in hindering net absorption (cf fig 2 A). This observation is one of many in favour of the countercurrent hypothesis. The interested reader is referred to the theses by Jodal⁴², Lundgren⁸, and Svanvik³⁰ for summaries of further experimental evidence. The rest of this article will be devoted to a brief survey of some other functional implications of the intestinal countercurrent exchanger.

Fig 2 The functional implications of the mucosal countercurrent exchanger schematically illustrated. The intervascular distance is greatly exaggerated for the sake of clarity (from Lundgren⁸).

Absorption of Sodium Chloride and Water

The present knowledge of sodium transport across the intestinal epithelium has almost exclusively been gained by means of various techniques *in vitro* when the blood stream is excluded. According to current concepts, sodium entrance into the epithelial cell is partly passive, partly carrier-mediated while sodium exit into the extracellular space is considered to be an 'active' process located at the 'tissue' side of the epithelial cell membrane⁴³.

The intestinal absorption of water is closely linked to the transfer of solutes, such as sodium chloride, and it is believed that a difference in osmolarity across the epithelium is a prerequisite for the movement of water. However, it has been experimentally demonstrated that water absorption can occur in the absence of, or even against, an osmotic pressure difference between intestinal lumen and plasma⁴³. To explain these experimental findings the existence of a hyperosmolar tissue region has been inferred, usually localized to the interstitial space between the epithelial cells^{43,44}. However, no experimental results have so far been reported supporting the presence of a hypertonic intercellular space in the small intestine.

The intestinal countercurrent exchanger may theoretically interfere during the absorption of sodium chloride in two ways. First, since sodium is a small ion even in its hydrated form, the actively absorbed sodium may cross diffuse from the subepithelial capillary network to the central villous vessel in the same way as illustrated in figure 2 A. This calls for 'pores' in the endothelial layer of both these vessels. If so, it may be possible that during NaCl absorption a slight difference in sodium concentration between the two limbs of the villous vascular loops may be 'multiplied' along the villous length creating an increasingly hyperosmotic interstitial fluid towards the villous tips in much the same way as in the kidney papillae. Secondly, the same end

result will be accomplished if water is transferred from central vessel to capillaries secondary to osmotic forces created by the active absorption of sodium. Water, being able to pass through the endothelial cells does not call for any conventional capillary 'pores' to be involved in this type of mechanism. Thus, a countercurrent multiplier may create a hyperosmolar region in the interstitial space of the villous tips. This hypothesis was substantiated in a series of experiments showing, among other things, that the amount of sodium per unit weight tissue protein is three to four times higher at the villous tip than at the base^{42,45,46}.

Absorption of Fatty Acids

It is generally agreed that in mammals the short-chain fatty acids (fatty acids with less than 10-12 carbon atoms) are absorbed from the small intestine mainly via the blood, while the long-chain fatty acids are predominantly transported via the lymph as triglycerides in chylomicrons. The factors determining this partition between blood and lymph are largely unknown⁴⁷, although it is usually explained in terms of the rapid esterification of the long-chain fatty acids in the apical parts of the epithelial cells, while this should not be the case with the short-chain fatty acids. Thus, this rapid esterification is supposed to hinder the long-chain fatty acids from reaching the subepithelial capillary network, while the short ones would diffuse freely through the epithelial cells to the blood stream.

These different routes of absorption may, however, also be explained by the intestinal countercurrent mechanism, since the exchanger may 'hinder' net blood absorption of the lipid-soluble, long-chain fatty acids, as shown in figure 2A. The predominantly water-soluble, short-chain fatty acids, on the other hand, may be less easily trapped in the exchanger, since they are mainly pore-restricted and therefore more delayed in their passage across the capillary walls. This hypothesis implies that the transcapillary movement of the long-chain fatty acid from the intravascular albumin molecules to the extracellular space or vice versa should in fact be a very rapid one. Model experiments on, eg, tumour cells, seem to support this assumption. The countercurrent hypothesis of fatty acid absorption is supported by a number of observations made in a recent series of experiments^{42,48,49,50}.

Pathophysiological Aspects

It has been reported repeatedly that mucosal ulcerations develop in the small intestine of various experimental animals and also in man during periods of low arterial perfusion pressure caused by, eg, haemorrhage^{51,52,53,54,55}. The development of these tissue lesions, which are located at the villous tips, is usually explained in terms of an intense vasoconstriction of the intestinal mucosal vessels, which together with the low perfusion pressure should reduce blood flow to such an extent as to induce tissue destruction⁵⁶. However, as described above, neither the lowering of perfusion pressure to the small intestine nor the activation of the sympathetic vasoconstrictor fibres induce any significant decrease of villous blood flow. Hence, none of the two haemodynamic adjustments that, apart from rheological disturbances, characterize the small intestine in, eg haemorrhagic

shock, induce any considerable decrease of volume flow of blood through the villi and, yet, mucosal lesions develop in this part of the intestine.

The countercurrent hypothesis offers an explanation for this apparent paradox^{55,57}. Some years ago it was demonstrated that an extravascular 'short circuiting' of oxygen probably occurs in the intestinal countercurrent exchanger of the cat, ie, oxygen diffuses from the central arterial vessel to the subepithelial capillaries along a concentration gradient (cf fig 2 B)⁵⁸. The intestinal countercurrent exchanger then acts as a 'hindrance' to net blood transport of oxygen to the villi. This results in a falling tissue P_{O_2} from the villous base towards the tip and the villous tips are hypoxic, relatively speaking, even at a normal arterial perfusion pressure. Although villous blood flow stays almost constant when reducing perfusion pressure, mean transit time through the villous hairpin vascular loops is greatly increased (see above) enhancing the time available for extravascular oxygen 'shunting' in the countercurrent exchanger. This, in turn, probably leads to such a pronounced villous tissue hypoxia as to cause cell death, particularly at the tips⁵⁹.

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