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MUCOSAL BLOOD CIRCULATION AND ITS INFLUENCE ON PASSIVE ABSORPTION IN THE SMALL INTESTINE

An experimental study in the cat

BY

JOAR SVANVIK

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Department of Physiology, University of Göteborg, Göteborg, Sweden

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This summary is based on studies reported in the following papers:

I. An indicator-dilution method for studying intestinal haemodynamics in the cat.
B. Biber, O. Lundgren, L. Stage and J. Svanvik.
Acta physiol scand. 1973. In press.

II. Intramural blood flow and blood volume in the small intestine of the cat as analyzed by an indicator-dilution technique.
B. Biber, O. Lundgren and J. Svanvik. Acta physiol. scand. 1973. In press.

III. Mucosal haemodynamics in the small intestine of the cat during reduced perfusion pressure.
O. Lundgren and J. Svanvik. Acta physiol. scand. 1973. In press.

IV. Mucosal haemodynamics in the small intestine of the cat during regional sympathetic vasoconstrictor activation.
J. Svanvik. Acta physiol. scand. 1973. In press.

V. The influence of blood flow on the rate of absorption of ^{85}Kr from the small intestine of the cat.
B. Biber, O. Lundgren and J. Svanvik. Accepted for publication in Acta physiol. scand.

VI. The effect of reduced perfusion pressure and regional sympathetic vasoconstrictor activation on the rate of absorption of ^{85}Kr from the small intestine of the cat.
J. Svanvik. Accepted for publication in Acta physiol. scand.

The papers are referred to by their Roman numerals in the text.

INTRODUCTION

The two important physiological functions of the small intestinal mucosa are absorption and secretion. Absorption takes place across the epithelial cells lining the luminal surface while secretion is supposed to occur mainly in the crypts. In the light of present knowledge the small intestinal mucosa is a structure of relatively low "passive" permeability but containing a variety of highly specific transfer systems for biologically important substances. However, the concept that the intestine absorbs almost everything present in the lumen in a diffusible form, independent of the body´s needs, nevertheless holds true and normally a variety of such substances enter the lumen. Thus, absorption is partly "active", dependent on the metabolism of the absorbing cells and partly "passive", controlled by the law of diffusion. Secretion is presumably also an "active" process that calls for an adequate supply of oxygen. The nutritional demands of the intestinal mucosa are also high, partly due to the rapid turnover rate of the epithelium where the total cell population appears to be replaced in about two days. A rapid cell renewal therefore occurs, probably in the crypts from which the cells are gradually displaced towards the villous tips.

The mucosal blood supply serves the nutritional demands of the tissues outlined above. There are, however, reasons to believe that the intestinal mucosa is often considerably "overperfused" in relation to its own nutritional oxygen demands, partly because mucosal blood is the transport vehicle for most of the absorbed substances and also partly because plasma is the raw material for secretion.

The intricate morphological features of the small intestinal mucosa include a complex vascular arrangement (vide infra), with separate circuits supplying the villi and the crypts. The functional consequences of this peculiar vascular design seems to be even more complex. Thus, it was recently shown that a countercurrent exchange of diffusible solutes occurs between the ascending and descending vessels in the villi (see Lundgren 1967). Due to the presence of this exchanger, easily diffusible substances injected intraarterially are shunted extravascularly from the arterial to the venous end of the villous hairpin vascular loop, diffusing across the vascular walls and the narrow tissue spaces. It was also demonstrated that lipid soluble substances were more easily "trapped" than water soluble ones, due to their different capillary permeability, in the exchanger thus created. Further, by increasing the intestinal blood flow and hence decreasing the time available for exchange diffusion, the efficiency of the countercurrent exchanger could be decreased. It was proposed that the existence of this countercurrent system would affect the intestinal

absorption and probably to a certain extent delay, or even hinder, net blood transport of absorbed substances. The system would be relatively selective in the sense that those substances, which most easily pass the intestinal epithelium (lipid soluble or low molecular weight substances) would also be most efficiently "trapped" in the mucosal countercurrent exchanger.

Furthermore, the characteristic vascular architecture of the intestinal mucosa-submucosa probably constitutes the anatomical prerequisite for the considerable plasma skimming that seems to occur in the intestine (Jodal and Lundgren 1970 a). The mucosal arterial vessels branch off more or less at right angles from the vascular network in the submucosa and/or in the deeper parts of the mucosa and these points offer a favourable situation for plasma skimming when flow rate is high enough. Accordingly, the superficial mucosal layers seem to be perfused by blood with an hematocrit only 50-60 per cent of the arterial hematocrit.

The functional implications of the countercurrent exchanger, as regards intestinal absorption, have so far not been subject to any experimental test. Moreover, most, if not all, investigators studying the relationship between blood flow and rate of absorption in the intestine have recorded total intestinal blood flow (for ref. see V and VI) due to a lack of appropriate methods for studying mucosal hemodynamics selectively. When approaches such as various accumulation techniques have been employed, they have allowed only one measurement per animal (for ref. see I). An inert gas washout technique that allows repeated determinations was recently utilized for a study of blood flow in the different layers of the intestinal wall (Lundgren 1967). However, the use of such easily diffusible tracers is for such purposes greatly complicated by the above mentioned extravascular transit of tracers between venous and arterial vessels in the intestinal mucosa.

The present series of experiments (I-IV) represents an attempt to develop a technique for studying quantitatively the blood circulation in the mucosa of the cat small intestine, using tracers that remain within the vessels thereby avoiding any extravascular passage of tracer in the countercurrent exchanger. The technique involves a close intraarterial injection of intravascular tracers (labelled with ^{32}P or ^{198}Au) which are traced with β-sensoring devices placed in the intestinal lumen. Since the volume of the region monitored by the detector is determined by the energy level of the β-radiation, ^{32}P-labelled red cells and plasma colloids were monitored from almost all the mucosa, while the ^{198}Au-labelled plasma colloid particles were registered only from the villi. Paper I deals with the theoretical background for the interpretation of the indicator-dilution curves

registered with the intraluminar detectors. It was shown in this study that mucosal (villous) blood flow could be estimated from the maximal height of the curve, mucosal (villous) blood content from the area under the curve and mean transit time within the monitored tissue volume from the area under the curve divided by the maximal height of the curve. In the following reports (II-IV) this method was used for the study of small intestinal mucosal (villous) blood circulation in different hemodynamic situations.

Knowing the hemodynamic features of the mucosal vascular bed it was thought relevant to investigate the relationship between mucosal blood flow and rate of absorption of a "passively" absorbed tracer. For this purpose, the easily diffusible inert gas ^{85}Kr was chosen as the first test substance since it had been used in earlier investigations on the gut and was known to be extravascularly "shortcircuited" in the mucosal countercurrent exchanger after i.a. administration (see Lundgren 1967). Thus, it was regarded of interest to study the same substance in its passage from lumen to the intestinal blood stream and to estimate the earlier proposed "trapping" effect of the countercurrent exchanger.

The absorption rate of this tracer was determined in experiments where the tracer luminal concentration of ^{85}Kr dissolved in saline was kept essentially constant. The experiments were performed under conditions similar to those earlier investigated with the indicator-dilution technique (II-IV). Thus, the absorption rate during "resting" conditions and hyperemia was studied in paper V and during reduced perfusion pressure and stimulation of the regional sympathetic nerves in paper VI.

Preliminary reports of parts of this series of experiments have previously been published (Lundgren and Svanvik 1968, Biber, Lundgren and Svanvik 1969).

ANATOMICAL CONSIDERATIONS

Vascular arrangements in the intestinal submucosa and mucosa.

The vascular morphology in the submucosa and mucosa of the small intestine has been studied by several authors in various animals. The techniques that have been used usually include i.a. infusions of opaque material and fixation of the tissue prior to microscopic inspection and thus the accuracy depends on a complete filling of the vascular tree. Furthermore, the submucosa and the mucosa except the villi have been investigated by intravital microscopy (Baez 1959). Differences in methodology are probably mainly responsible for the differences in the results obtained, but there does seem to be considerable morphological variation between species, as pointed out by Noer (1943).

The submucosa receives vessels that obliquely pass the muscularis coat from the serosa, forming a dense plexus of arteries and veins, which seems poor of capillaries (Mohiuddin 1966). Mall (1888) in the dog, and Spanner (1932) in the cat, describe a characteristically structured "arterio-venous anastomosis" (Venenbällchen). This structure could, however, not be recognized in the rat by Baez (1959) or Mohiuddin (1966). Similar arterio-venous communications have been described in the small intestine of man but they seem to be more frequent in the gastric wall (Boulter and Parks 1959).The functional significance of these structures seems so far not to have been fully established and no large arterio-venous vessels were demonstrated in dog experiments with i.a. injected microspheres (Delaney 1969). Neither could Dresel et al. (1966) find any evidence of true blood shunting in the cat intestine, in the sense that any sizable portion of the blood could be excluded from nutritional exchange.

In all cases, the arterial vessels emanating from the submucosa supply two capillary networks in the mucosa, one located around the crypts and one in the intestinal villi. A great number of studies on man, dog, cat and rat point to separate arterial vessels from the submucosa to these two capillary networks (Heller 1872, Mall 1888, Jacobson and Noer 1952, Mohiuddin 1966) thus providing the basic conditions for a separate control of blood supply to the tissue around the crypts and to the villi. A schematic illustration of this vascular anatomy is shown in Fig. 1.

The tissue around the mucosal crypts is provided by a dense capillary network supplied by numerous small arteries from the submucosa (Heller 1872, Mall 1888). This network seems denser in the jejunum than in the ileum (Reynolds, Brim and Sheehy 1967).

The villi, as pointed out above, seem to be provided with separate arterial vessels from the submucosa. In the dog Mall (1888) describes these arterial vessels as penetrating the muscularis mucosa and then dividing into 8-10 branches, each supplying one villus and losing their smooth muscle coat at the villous base. Although different studies disagree as to the arrangement of the arterial and venous vessels in the villi, all authors describe a descending mono-layered capillary network in close contact with the epithelial cells. Electron microscopy has shown that these capillaries have fenestrations with a diameter of 500 Å, facing the epithelial cells, often covered by a thin basement membrane (Horstman 1966, Clementi and Palade 1969, Casley-Smith 1971). The arterial supply to this network is described by most authors as a non-branching arteriole lacking smooth muscles and connected to the capillaries at the villous tip (Heller 1872: man, dog, cat and rabbit; Mall 1888: dog; Nisioka 1927: cat; Spanner 1932: man, dog and cat; Jacobson and Noer 1952: man, dog and rabbit; Mohiuddin 1966: rat). In the cat the drainage from these capillaries occurs via veins in the villous base (Heller 1872, Nisioka 1927) although in man, dog and monkey there seem to be veins in the upper part of the villus (Heller 1872, Mall 1888, Jacobson and Noer 1952, Reynolds and Swan 1972), conveying the blood to the submucosal plexus.

A schematic illustration of this vascular anatomy is shown in Fig. 1. In plate A, B and C are seen sections of a cat's vasodilated jejunum, where the tissue is cleared according to Spalteholz (1888) after *in vivo* infusion of India ink into the superior mesenteric artery.

Nerve supply of the intestinal submucosal and mucosal blood vessels.

The arteries and arterioles in the wall of the small intestine are densely innervated by adrenergic nerve fibres while the venous vessels are most sparsely supplied (Norberg 1964, Jacobowitz 1965). Thus, the arterial vessels in the submucosa and in the mucosa, particularly in the layer between the muscularis mucosa and the base of the intestinal crypts have a rich innervation while the number of adrenergic nerves decreases progressively as the lumen is approached (Silva, Ross and Osborne 1971). Since the small arterial vessels supplying the villi soon lose their smooth muscles their constrictor fibre supply must be concentrated to the most proximal parts where they emerge in the deepest mucosa.

Cholinergic fibres around arteriolar vasculature are sparse but acetylcholinesterase staining fibres are numerous in the lamina propria in the villi (Jacobowitz 1965). The function of these latter fibres, however, is not clear.

Fig. 1. A schematic illustration of the vascular anatomy of a cat's jejunal mucosa. For details see text. Squares refer to roughly corresponding sections seen in plate A, B and C.

Plate A. The villous vascular bed of a cat's vasodilated jejunum. The ascending arterial vessel can be seen in the middle villus and the subepithelial capillary networks, with their numerous cross connections, are also visible.

Plate B. The vascular anatomy at the base of the villi in a cat's vasodilated jejunum. An ascending villous arterial vessel can be seen in the middle of the picture. The villous capillaries can be seen to collect into veins in the middle and lower part of the picture.

Plate C. The vascular anatomy at the mucosal crypts and the submucosa in a cat's vasodilated jejunum. Coarse vessels belonging to the submucosa are seen in the middle part of the picture. In the lower part vessels of muscularis proper and serosa are seen.

Plates A, B. and C. After *in vivo* infusion of India ink into the superior mesenteric artery at intestinal vasodilatation (isopropylnoradrenaline) the tissue was treated according to Spalteholz (1888), x 100-150. The discontinuity of some vessels is due to their running out of focus.

The plates are reproduced in collaboration with Drs Elof Eriksson and Rhagnar Myrhage, Laboratory of Experimental Biology / Chief: Professor P.-I. Brånemark / Department of Anatomy, University of Göteborg.

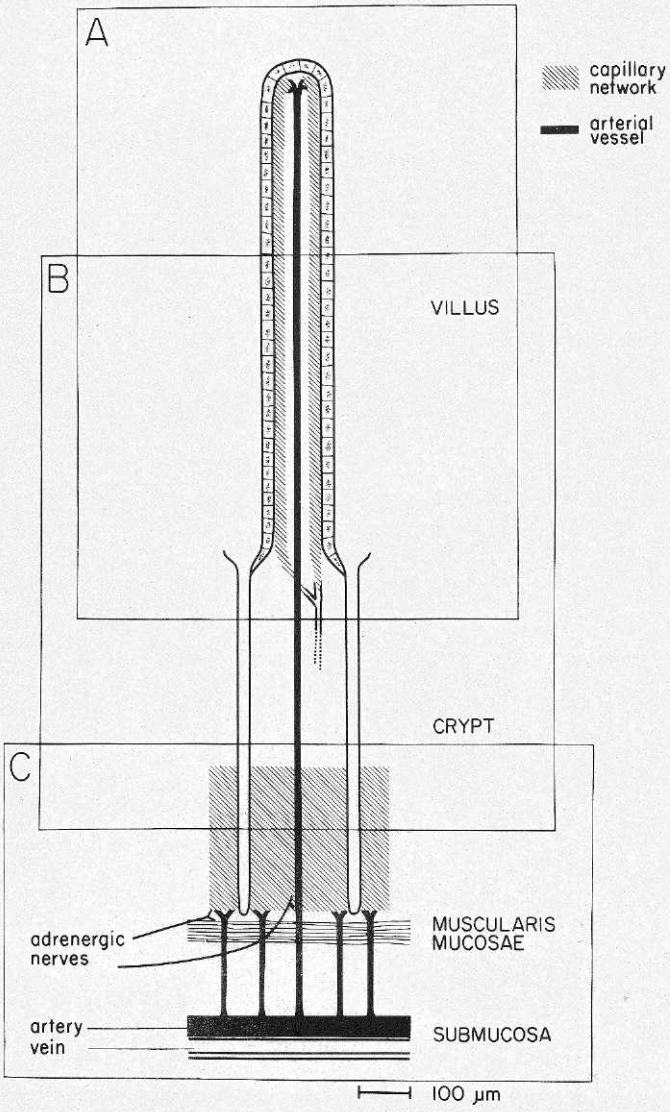
A
B
C
capillary network
arterial vessel
VILLUS
CRYPT
MUSCULARIS MUCOSAE
adrenergic nerves
artery
vein
SUBMUCOSA
100 µm

FIG. 1.

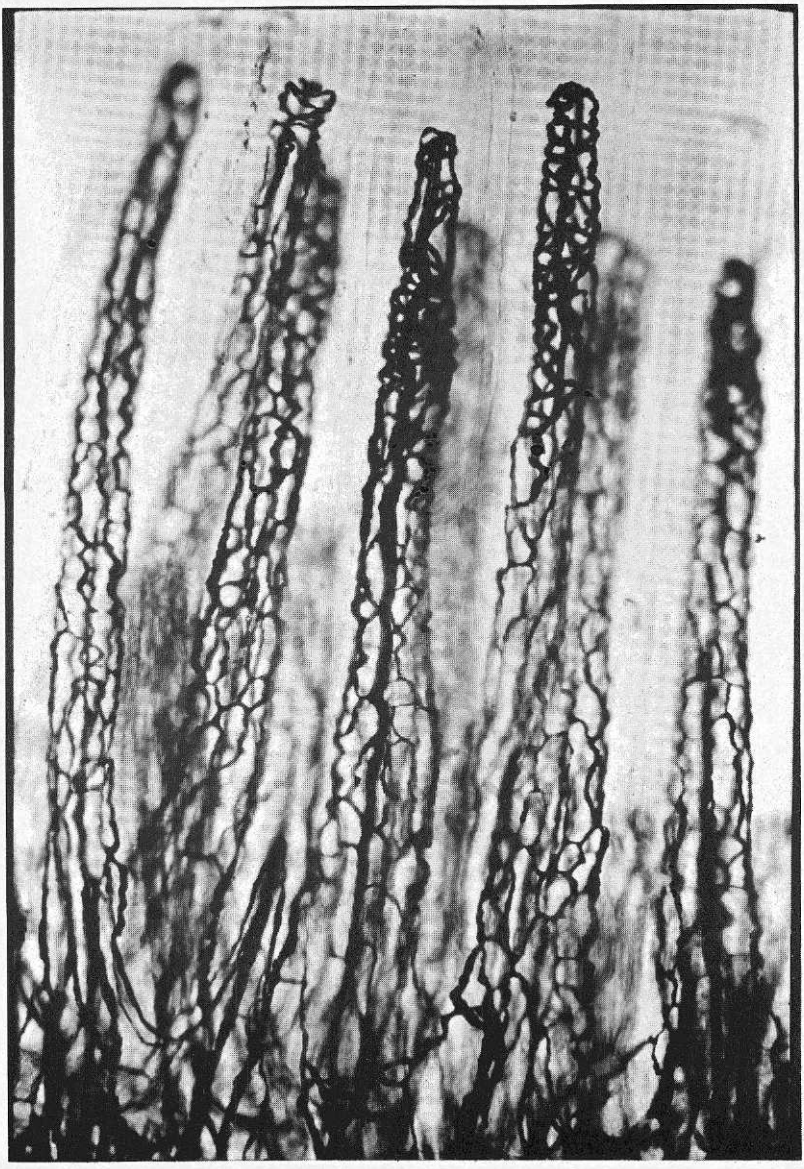

PLATE A.

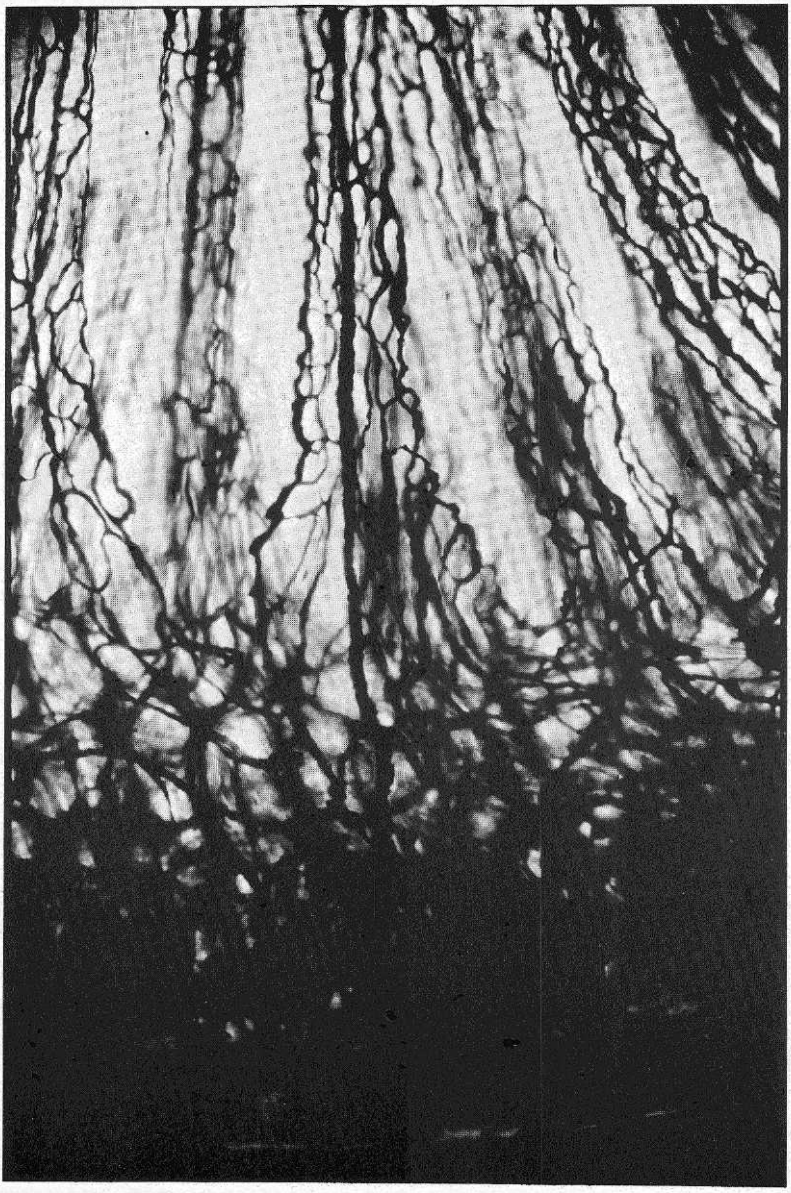

PLATE B.

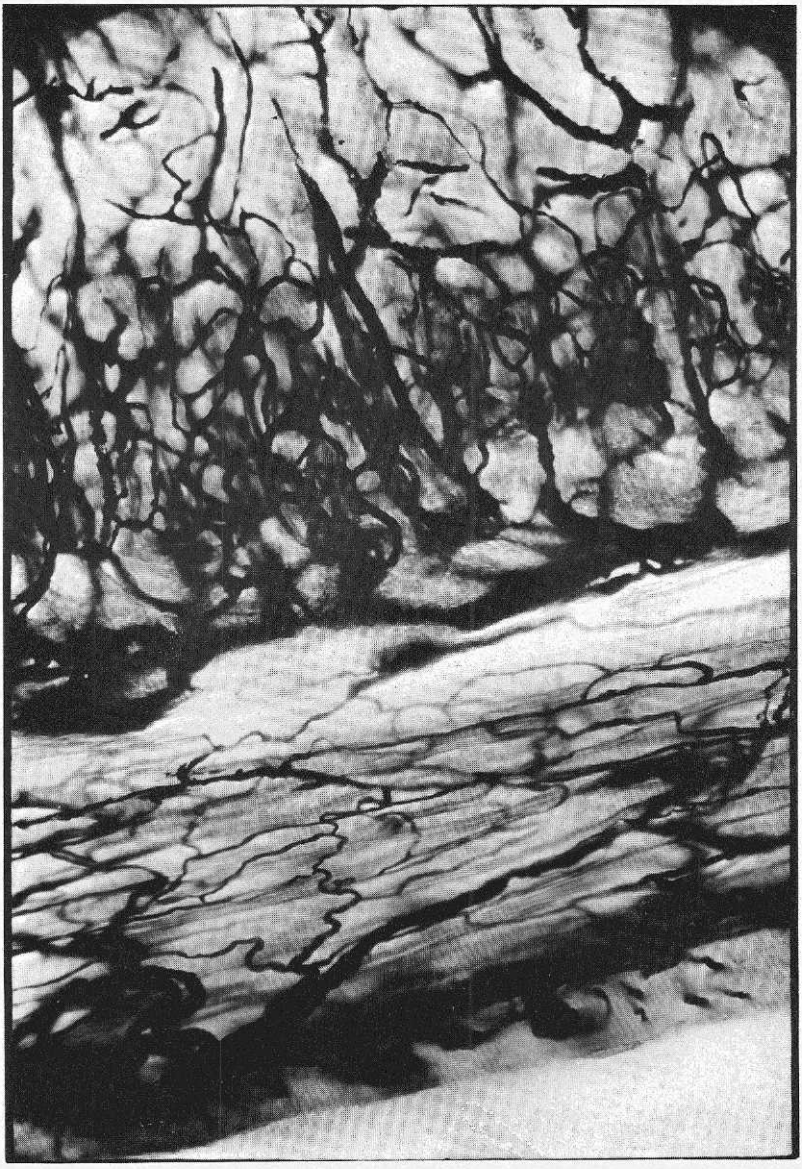

PLATE C.

GENERAL METHODOLOGY

Observations were carried out on 110 cats, anesthetized with chloralose i.v. (40-70 mg/kg b.w.) after ether induction. The cats had been deprived of food for at least 24 hours and had no obvious signs of intestinal infection. The isotope methods used for the blood circulation studies and the investigations on absorption are fully described in paper I and V, respectively, and will be discussed also in connection with the results (vide infra). A presentation of general procedures is given below.

Operative procedures

The operative procedures used were similar to those of previous studies of intestinal blood circulation (cf. Folkow, Lundgren and Wallentin 1963, Kampp, Lundgren and Sjöstrand 1968) and were, except for minor details, identical in studies I-VI.

The abdomen was opened in the midline and the greater omentum and the spleen were extirpated. The spleen was electrically stimulated to expell its blood before extirpation. A segment of the jejunum, weighing 10-30 g, was isolated and the remainder of the intestinal tract removed. The lumen of the jejunal segment was flushed with bodywarm saline or Tyrode's solution until the effluent was clear. The mesenteric vein, which in a preparation like this drains all the blood from the intestinal segment and its lymph nodes was cannulated after heparinisation and connected to a drop recorder unit operating an ordinate writer. The blood was returned to the animal via a funnel connected to the jugular vein. Venous outflow pressure was set at a "control" level of about 10 mm Hg by adjusting the height of the tube draining the drop recorder. Mean arterial blood pressure was recorded from the left femoral artery by a Statham pressure transducer. Small branches of the superior mesenteric artery were cannulated to permit close arterial injections or infusions to the intestinal preparation, or for registration of the arterial inflow pressure to the small intestine.

The prevailing influence of the autonomic nervous system was eliminated by giving atropine i.v. (1-1.5 mg/kg b.w.), cutting the splanchnic nerves bilaterally and by denervating the left adrenal gland and by exclusion of the right one from the circulation by ligatures.

Bleeding was carefully avoided during the operative procedures and, if occurring, substitution was performed by i.v infusions of bodywarm Dextran-Tyrode solution.

During radioactive measurements, the intestinal segments were placed outside the abdomen on a lead plate covered with gauze soaked

by bodywarm saline and in turn covered by plastic film. The temperature of the intestinal tissue was continuously controlled with a thermocouple thermometer placed in the lumen or on the serosa of the gut.

To induce graded vasodilatations in the intestinal segment a constant i.a. infusion of isopropylnoradrenaline was made via a thin catheter in a small branch of the superior mesenteric artery. Arterial inflow pressure to the intestinal segment, which could be reduced by means of an adjustable clamp around the superior mesenteric artery, was registered from a small branch to this artery. Venous outflow pressure in the intestinal segment could be changed from the "control" level of about 10 mm Hg by adjusting the height of the tube draining the drop recorder. Electrical stimulation of the regional sympathetic nerves were performed via a bipolar, silver electrode mounted on the peripheral ends of the divided nerve fibres surrounding the superior mesenteric artery.

At the end of each experiment the weight of the intestinal preparation was determined for calculations of blood flow and absorption rate per unit tissue weight.

Protection from radioactivity

The handling of the concentrated radioactive solutions was carried out manually behind a lead glass window. When ^{32}P and ^{198}Au were used, rubber gloves (material thickness 0.5 mm) were worn. During experiments, recorded background radioactivity was kept low by covering syringes and reservoirs containing radioactive tracer solutions with lead plates. All personel continuously working with these radioactive experiments were wearing individual dosimeter plates.

BLOOD CIRCULATION IN THE SMALL INTESTINAL MUCOSA

The parallel-coupled vascular circuits in the wall of the small intestine have been studied by means of various "accumulation techniques", in most investigations by means of diffusible tracers (for ref. see paper I). However, these methods do not give any reliable flow values for the mucosal circulation, and particularly not for the villous circulation, since the i.a. administered diffusible tracers will partly be excluded from the villi due to the mucosal countercurrent exchanger (Lundgren 1967, Kampp, Lundgren and Sjöstrand 1968). An indicator-dilution method, which is not influenced by the mucosal countercurrent exchange, was therefore developed for a quantitative and separate study of the villous circulation and also of the entire mucosal circulation. The theoretical background and the experimental procedures for this method were described in paper I. A short presentation of the method and some methodological aspects are given below.

Methodological considerations

The present method was developed to allow quantitative estimations of the mucosal circulation and, particularly, of the villous circulation, which are of prime importance for intestinal function with respect to absorption and secretion. To circumvent the mucosal blood countercurrent exchanger, tracers confined to the intravascular compartment were used. For this purpose radioactively labelled blood cells and plasma particles were introduced into the circulation.

a. Experimental procedures

The technique involves a slug injection of a known amount of blood or plasma, labelled with the β-emitting tracers ^{32}P or ^{198}Au, administered into the superior mesenteric artery and detected by means of sensing devices placed in the gut lumen in close approximation to the villi. Thus, the intravascular transit of the tracer particles were registered by means of cylindrical detectors with their sensitive surface in close mucosal contact. Since the tissue volume monitored by the detector depends on the energy level of the β-radiation, the ^{32}P-labelled red cells and plasma colloids were monitored largely from the entire mucosa, while ^{198}Au-labelled plasma particles were registered essentially only from the villi (I). The total blood supply to the intestinal segment studied was estimated from a continuous registration of the venous outflow.

The appearance of the tracer in the mucosal vascular compart-

ments after a slug injection was recorded as an indicator-dilution curve which was then used for calculating mucosal blood circulation parameters. The possibilities of measuring regional blood flow, blood volume and mean transit time from these curves will be discussed below. It should be pointed out that what is actually measured in the present series of experiments (I-IV) are the flow, regional volume and mean transit time for red cells, when using them as tracer vehicles, and the same parameters for plasma, when using colloid tracer particles.

b. Estimation of regional blood flow

When the amount of tracer and the blood flow in the "injection" artery are known the blood flow in the tissue region monitored by the detector can be estimated from the maximal height of the recorded indicator-dilution curve provided certain conditions are met (paper I). These conditions include even distribution of the injected tracer within the monitored tissue volume when the curve reaches its maximal height. If this is the case, the measured tracer concentration will be proportional to the blood flow in that region. When using ^{198}Au for determination of "villous" blood flow there are good reasons to believe that this assumption is justified since the villous capillaries are arranged as a dense plexus. Also when using ^{32}P for determinations of "mucosal" blood flow, the curve maximum probably represents a situation where the tracer particles are fairly evenly distributed within capillaries since most of the afferent and efferent vessels are in fact more deeply situated and therefore, generally speaking, recorded with a lower efficiency than the capillaries. However, the intravascular compartment is probably unevenly distributed within the monitored volume in the ^{32}P experiments (I). Attempts to verify experimentally these inherent assumptions of the present technique were presented in paper I, to which the reader is referred for details.

c. Estimation of regional blood volume

1. "Perfused volume": If the amount of injected tracer and the flow in the "injection artery" are known the blood volume in the monitored tissue region can be estimated from the area under the curve under certain conditions (paper I). These conditions include an even distribution of tracer in the intravascular volume being monitored and also good mixing between tracer and blood.

if the injected bolus is incompletely mixed with the blood, this will mean that the population of pathways used by the tracer particles will not be representative for the blood flow distribution. However, if

the mixing is incomplete in a randomized way such an error will be largely eliminated when repeated injections are performed (cf. the theoretical situation of repeated injections of only one tracer particle). It was shown experimentally (1) that a fairly good mixing occurred between tracer and blood and since repeated injections were made there are reasons to believe that the regional blood and plasma volumes are accurately measured, both when using ^{198}Au- and ^{32}P-labelled blood. When ^{198}Au is used a recirculation of blood (and tracer) particles in a mesh of the capillary network of the villi may, however, add to the measured volume which is not the case when the volume is estimated as described below (see 2). Further, the plasma or red cell volume, measured with the slug injection technique, includes only those vessels which were open for perfusion at the time for injection. It was therefore named "perfused" regional red cell or plasma volume.

2. "Total equilibrated volume": Another way to estimate the regional blood volume is to let tracer particles equilibrate in the circulating blood and then compare the tracer concentration in the blood with that of the tissue. If the time for equilibration is sufficiently long the volume thus estimated will also include the content of vessels that are intermittenly closed and was therefore named "total equilibrated volume". This technique could only be used for labelled red cells since the colloid particles if present in the blood for longer periods are in part trapped by reticulo-endothelial cells in the monitored tissue.

d. Estimation of mean transit time and linear flow rate.

From the known relationship between flow, volume and mean transit time it is evident that the mean transit time in this case can be calculated as the area of the indicator-dilution curve divided by its maximal height. This value is not dependent of a perfect mixing between tracer and blood. When using ^{198}Au-labelled plasma particles, their passage along the central arterial vessel of the villi adds very little to the transit time since the blood volume of the subepithelial capillary network is some 10 times larger than that of the central artery. Knowing the height of the villi the average flow rate in the villous capillaries can be calculated. If some recirculation occurs in the mesh of the villous capillary network, this will influence the curve area but probably not the curve height and will therefore be measured as a slower transit. Thus it is mainly the linear flow rate from villous tip to base that will be estimated.

Using ^{32}P as the tracer the transit time in capillaries will probably dominate but transit in venous vessels will also to a certain extent influence the curve.

Results

The mucosal blood circulation of the small intestine was studied in animals deprived of food for 24 h and after acute intestinal denervation, during "resting" conditions (II), during hyperemia (II), during reduced perfusion pressure (III) and during direct stimulation of the regional sympathetic nerves (IV).

Regional flow and volume are expressed per unit regional tissue weight, below and in Table 1. Mucosal weight constitutes 45 per cent of the total intestinal weight (Jodal and Lundgren 1970 b) and villi about 15 per cent as estimated in the present studies (I). Villous blood flow was calculated from the plasma flow passing through the villi, as monitored by the ^{198}Au - labelled plasma particles (I). All parameters measured with this tracer are therefor designed "villous". On the other hand, ^{32}P - labelled blood particles were "seen" by the detector largely throughout the mucosa and all parameters estimated with this tracer are therefor denoted "mucosal".

a. Volume flow of blood.

The total blood flow of the intestinal segment with its mesentery and lymph nodes was 15-30 ml/min x 100 g during "resting" conditions, a value somewhat lower than that earlier reported for the fasting cat (Lundgren 1967). This discrepancy is probably due to the fact that shorter intestinal segments were used in the present experiments, implying that lymph nodes, with their somewhat lower blood flow, constituted a higher weight fraction.

The "mucosal" blood flow was 20-25 ml/min x 100 g mucosa at "rest", i.e. it almost equals the total blood flow per unit weight intestinal tissue. The "villous" plasma flow during "resting" conditions varied between 10 and 25 ml/min x 100 g, a comparatively large variation, possibly explained by the villous arterioles being highly sensitive to metabolic factors (see below). Assuming a villous hematocrit of only 60 per cent of the arterial one (Jodal and Lundgren 1970a) and a similar linear flow rate for red cells and plasma in the villous capillary network, the villous blood flow can be calculated to 15-30 ml/min x 100 g villous tissue. Since the weight of the villi amounts to about 15 per cent of the total intestinal weight, 10-20 per cent of the "resting" intestinal blood flow was distributed to the villi.

During close i.a. infusions of isopropylnoradrenaline (II) the

total intestinal blood flow was increased maximally to about 200 ml/min x 100 g. The "mucosal" blood flow during the same conditions amounted to 175-200 ml/min x 100 g. The "villous" plasma flow increased relatively more than the total intestinal blood flow, corresponding to a "villous" blood flow of 300-400 ml/min x 100 g which in this situation constitutes 30-35 per cent of the total intestinal blood flow.

During graded reductions of the arterial inflow pressure (III) the total intestinal blood flow was reduced relatively less than the perfusion pressure, illustrating the wellknown autoregulation of intestinal blood flow (e.g. Johnson 1964). During these conditions, the "mucosal" blood flow behaved like the total intestinal blood flow, while the "villous" blood flow exhibited the most pronounced autoregulation, remaining almost unaltered down to pressure levels around 30 mm Hg. As arterial inflow pressure was lowered an increasing fraction of the intestinal blood supply was therefore distributed to the villi, increasing from 10-20 to 30-35 per cent at the lowest perfusion pressures.

As venous outflow pressure was raised the total intestinal blood flow was reduced out of proportion to the perfusion pressure decrease due to a rise of the regional flow resistance. This response, ascribed to a constriction of arteriolar vessels, has repeatedly been described and named the "venous-arteriolar response" (see Johnson 1964). When venous outflow pressure was raised from 10 to about 25 mm Hg "mucosal" as well as "villous" blood flow seemed to be reduced somewhat less than the total intestinal blood flow.

Stimulation of the regional sympathetic nerves induced a characteristic change of the total intestinal blood flow (Folkow et al. 1964, Wallentin 1966; for further ref. see Shanbour and Jacobson 1971). First a strong but transient reduction occurs, which, however, partly disappears after 1-2 min despite continued stimulation ("autoregulatory escape from vasoconstrictor fibre influence") after which flow stabilized somewhat below control ("steady state phase"). When stimulation is stopped a transient hyperemia exceeding prestimulatory control occurs.

Both "mucosal" and "villous" flow showed an initial strong reduction upon vasoconstrictor fibre stimulation. During the "steady state phase" the "mucosal" blood flow had returned towards control while the "villous" blood flow exceeded control in face of a reduced overall intestinal flow. Thus, a considerable redistribution of the intestinal blood flow had evidently occurred during the "steady state phase", villous blood flow being increased while flow in some deeper part, probably around the crypts, had decreased. This becomes clear

if one subtracts villous blood flow from that of the total mucosa in the "steady state phase" of neurogenic vasoconstriction, and is also supported by the observation that the "mucosal" but not the "villous" vessels exhibited a poststimulatory hyperemia.

b. Blood content.

The "resting" blood content in the mucosa, as estimated from the total red cell content and the hematocrit in the perfused "mucosal" vessels, amounted to 4.0-4.5 ml/100 g but only 2.5-3.5 ml/100 g of this volume was constituted by perfused vessels in this situation. The plasma volume within the perfused "villous" vessels amounted to 1.0-2.0 ml, or 1.5-3.0 ml of blood, per 100 g villous tissue. During intense hyperemia, induced by isopropylnoradrenaline, the "mucosal" blood content increased to 5.0-6.0 ml/100 g and the "perfused mucosal" to at least 4.5-5.0 ml/100 g. Concomitantly, the "villous" capillaries increased their plasma content to 3.5-4.0 ml, or to 4.5-5.0 ml of blood, per 100 g villous tissue. It can be calculated that this would correspond to a situation, where capillaries cover roughly one third of the inner surface of the villous epithelial cells.

During reductions of the arterial inflow pressure, "mucosal" blood content increased slightly and a larger portion of the mucosa was now steadily perfused. Thus, at an arterial pressure of 30 mm Hg the perfused blood volume amounted to about 4.0 ml/100 g mucosa, while the volume of perfused "villous" capillaries was almost doubled compared to rest, i.e. 3.5-4.5 ml of blood per 100 g villous tissue.

When raising venous outflow pressure to 25 mm Hg, a prominent increase of "mucosal" red cell content was seen, probably reflecting distended veins in deeper parts. The volume of perfused "mucosal" vessels increased to only a small extent and that of perfused "villous" capillaries was hardly affected.

During sympathetic stimulation both the total and perfused mucosal blood volumes were initially reduced but increased during the "steady state phase", the perfused "mucosal" blood volume being then 3.5-4.0 ml/100 g, i.e. distinctly larger than "resting" control. Concomitantly the blood volume, within the perfused "villous" capillaries was increased roughly 50 per cent.

c. Linear flow rates.

The average linear flow rates can be estimated from the mean transit time ($t_{A/h}$) if the length of the vascular pathways is known. The average linear rate of plasma flow in the "villous" capillaries was calculated in absolute figures, assuming a villous length of 0.7 mm,

TABLE 1

	BLOOD FLOW, ml/min x 100 g			Fraction blood flow to villi, per cent	BLOOD VOLUME, ml/100 g			Linear flow rate in villi mm/s
	Total "intestinal"	"Mucosal"	"Villous"		Total "mucosal"	Perfused "mucosal"	Perfused "villous"	
"RESTING" BLOOD FLOW	15-30	20-25	15-30	10-20	4.0-4.5	2.5-3.5	1.5-3.0	0.10-0.15
HYPEREMIA (isopropylnoradrenaline)	200	175-200	300-400	30-35	5.0-6.0	4.5-5.0	4.5-5.0	0.70
REDUCED ARTERIAL INFLOW PRESSURE (30 mm Hg)	7-8	8-10	11-17	30-35	4.5-5.0	3.5-4.5	3.5-4.5	0.03-0.05
RAISED VENOUS OUTFLOW PRESSURE (25 mm Hg)	10-15	14-16	10-15	13-17	4.5-5.5	3.5-4.0	1.5-3.0	0.06-0.08
SYMPATHETIC STIMULATION (8 Hz)	15-20	20-25	23-27	17-27	4.0-4.5	3.5-4.0	2.0-3.0	0.15-0.20

while that of the entire mucosa was determined only in relative terms.

During "rest" the average linear rate of "villous" plasma flow amounted to 0.10-0.15 mm/sec at a volume flow of blood corresponding to 15-30 ml/min x 100 g villous tissue. The linear flow rate increased to 0.70-0.80 mm/sec during intense hyperemia in which situation the villous blood flow was some 3-400 ml and total intestinal blood flow some 200 ml/min x 100 g. Concomitantly the red cell and plasma linear flow rates in the mucosa were increased about five times. Red cell transit was faster than that of plasma, probably reflecting the axial streaming of blood cells. During arterial pressure reduction these mean transit times were reduced to 1/3 - 1/4 of control at pressures around 30 mm Hg, while the average linear rates of villous plasma flow was then only 0.03-0.05 mm/sec. Upon increases of venous outflow pressure, red cell and plasma flow rates in the mucosa were considerably reduced while that of the villi was less affected.

During the initial phase of vasoconstrictor fibre stimulation linear flow rates were markedly reduced in both the mucosa and in the villous capillaries, while neither of them differed significantly from control in the "steady state phase".

Discussion

Mucosal blood circulation in the small intestine has been studied by several authors using different "tracer accumulation techniques" (for ref. see paper I and II). The present studies were performed with a new technique allowing a differentiation of the circulation in the intestinal villi as compared with that of the entire mucosa, thus including both villi and the tissue surrounding the crypts. The use of this method is, however, restricted to studies on animals in which intestinal motility is largely eliminated, implying that the influence of motility on mucosal hemodynamics cannot be studied in this way. However, intestinal motility, as induced by vagal stimulation at the "physiological" range of frequencies, hardly at all affects either total intestinal blood flow (Kewenter 1965) or intestinal capillary filtration coefficient (Lundgren, personal communication).

Every vascular bed consists of a number of specialized series-coupled sections, i.e. resistance vessels, exchange vessels and capacitance vessels (see e.g. Mellander 1960, Folkow 1967). Plethysmographic and gravimetric techniques have made it possible to study reactions within these vascular sections also in the small intestine

(e.g. Johnson and Hansson 1962, Folkow et al. 1963). However, no attempts have then been made to study separately e.g. the mucosal vessels from this particular point of view. The indicator-dilution technique makes it possible to follow separately the reactions of the mucosal resistance and capacitance vessels, and also those affecting the exchange vessels, and the results will be discussed along these concepts.

The resistance function within the villous and mucosal circuits is reflected in the flow values obtained with ^{198}Au- and ^{32}P-labelled blood particles, respectively. When comparing the present mucosal flow values with those of earlier investigations, the present ones are usually higher. This difference is probably explained mainly by the partial exclusion of diffusible tracers from parts of the mucosa due to their shortcircuiting in the intestinal countercurrent exchanger (Lundgren 1967, Kampp, Lundgren and Sjöstrand 1968), a drawback not involved when intravascular tracers are used. Thus, Grim and Lindseth (1958), utilizing labelled microspheres, found that 50 per cent of injected spheres (diameter 20 μm) were trapped in the mucosa during resting blood flow conditions, reflecting a blood flow distribution similar to that of the present studies where about 45 % of the flow was diverted to the mucosa.

A comparison of the results obtained with the two tracers used suggests that the mucosal blood flow is inhomogenous, the "villous" blood flow being considerably higher during maximal dilatation than the average one of entire mucosal section. Hence, its deeper parts must contain a less well-perfused section. However, it appears that another extremely well-vascularized area exists in deeper parts, probably associated with cell renewal and secretion at the base of the crypts (Lundgren 1967).

The present study clearly indicates that the "villous" resistance vessels exhibit an extraordinary high "resting" tone since villous plasma flow could be increased almost 15 times (from 20 to 275 ml/min x 100 g) by vasodilator drugs, implying maximal blood flow values around 400 ml/min x 100 g of villous tissue. Total "mucosal" blood flow, on the other hand, could only be increased 8 times above "resting" level (from 25 to 180 ml/min x 100 g). The supplying arteries to the villi and to the remaining mucosal parts are identical up to the submucosal level. Therefore, the mentioned differentiated control of the "villous" circulation must be localized to those sections of the ascending villous vessels which pass between the crypts, since they lose their smooth muscle coat when entering the villi.

Further, villous blood vessels seem to be highly sensitive to

local metabolic factors. This was clear from the pronounced autoregulatory capacity of the villous vessels following reductions in arterial pressure. In fact, lowering perfusion pressure from 100 to below 30 mm Hg did not significantly decrease villous plasma flow (III). This observation may in part be due to "myogenic" factors, i.e. the modulating effects of transmural pressure on inherent vascular smooth muscle activity (Folkow 1964). Since, however, an elevated venous pressure reduced villous blood flow in direct proportion to the reduced perfusion pressure without clear signs of any villous vasoconstrictor response, it appears that metabolic factors are dominant in the control of villous blood supply.

The dominance of local factors in villous blood flow regulation may also be corroborated by the regional response to sympathetic discharge. Thus, the initial resistance increase in the villous vascular bed was overridden within 1-2 min by antagonistic factors that may well be metabolic in origin.

By comparing the "villous" vascular reactions with those of the entire mucosa the vascular reactions in deeper mucosal layers could be studied indirectly. The "resting" (basal) vascular tone seemed to be less pronounced in these deeper resistance vessels than in the "villous" ones to judge from the effect of vasodilator durgs. Further, this vascular region showed a less pronounced autoregulation to pressure changes than the villous vessels and prolonged constrictor fibre stimulation caused a more sustained reduction of blood flow. It is difficult to assess the response of the crypt circulation to an increased venous outflow pressure but there may well have been a certain reduction of blood flow. Thus, these vessels seem to be more affected by nervous influences than the villous vessels and may possibly also be more sensitive to transmural pressure changes.

The capacitance function, reflected in the measured blood content of the mucosa, was estimated from the total red cell volume when using the equilibration method. The volume values obtained by the slug injection technique reflected the capacitance changes only in the perfused vessels, and varied probably more due to opening up or closure of capillary and small vein sections as regulated by e.g. arteriolar or sphincter activity.

The mucosal blood content, as calculated from "total" red cell volume and the regional hematocrit estimated with the "slug injection" technique (II), ranged between 4 and 5 ml/100 g mucosa during "rest" and increased to about 6 ml/100 g during hyperemia or when venous outflow pressure was raised from 10 to about 25 mm Hg. Thus, the maximal "mucosal" change of total intestinal blood volume was only

about 1 ml/100 g, which should be contrasted to the values obtained when studying an entire intestinal segment including its mesentery. Thus, Wallentin (1967) found that the "resting" blood content in the intestine and its mesentery could be either increased or decreased about 3 ml/100 g intestine. The observed difference reflects the fact that a considerable part of the total intestinal blood volume is actually confined to the mesenteric veins.

The precapillary "sphincter" function of the intestinal vascular bed was indirectly reflected in the present measurements of the perfused "villous" plasma (blood) volume and also in the difference between perfused and total "mucosal" blood volumes (II). The basis for considering the perfused "villous" plasma volume as an indirect measure of precapillary "sphincter" activity is that the villous vascular bed consists almost exclusively of capillaries (cf. Fig. 1) implying that this plasma volume would estimate the number of perfused capillaries. If so, the present experiments suggest that only 30-40 per cent of the villous capillaries are simultaneously open to flow during "resting" conditions, while vasodilator drugs or a reduced arterial inflow pressure leads to an opening of almost all the capillaries to flow. During the steady state phase of sympathetic stimulation the fraction of perfused villous capillaries exceeded control slightly, while it was hardly affected by increases of venous pressure. Thus, the villous precapillary "sphincters" showed responses similar to the villous resistance vessels, both being e.g. highly sensitive to metabolic factors (see above). It is, in fact, likely that the resistance and precapillary functions of the villous vascular bed are anatomically overlapping and localized in the deeper part of the ascending arterioles where a smooth muscle coat is present. If so, a "sphincter" closure is likely to close off temporarily almost the entire flow of blood to a given villus.

Therefore, the present results suggest that the perfused volume in the villous tissue is largely proportional to the number of perfused villi, though it is possible that local rheological factors may also influence the flow within the villous capillary meshwork. The findings during direct mucosal inspection upon slug injections of plasma coloured by Evans blue corroborates the hypothesis of the villus being the smallest "unit of blood flow regulation", since well defined uncoloured spots were seen during rest but disappeared during maximal vasodilatation (I).

The precapillary "sphincter" activity within the mucosal circuit as a whole can be estimated from the difference between total and perfused red cell, or plasma, volume. This volume difference is pro-

bably explained by the presence of vessels, mainly capillaries, which are not perfused by blood at the time of the slug injection because of upstream closure of "sphincter sections". The precapillary sphincter function of the entire mucosa showed largely similar reactions as was described for the villi. Thus only about 50-60 per cent of the mucosal vascular bed appeared to be perfused during "rest", while all vessels could be opened up by e.g. vasodilator drugs. Similarily, when reducing the arterial blood pressure a compensatory sphincter relaxation was reflected as a reduced difference between total and perfused volumes. Further, a raised venous outflow pressure appeared to close some sphincters, while sympathetic stimulation during the "steady state phase" did not markedly alter the sphincter activity.

A possible functional arrangement of the mucosal vascular bed. According to classical studies on the mucosal vascular arrangement in the small intestine (see Morphological considerations) the capillary networks in the villi and around the crypts are supplied by separate arterial vessels from the level of the submucosa. The arterial vessels to the villi are non-branching arterioles ascending to the villous tips, losing their muscular coats already at the villous base. The major part of the adrenergic nerve endings in the mucosa are situated in the deeper part of the crypt region. Furthermore, from the present studies it seems probable that the arterial vessels supplying the villi are highly sensitive to metabolic factors while those supplying the crypts may be more sensitive to myogenic factors (see above).

Based on these two observations it is proposed that the arterial vessels, supplying the villi, are to a large extent controlled by the metabolic environment in the crypt region, i.e. far from the villous capillary network that is exposed to an environment widely varying in its composition due to the impact of the intestinal contents. The chemical environment of the crypt region is probably dependent mainly upon the metabolic activity in the secretory cells and in the region where cell renewal occurs. Assuming such an arrangement and assuming that the capillaries around the crypts are highly porous, one may explain the observations reported earlier, and in this study, concerning the reactions of the consecutive vascular sections during various experimental conditions.

Thus, the autoregulatory escape from vasoconstrictor fibre influence would be explained as follows. Initially both villous and crypt arteriolar vessels constrict. However, the accumulation of local chemical factors in the tissues surrounding the crypts eventually overrides the nervous effect on the villous arterioles, while those running

to the crypts remain constricted, thereby producing a local chemical environment that opens up the closely adjacent villous arterioles. Thus, blood flow is redistributed from the highly porous capillaries of the crypts proper to the villi, explaining the reduced capillary filtration coefficient (CFC) observed during these conditions (Folkow et al. 1964 a,b)

An increase of the venous outflow pressure constricts predominantly the arteriolar vessels supplying the crypts due to their response to an increased distending pressure. Metabolites then accumulating in the crypt tissues tend to antagonize a possible constriction of the villous arterioles that seem to be especially sensitive to metabolic influences. Thus, blood flow is redistributed from the highly porous crypt capillaries to the villi in a similar way as during neurogenic vasoconstriction. A marked reduction of intestinal CFC upon venous pressure increases has also been reported by Johnson (1964).

Upon marked reductions in arterial pressure an accumulation of metabolites in the crypt region will dilate the villous arterial vessel and to such an extent that villous blood flow stays largely constant despite the lowered perfusion pressure. Most "villous" precapillary "sphincters" open up as reflected in the markedly increased perfused "villous" plasma volume (III). Concomitantly, intestinal CFC increased 50 per cent above control (Haglund and Lundgren 1972). If "villous" plasma volume is augmented to the same extent by i.a. infusions of isopropylnoradrenaline, a 4-6-fold increase of CFC is observed (Folkow, Lundgren and Wallentin 1963). According to the present hypothesis these observations are explained by the fact that the drug causes vasodilatation in all intestinal wall layers, including the crypt vascular circuit with its highly porous capillaries while these are opened up to a far less extent during arterial hypotension.

PASSIVE ABSORPTION IN THE SMALL INTESTINE DURING DIFFERENT BLOOD FLOW CONDITIONS IN THE MUCOSA

The relationship between total intestinal blood flow and rate of intestinal absorption has been studied by several authors. Thus, the absorption of basic nutrients like glucose and amino-acids was found to be dependent on intestinal blood flow though primarily because of its importance for the metabolism of the actively absorbing cells (for ref. see paper V). The absorption of water, as well as of a number of pharmacological substances and different gases, has also been studied with respect to blood flow dependence. However, in all these studies changes of total intestinal blood flow were induced without knowing how exactly the experimental procedures affected the blood flow in the superficial mucosal layers where absorption takes place. Since the villous tissue constitutes only about 15 per cent of the small intestinal intramural tissue weight, it seems probable that large variations of blood flow may occur in this tissue compartment without being reflected as corresponding changes of the total intestinal blood flow. This conclusion is corroborated by observations described in the preceding chapter, clearly showing that the villous blood circulation does not necessarily vary in direct proportion to changes of total intestinal blood flow.

Knowing the hemodynamic characteristics of the mucosal vascular bed from the presently described studies, it was regarded of interest to study in the first hand the passive absorption from the intestinal lumen in an attempt to clarify the relationship between this absorption and the blood flow rate. As regards this relationship, Winne (1967, 1971 b) has outlined a theory for the movement of substances from the lumen of the small intestine to the intestinal blood stream, using theoretical models with two to four compartments. However, these theoretical models seem to be based on simplified conditions where e.g. the countercurrent exchange between ascending and descending vessels of the mucosa are not taken into account.

In the present investigations absorption is measured as the appearance of a test substance in the venous blood draining the small intestine. Thus, the absorption is here discussed with reference to a system made up of two compartments (lumen and blood) though interposed by an unknown number of not defined compartments. With respect to hemodynamic changes, countercurrent exchange, plasma skimming, etc., the mucosa is in fact so complex as to hardly allow at present the construction of any detailed model for the passive absorption from the lumen.

An easily diffusible, lipid soluble gas, ^{85}Kr, was chosen as the

test substance since it is metabolically inert and largely excluded from the circulation after a single pulmonary passage, keeping the arterial concentration virtually at zero. Furthermore, ^{85}Kr has been shown to be extravascularly shunted in the mucosal countercurrent exchanger after intra-arterial administration (see Lundgren 1967), a mechanism that has been proposed to delay net absorption of easily diffusible solutes.

Methodological considerations

The primary interest in these studies was to investigate the correlation between mucosal blood circulation and rate of absorption. In the experimental technique used, attempts were therefore made to eliminate other factors of importance for absorption. For this purpose saline containing ^{85}Kr, an inert and rapidly diffusible radioactive isotope, was perfused through the lumen of a gut segment at a rate high enough to largely eliminate intraluminal concentration differences. The absorbed tracer amount was estimated from its appearance in the intestinal venous blood, as continuously measured with a well type scintillation counter. The recorded radioactivity gave a direct measure of the amount absorbed since the tracer concentration in the arterial blood was negligible, ^{85}Kr being largely excluded from the circulation after a single pulmonary passage. Since the mesentery with its vessels was covered with Mylar® (Du Pont) this prevented significant diffusion losses of the tracer, as was also checked in control experiments.

The absorption rate could then be calculated as the product of the venous outflow and its tracer concentration and could be directly compared to the tracer concentration in the luminal perfusate. In analogy with the clearance concept in the kidney, it is possible to calculate the amount of intraluminal fluid that per unit time is "cleared" of the tracer. However, since the primary interest was to relate the rate of absorption to the blood flow it appeared more useful to express the absorptive capacity in terms of the volume of intestinal blood that per unit time was fully equilibrated with the luminal contents. Knowing the partition coefficient for ^{85}Kr between saline and blood the mentioned absorptive capacity could easily be estimated from the measured parameters.

To study the distribution volume in the intestinal wall of an easily diffusible substance during absorption, an autoradiographic study was performed using another tracer, antipyrine-N-methyl-^{14}C. ^{85}Kr was not suitable for this part of the study because of its comparatively high energy β-radiation and the difficulties inherent in avoiding its evaporation from thin tissue slices. The localisation of the tracer in

the intestinal wall, as indicated by the blackness of the autoradiographs, was determined by simultaneous microscopical examination of the histological sections and the corresponding autoradiographs.

Results

The absorption of ^{85}Kr from the lumen of the small intestine was studied during "resting" blood flow, during hyperemia (V), during reduced arterial inflow pressure, during raised venous outflow pressure and during the influence of vasoconstrictor fibre activity (VI).

"Resting" blood circulation. At a total intestinal blood flow of 25 ml/min x 100 g about 4-5 ml of blood per min and 100 g intestine was fully equilibrated with the luminal contents, i.e. about 17 per cent of the intramural blood flow was fully equilibrated with the luminal ^{85}Kr concentration. Autoradiographic studies showed that an easily diffusible lipid soluble substance, when introduced from the lumen during the present experimental conditions, becomes spread throughout the entire mucosal tissue layer, which during "rest" is supplied with about 45 per cent of the total intramural blood flow, while the concomitant part to the villi is about 15-20 per cent.

Hyperemia. During infusion of isopropylnoradrenaline in a dose that produces a moderate intestinal hyperemia, about 100 ml/min x 100 g, the amount of absorbed ^{85}Kr was increased to about 13 ml/min x 100 g, while the fraction of intestinal blood flow that was fully equilibrated with the intestinal contents decreased to about 12 per cent. Thus, the absorption rate increased proportionally less than the intestinal blood flow. Autoradiographic studies demonstrated that the distribution volume for an absorbed lipid soluble substance was during hyperemia confined only to the villi. At these levels of total intestinal blood flow 30-35 per cent is distributed to the villous capillaries (II).

Reduced arterial inflow pressure. When the arterial inflow pressure was reduced, the absorption rate showed a reduction in proportion to the decreased total intestinal blood flow. Thus, at an arterial pressure of 25-30 mm Hg and a venous outflow of 5 ml/min x 100 g the absorption rate was only 0.9 ml/min x 100 g. Concomitantly, the fraction of intramural blood flow that was fully equilibrated with the luminal contents showed a slight reduction as compared to "rest", probably due to some tracer diffusion from the venous blood to the surrounding air. The autoradiographic experiments demonstrated a distribution volume, which included the entire mucosa as during "resting" flow. During this conditions the mucosal blood flow constitutes about 50 per cent and the "villous" blood flow about 30-35 per cent of total

intestinal blood flow (III).

Raised venous outflow pressure. During increases of venous outflow pressure the absorption rate showed a similar relationship to total intestinal blood flow as that observed upon reduction of the arterial pressure. Thus, at a venous outflow pressure of about 25 mm Hg and a venous outflow of 14 ml/min x 100 g the absorption rate was about 2.2 ml/min x 100 g corresponding to a fraction of intramural blood flow fully equilibrated with the luminal contents about 15 per cent. During these conditions the distribution volume included the entire mucosa The fraction of intramural blood flow that passes through the villous capillaries is then slightly increased compared to rest (III)

Stimulation of regional sympathetic nerves. During the "steady state phase" of sympathetic nerve stimulation the absorption rate was similar to prestimulatory control despite a moderate reduction of venous outflow. The fraction of the intraluminal blood flow fully equilibrated with the luminal contents increased during the same conditions to about 22 per cent. The autoradiographic studies showed that the tracer was distributed within the entire mucosa. The fraction of intramural blood flow that passes through the entire mucosa then shows a slight increase while the fraction of flow diverted to the villous capillaries during nerve stimulation is considerably increased compared to "rest" (IV).

Discussion

In this series of experiments it was shown that the absorption rate of ^{85}Kr from the small intestine could be markedly changed by altering its total blood supply. However, the absorption rate was during "resting" blood flow conditions lower than what could be expected from the concomitant mucosal blood supply. Intestinal hyperemia, as induced by isopropylnoradrenaline, increased the absorption rate compared to control, while a raised venous outflow pressure or a reduced arterial inflow pressure decreased the rate of absorption. Increased activity in the regional sympathetic nerves, on the other hand, did not markedly affect the absorption rate, despite a concomitant reduction of total intestinal blood flow.

Generally speaking, earlier reports in the literature concerning the absorption of easily diffusible solutes are in agreement with the present findings. Grim, Lee and Visscher (1955) reported that only 5 per cent of the small intestinal blood flow became fully equilibrated with D_2O placed in the lumen of the gut in a dog. The concomitant

tracer concentration in the mucosa was 25 per cent of the luminal one. Thus, if about half of total intestinal blood flow is distributed to the mucosa the tracer concentration in the venous blood would be expected to be 10-15 per cent. Furthermore, Winne (1971 a) studied in rats the effects of changed intestinal blood flow on the rate of absorption for a variety of substances. When increasing the intestinal blood flow, an increased absorption rate was seen for lipid soluble solutes (e.g. antipyrine, methanol) and for small molecular, unionized water soluble solutes (e.g. tritiated water), while absorption rate of water soluble solutes of larger molecular weight (e.g. urea, erythrit) was largely unaffected by blood flow.

Intestinal absorption of gas with regard to intestinal blood flow has been studied by several authors. Thus, Schoen (1925) considered the blood flow as an important factor in elimination of gas from the small intestinal lumen of the dog, since the absorption rate for several gases studied was found to be proportional to their solubility in blood. Further, Monroe et al. (1926) showed that the intestinal absorption of gaseous O_2, CO_2 and H_2 was retarded during induced reductions of the intestinal blood flow, which also was recently demonstrated for gaseous CO_2 by Pals and Steggerda (1966). In a study by Coburn (1968) the elimination of gaseous carbon monooxide from the intestinal lumen of the rabbit was shown to be highly dependant on blood flow while Hamilton, Dawson and Webb (1967) failed to find any correlation between the absorption of ^{133}Xe, dissolved in saline, and intestinal blood flow. Further, the concentration of ^{133}Xe in intestinal venous blood was only 2-5 per cent compared to the luminal fluid but the intestinal segment was not continuously perfused with the ^{133}Xe solution which to some extent may explain the findings. Thus, it is evident from earlier studies that intestinal blood circulation is an important factor for the elimination rate of gas in the intestinal lumen.

The passive absorption of different substances by the small intestine may be limited by diffusion, by blood circulation or by a combination of these factors. The former type of limitation implies that the absorption rate is determined by the properties of the test substance with respect to its diffusion in the tissues, while in the latter case the absorption rate is determined mainly by the mucosal blood flow and its arrangement as well as by the solubility of the test substance in blood (see Forster 1967). The results of the present studies will be discussed along these lines. A comparison between the absorption rate and the rate of mucosal blood flow during the present experimental conditions and mucosal hemodynamic situations may render it possible to elucidate which variables that are the most important ones for absorption.

Absorption rate and blood flow. As regards the blood flow of the entire intestinal wall, it is evident that this flow cannot be the only factor determining the absorption rate. Thus, the intramural blood flow could be reduced by activation of the sympathetic vasoconstrictor nerves without any concomitant reduction of the absorption rate.

When comparing the absorption rate with the mucosal blood flow it is evident that the absorption rate during e.g. "resting" conditions was lower than what could be expected if the luminal contents were equilibrated with the entire mucosa which, in fact, was suggested by the autoradiographic studies. It might, however, be argued that a concentration gradient existed between lumen and capillary blood in all, or at least in the more deeply situated mucosal capillaries and that a combination of flow and diffusion limitations in this way was at hand. If this were so it would be possible to increase the tracer concentration in the venous blood draining the mucosa by reducing mucosal blood flow. However, decreasing the mucosal blood flow whether by reducing arterial inflow pressure or by raising venous outflow pressure, did not increase the mucosal venous tracer concentration (see Fig. 2).

Finally, the villous blood flow might be the rate limiting factor for the absorption. In fact, the villous blood flow and the absorption rate, when expressed as ml of blood that is fully equilibrated lumen per time unit agreed well during "resting conditions". However, the autoradiographic findings of a distribution volume that included also deeper mucosal parts during "resting" conditions", argue against villous flow being the sole rate limiting factor. Further, it is evident from Fig. 2 that there was a great divergence between villous blood flow and absorption rate during moderate hyperemia. A possible diffusion limitation across the intestinal epithelium was ruled out by calculations based on physical and morphological data (paper V), which show that the tissue sheet interposed between lumen and villous capillary blood will not constitute any significant diffusion barrier for ^{85}Kr. Further, the findings of an increased divergence between villous blood flow and absorption rate during a reduced villous blood flow cannot be explained by a diffusion limitation.

To conclude, it seems difficult to ascribe the regulation of the intestinal absorption rate for an easily diffusible, lipid soluble substance to changes in either total intestinal blood flow, mucosal blood flow or in villous blood flow when taken alone. A combination of diffusion and flow limitations is also ruled out, as discussed above.

Absorption rate and capillary surface area. If blood flow to some area of the intestinal mucosa is temporarily stopped, by e.g. pre-

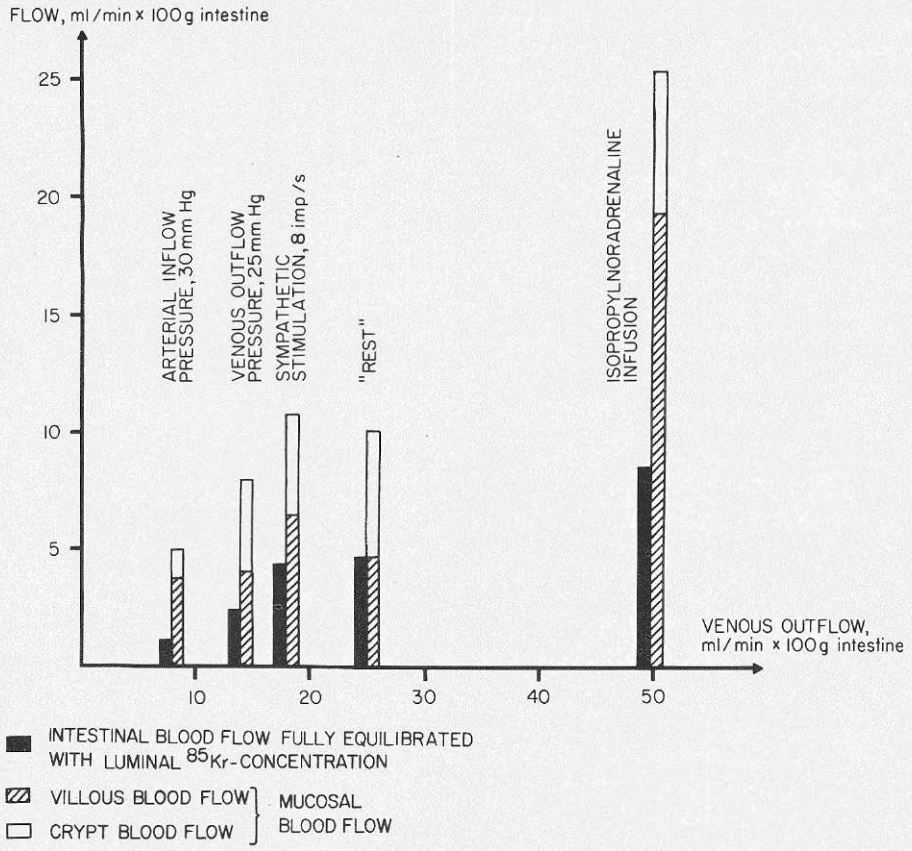

Fig. 2. Approximate values on villous blood flow, crypt blood flow and amount of blood that is fully equilibrated with the lumen during different experimental conditions in the small intestinal vascular bed. All parameters are expressed in ml/min x 100 g intestinal tissue. Crypt blood flow was calculated by subtracting "villous" flow from the "mucosal" flow.

capillary sphincter activity, it could be suspected that this would influence the absorption rate.

From the hemodynamic studies it seems evident that a high "sphincter" activity does occur in the mucosal vascular bed during conditions of "rest", raised venous outflow and sympathetic stimulation. During reductions of the arterial inflow pressure and during hyperemia there seems to be a more even perfusion of largely all the capillaries.

Further, the precapillary sphincter activity in the vascular bed of the villus and the crypt tissues seem to be changed largely in parallel during the studied conditions with the possible exception of sympathetic stimulation.

Comparing the conditions with a low sphincter activity (hyperemia and arterial inflow pressure reduction) it seems evident that the perfused capillary surface area cannot be the dominating factor for the regulation of the absorption rate at least not for easily diffusible, lipid soluble substances, since the absorption rate widely differs during these conditions. This also holds true when the absorption rate is related to the mucosal blood flow. Thus, the blood leaving the mucosa during moderate hyperemia contains about 30 per cent but during a reduced arterial inflow pressure only 15-20 per cent of the luminal tracer concentration (see Fig. 2).

Comparing conditions with a high level of precapillary "sphincter" activity, the absorption rate may also markedly differ, as when resting conditions are compared to the situation during raised venous outflow pressure. In the latter situation the absorption rate is considerably below that during "rest", both in absolute figures and when related to the respective levels of mucosal blood flow. Thus, at "rest" the blood leaving mucosa contains about 45 per cent of the luminal tracer concentration but during a raised venous outflow pressure only 30 per cent.

Thus, during conditions when roughly the same precapillary sphincter activity prevails in the mucosal vascular bed, the absorption rate may differ widely and this also when related to the prevailing levels of mucosal blood flow. These results indicate that the size of the available capillary surface area, as regulated by the precapillary "sphincter" sections, is not of paramount importance for the rate of absorption of easily diffusible, lipid soluble substances.

Absorption rate and linear flow rate for blood in the mucosal vessels. From the measurements of mean transit time $t_{A/H}$ it is possible to estimate in relative terms the average linear flow rate for red cells and plasma particles from $1/t_{A/H}$. In Fig. 3 the absorption rate is plotted versus the average linear flow rates observed during the various circulatory conditions studied in the present series of experiments. The illustrated values represent mean values taken from papers II-VI. It is evident that there is a high correlation between absorption rate for ^{85}Kr and the linear flow rates for blood particles, both in villi and in the entire mucosa. Thus, there is e.g. a strongly reduced absorption rate during low arterial inflow pressure (VI), despite the fact that villous blood flow then stayed almost constant compared to rest and the number of perfused villous capillaries was increased. However, the

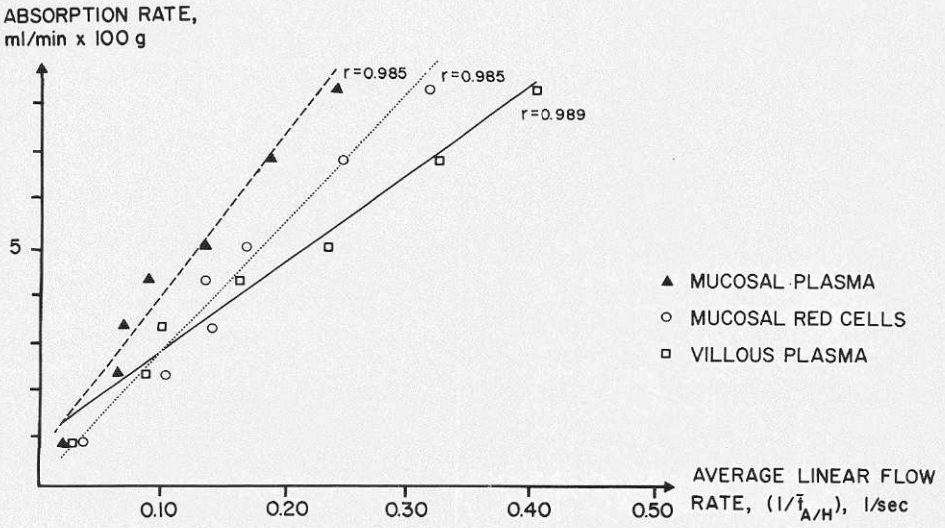

Fig. 3. Absorption rate of ^{85}Kr (expressed in ml of blood that per min is fully equilibrated with the luminal tracer concentration) plotted versus average linear flow rates for red cells and plasma in "mucosal" and "villous" vessels (expressed as $1/t_{A/H}$) during the different experimental condition of the present study. The range of linear flow rates corresponds to a total intestinal blood flow between 5 and 50 ml/min x 100 g. The illustrated points represent observations made during "rest", hyperemia induced by isopropylnoradrenaline (2 levels), reduced arterial inflow pressure (2 levels), raised venous outflow pressure and sympathetic stimulation. Lines constructed by the method of least squares. r = correlation coefficient.

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linear flow rate in these capillaries and in the mucosal vessels was strongly reduced, thus showing the important influence of the linear flow rate on the absorption rate.

These findings concerning a close correlation between rate of absorption and linear flow rate for blood in the mucosal vascular hairpin loops agree well with the proposed function of the villous-mucosal countercurrent exchanger in the small intestine (see Lundgren 1967) as will further be discussed below.

The countercurrent exchange in the small intestinal mucosa as a factor limiting absorption of easily diffusible substances.

The present findings of a low ratio between mucosal blood flow and intestinal absorption rate for an easily diffusible test substance suggest that other factors than the volume flow of blood limit the absorption. This limitation cannot, however, be ascribed to a diffusion barrier between lumen and blood, whether alone or in combination with a blood flow limitation (see above). It is proposed that the present findings of a comparatively low absorption rate of ^{85}Kr is explained mainly by the existence of a countercurrent diffusion exchange between ascending and descending vessels in the villi and adjacent parts of the mucosa, delaying net intestinal absorption (Lundgren 1967).

According to this hypothesis the absorbed solute diffuses along a concentration gradient from the subepithelial capillary network to the central arteriolar vessel of the villus, being thus again brought towards the villous tip. In such a way easily diffusible solutes are delayed in entering the venous effluent by being "trapped" in the mucosal countercurrent exchanger.

The countercurrent hypothesis is corroborated by the high correlation observed between absorption rate and linear flow rate of blood in the mucosal hairpin vascular loops, since the time available for exchange diffusion is determined by the linear rate of flow and, hence, by the mean transit time. Thus, it was demonstrated that the countercurrent exchange of arterially injected, blood borne substances became insignificant when intestinal blood flow was sufficiently increased, e.g. for urea at a total intestinal blood flow of 100 ml/min x 100 g and for ^{85}Kr and antipyrin at 150 ml/min x 100 g (Lundgren 1967).

The results of the present studies made it possible to compare the actual absorption rate with that present in case the mucosal blood flow had become saturated with the tracer. If a difference is observed and it cannot be ascribed to diffusion obstacles, it is believed to be largely due to the countercurrent exchange mechanism. If so the efficiency of this mechanism can be estimated from the size of ratio between the expected and the measured absorption rate. Such a comparison is, however, complicated by the fact that uptake of tracer seems to take place also in deep mucosal vessels during a low mucosal blood flow, while it seems to be largely confined to the villous capillaries during intense hyperemia (V). Thus it is a question of which part of the mucosal blood flow that should be considered as "absorptive".

However, during a reduced arterial inflow pressure and during moderate hyperemia, the villous blood flow constitutes the larger part

of the mucosal blood flow (see Fig. 2) and a rough comparison can then be made. In these two experimental situations no diffusion limitation will exist between lumen and villous capillary blood (V). It can be calculated from Fig. 2 that the ratio between expected and actual absorption rates is 3-4.5 at an arterial inflow pressure of 30 mm Hg, the range of the observed values being due to which flow value that is chosen ("villous" or "mucosal"). The corresponding values during moderate hyperemia are 2.2-3.0. There are reasons to believe that almost the entire mucosal blood flow becomes equilibrated with luminal contents during a low flow state (VI) and thus the ratio would be more close to 4.5 than to 3.1 under those circumstances. During hyperemia, on the other hand, the intraluminar tracer appears to be mainly distributed to the villi and the discussed ratio would then be closer to 2.2 than to 3.0. Thus an increase of intestinal blood flow, and linear rate of flow in the mucosa, reduces the difference between expected and actual absorption rate, probably reflecting a decreased "efficiency" of the mucosal countercurrent exchanger.

The discussion above suggests that the "hindering" effect on absorption of the mucosal countercurrent exchange becomes decreased when blood flow is increased. One may then pose the question if it is possible to increase intestinal blood flow to such an extent that virtually no exchange diffusion of ^{85}Kr can occur any longer. Fig.3, showing the linear relationship between absorption rate and linear rate of flow, makes it possible to answer this question, if it is assumed that the linear correlation of Fig. 3 can be extrapolated to higher blood flows. If so, such an extrapolation shows that, within a physiological range of flow, the absorption rate of ^{85}Kr will not be able to reach the values expected from the villous blood flow observed at maximal intestinal vasodilatation. Since no diffusion limitation could exist between lumen and villous blood in the range where the extrapolation was made, it may be concluded that the countercurrent exchange of absorbed ^{85}Kr cannot be entirely eliminated even at intense intestinal hyperemia. This should be contrasted to the findings that the countercurrent exchange for blood borne ^{85}Kr and oxygen became fairly insignificant already at intestinal blood flows above 150 ml/min x 100 g. This difference in countercurrent efficiency can be explained by the vascular arrangement in the villi with a high linear flow rate in the ascending arterial vessel and a slow one in the descending capillaries. Such an arrangement will imply a higher efficiency for the countercurrent exchange when a test substance is introduced in the slower stream as was demonstrated in model experiments by Niesel and Röskenbleck (1963).

It is thus possible to imagine a situation where villous blood flow is increased to the extent that oxygen fully reaches the villous tips, while there is still an impeding effect on the entrance of easily diffusible substances from the intestinal lumen to the intestinal venous blood.

It should in this connection be underlined that the present technique for studying absorption was "unphysiological" in the sense that fluid containing ^{85}Kr was perfused through the lumen of the gut at a very high rate. This experimental arrangement probably exposes a larger intestinal epithelial area to the intraluminal contents than would occur during more physiological conditions, since it seems probable that only the upper parts of the villi are normally in "efficient" contact with the luminal contents. The latter situation, with absorption taking place mainly around the hairpin bends, constitutes a situation with a high "efficiency" for the countercurrent exchange mechanism, the more so since exchange diffusion of easily diffusible solutes like ^{85}Kr apparently occurs also in the deeper parts of the mucosa, possibly even in the submucosa (cf. Lundgren 1967).

SUMMARY AND CONCLUSIONS

1. A method is described for studying separately and quantitatively the blood circulation in the small intestinal mucosa of the cat. The technique involves i.a. injections of β-radiating, labelled blood particles, the transit of which is detected in the intestinal tissue with β-detectors placed in the gut lumen. Due to the energy level of that β-radiation, ^{32}P-labelled blood particles were monitored from the entire mucosa, while ^{198}Au-labelled plasma colloid particles were registered only from the villi. From the recorded indicator-dilution curve and the measured total intestinal blood flow, it was possible to estimate "mucosal" or "villous" blood flow, blood volume and linear flow rate (I).

2. The following observations on the blood circulation in the small intestinal mucosa were made.

a. At "resting" levels of total intestinal blood flow (20-30 ml/min x 100 g of intestinal tissue) "mucosal" blood flow amounted to 20-25 ml/min x 100 g mucosal tissue and about 45 per cent of the intestinal blood flow was diverted to the mucosa. "Villous" blood flow was then 15-30 ml/min x 100 g villous tissue and 10-20 per cent of the intramural flow was distributed to the villi. The blood content in the mucosal tissue was about 4.0-4.5 ml/100 g and the "villous" blood volume amounted to 1.5-3.0. Only 50-60 per cent of the mucosal vessels and only 30-40 per cent of the villous capillaries were perfused during "resting" conditions. The linear flow rate for blood in the "villous" capillaries was estimated to 0.10-0.15 mm/s.

b. During intense vasodilatation (total intestinal blood flow around 200 ml/min x 100 g) induced by isopropylnoradrenaline the "villous" blood flow amounted to 300-400 ml/min x 100 g villous tissue and 30-35 per cent of intestinal blood flow was now diverted to the villi. The corresponding values for "mucosal" blood flow were 200 ml/min x 100 g mucosal tissue and 45 per cent. The blood content of the mucosa amounted to 5.0-6.0 ml/100 g and in the villi to 4.5-5.0 ml/100 g. Almost all vessels within the mucosa seemed to be perfused by blood. The linear flow rate of blood in the villous capillaries now amounted to about 0.70 mm/s.

c. When reducing perfusion pressure by lowering arterial inflow pressure or raising venous outflow pressure, "villous" blood flow was less affected than "mucosal" blood flow, indicating that blood flow was reduced during these procedures in a deeper mucosal, vascular compartment, probably located around the crypts. The "villous" blood flow exhibited an extremely high capacity for autoregulation and stayed

almost unchanged when arterial inflow pressure was reduced from 120-100 to 30-40 mm Hg. At such a low arterial pressure most "villous" capillaries were open for perfusion then at a linear blood flow rate of only 0.05 mm/s.
d. During the "steady state" phase of sympathetic vasoconstrictor activation, "villous" blood flow was slightly increased as compared to control, while there seemed to be a consistent reduction of blood flow in the deeper part of mucosa. The linear flow rates of blood in the mucosal vessels did not differ from "resting" control conditions.

3. The results of the present study suggest that the blood vessels supplying the villi are highly sensitive to local chemical factors, while nervous and myogenic factors probably dominate the resistance vessels supplying the deeper parts of the mucosa.

4. A method was presented for studying passive absorption of an easily diffusable lipid soluble substance (^{85}Kr) from the small intestinal lumen during various circulatory conditions in the small intestine. Absorption rate was estimated from the amount of tracer appearing in the mesenteric vein and expressed as volume of blood that per unit time was fully equilibrated with the luminal tracer concentration. Intramural concentration gradients were eliminated by perfusing the gut lumen with a saline solution containing ^{85}Kr at a constant high rate.

5. With the technique described above the following observations were made:
a. During "resting" condition 15-20 per cent of intramural blood flow was found to be fully equilibrated with the luminal contents. Absorption rate then amounted to 5 ml/min x 100 g intestinal tissue.
b. During a moderate intestinal hyperemia, induced by isopropylnoradrenaline, the absorption rate of ^{85}Kr increased and amounted to about 15 ml/min x 100 g intestinal tissue at a total venous outflow of 100 ml/min x 100 g intestine, i.e. 15 per cent of the intestinal blood flow was fully equilibrated with the intestinal contents.
c. During a reduced perfusion pressure induced by lowering arterial inflow pressure or raising venous outflow pressure the absorption rate was reduced in proportion to the total intestinal blood flow.
d. During the "steady state" phase of sympathetic vasoconstrictor activation, the absorption rate was not reduced despite a concomitant reduction of total intestinal blood flow.

6. It was concluded from these observations that neither volume blood

flow nor diffusion constitute the rate limiting factor for the passive absorption of lipid soluble, easily diffusible solutes. Furthermore, the villous capillary surface area was also found not to be a major determinant of the absorption rate of ^{85}Kr. On the other hand, a close correlation was observed between linear blood flow rate and rate of absorption of ^{85}Kr, suggesting an important function of the countercurrent diffusion exchange between ascending and descending vessels in the mucosa of the small intestine.

7. Some functional characteristics of the mucosal countercurrent exchanger with respect to the intestinal absorption of easily diffusible lipid soluble substances have been discussed.

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