of the extracellular volume by the hypo-oncotic protein solution; an effect on the hormone level would have been expected to show opposite movement in the urine flow and urine conductivity. Injection of the oxytocinase preparation did, indeed, cause an increase in the urine flow and a decrease in the urine conductivity, the effect being dependent on the dose of the enzyme (Figure 1). The changes in the 2 parameters were approximately matched, as they would be if the rate of infusion of the hormone had been decreased at the moment the enzyme was injected. For 2 h after the injection there was little further change in the antidiuretic response, indicating that the enzyme activity was practically unchanged over this period. The effect of a given dose of the enzyme on the response to oxytocin was much greater than on the response to lysine vasopressin. Since serum oxytocinase[17] or pregnancy serum[18] inactivate both oxytocin and vasopressin at about the same rate in vitro, it is unlikely that this difference reflects the specificity of the enzyme; it may be a consequence of different distribution patterns for the 2 hormones in the organism.

The change with time in the level of exogenous oxytocinase activity in rats is shown in Figure 2. A first, relatively rapid, exponential phase (half-time 7.16 h) during which the activity decreases over 24 h to only about twice the control value, is followed by a second, slow, exponential phase. The half-life of the enzyme in the circulation is thus higher than that of other exopeptidases[10] but still considerably lower than that of the globulins[19].

The highest dosages of enzyme used in our experiments were calculated so as to increase oxytocinase activity in the rat plasma (assumed to be 4% of body weight) to approximately the same level as that found in the plasma of pregnant women nearing term (about 0.12 milliunits/ml). The actual maximal enzyme level found was only $^1/_2$ to $^1/_5$ of this value, and rapidly decreased with time. If the inactivation rate and distribution pattern of exogenous enzyme in humans is similar to that observed in our experiments, repeated doses of the enzyme would be required in clinical use to maintain a useful level of activity in the blood, e.g. in toxemia of pregnancy associated with low levels of endogenous oxytocinase activity[20,21]. The behaviour of exogenous enzyme in human patients would appear to be the most important consideration for its use at the present time[22].

Zusammenfassung. Nach i.v. Dauerinfusion von Lysin-Vasopressin oder Oxytocin wird bei der experimentellen Analyse der Wirkung menschlicher Oxytocinase eine Erniedrigung des antidiuretischen Effekts gefunden; diese rührt vom Absinken der Peptidkonzentration sowohl im Blutplasma als auch am Wirkort her.

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Extravascular Short-Circuiting of Oxygen Indicating Countercurrent Exchange in the Intestinal Villi of the Cat

Countercurrent exchange of materials between arterial and venous segments of capillaries is firmly established in the mammalian kidney[1] and in the swimbladder of many fishes[2]. The countercurrent mechanism is dependent upon the close association of the venous and arterial limbs of a vascular loop. Such a special vascular anatomy is present in the intestinal villus of many mammals, in which ascending non-branching central arterioles are surrounded by a descending dense subepithelial capillary network[3]. The distance between the arterial and venous parts of this vascular loop is estimated to be 10–30 μ and can be traversed by easily diffusible lipid-soluble agents, such as oxygen, in a fraction of a second. Whether water-soluble materials will pass depends upon the presence of endothelial 'pores' in the ascending arteriolar limb. Anyhow, anatomical prerequisites should exist for an extravascular diffusion of oxygen from ascending to descending limbs of the loop. Experiments were performed to determine whether such an extravascular shunting of oxygen existed, by comparing venous appearance-time of oxygen with that of red cells after injection into the superior mesenteric artery.

Methods. 5 cats (2–4 kg) were fasted for at least 24 h and anaesthetized with chloralose (50–70 mg/kg). Venous outflow from jejunal sections weighing 40–60 g was recorded by means of a drop recorder unit operating an ordinate writer. Arterial blood pressure was monitored from the left femoral artery by a mercury manometer. Atropine (1 mg/kg) was given and the splanchnic nerves cut bilaterally.

3 different types of blood mixtures were administered to the experimental animals via a thin polyethylene catheter (PE 10) inserted into a branch of the superior mesenteric artery: (1) blood equilibrated with pure oxygen ('oxygenated blood'); (2) blood treated with 1% sodium nitrite and washed with isotonic saline to produce

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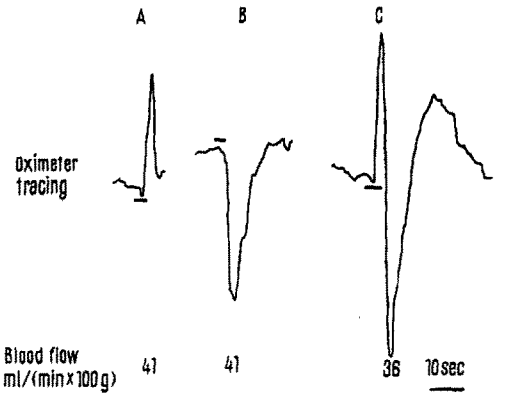
methemoglobinemic cells ('methemoglobin blood')[4,5]; and (3) a mixture of 1 and 2 ('mixed blood'). Densitometric deflections of the same order of magnitude were produced by mixing 1 vol. of 'methemoglobin blood' with 3–5 vol. of 'oxygenated blood'. Between 0.2 and 1.6 ml of the blood samples described were injected during a period of 1–6 sec.

Light absorption of the venous blood was recorded continuously by means of a cuvette densitometer[6]. The blood was drawn at a rate of 3.7 ml/min for 2–5 min through a thin polyethylene catheter (PE 50) branching off from the venous outflow of the intestinal segment. The difference between the outputs of 2 photocells, registering at wavelengths of 625 and 805 nm, was recorded.

Results. The results illustrated in the Figure are representative for 'resting' blood flow in the denervated intestinal loop, i.e. venous outflow less than 50 ml/min · 100 g tissue. The upward deflection of the oximeter tracing in (A) indicates increased light transmission of the intestinal venous blood at 625 nm. This is due to increased oxygen saturation of the hemoglobin, induced by injecting over a period of 4 sec 0.8 ml 'oxygenated blood'. The deflection began about 2.5 sec after the onset of the injection. The venous outflow recorded concurrently amounted to 41 ml/min · 100 g.

In (B) of the Figure, 0.4 ml of 'methemoglobin blood' was diluted to 0.8 ml with isotonic saline and injected as before. About 4 sec after the start of the injection, a downward deflection of the oximeter tracing occurred, indicating a reduced light transmission resulting from the presence of methemoglobinemic cells in the venous blood. The venous outflow was 41 ml/min · 100 g.

The difference of 1–2 sec in appearance-time illustrated in (A) and (B) of the Figure between 'oxygenated blood' and 'methemoglobin blood' was noted in most experiments when 2 equal injections were made at similar blood flow levels. To eliminate the difficulties inherent in comparing 2 different injections, the type of experiment shown in (C) of the Figure was performed[4]. A well-mixed blood sample containing both 'oxygenated blood' (1.2 ml) and 'methemoglobin blood' (0.4 ml) was injected over a period of 5 sec. About 2.5 sec after onset of injection, an upward deflection of the oximeter tracing was recorded, immediately followed by a downward deflection of somewhat greater magnitude. The venous outflow in this case was 36 ml/min · 100 g.



Cat, 2.7 kg. Tracings recorded from a cuvette oximeter connected to the venous outflow of an intestinal segment following intra-arterial injections of (A) 'oxygenated blood', (B) 'methemoglobin blood', and (C) a mixture of both blood preparations. The horizontal bars mark the time of injection. Blood flow through the segment, measured concurrently with a drop recorder, is indicated below.

These experiments show that oxygen appears 1–2 sec earlier than methemoglobinemic cells in the mesenteric vein when both are injected intra-arterially under equal conditions.

Discussion. Because of the laminar flow of blood and the tendency of blood cells to move in the fast axial stream in the vessel, red cells pass through the vasculature of a tissue faster than any other component of the blood. Experimental evidence in support of this assumption in the splanchnic area has been presented by CHIEN[7]. In spite of this, red cells labelled with methemoglobin appeared 1–2 sec later in the intestinal vein than oxygen under conditions of simultaneous intra-arterial injection of a mixture of oxygenated red cells and methemoglobinemic red cells. This finding might be explained in terms of an arterio-venous plasma shunt based on extensive and highly efficient plasma skimming. However, no other data on the cat seem to support such a hypothesis since it would call for a degree of plasma shunting unknown in any other tissue, including the kidney[8]. A more reasonable interpretation of the present data is the following: oxygen passing through the intestine leaves the vascular system at one point and then re-enters by short-circuit by diffusion at some other point downstream. This has been shown to occur in the renal medulla[4,5].

From the present experiments it is not possible to draw further conclusions concerning the localization of the extravascular short-circuiting of oxygen. As indicated in the introduction, however, the special architecture of the vascular system of the villus strongly suggests that countercurrent exchange occurs here. This hypothesis is further strengthened by experiments utilizing other techniques[9]. It is therefore proposed that the shunting of oxygen observed in the intestine of the cat takes place mainly between the ascending and descending limbs of the vascular loops of the villi[10].

Zusammenfassung. Nach Injektion (Mesenterialarterie) einer Mischung zweier Blutproben – die eine mit Methämoglobin, die andere mit Sauerstoff markiert – erscheint der Sauerstoff 1–2 sec früher in der Mesenterialvene als die mit Methämoglobin markierten Erythrozyten. Die Existenz eines Gegenstromaustausches in den Darmzotten der Katze scheint damit bewiesen zu sein.

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