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# The Concentration of Steroid Hormones in Blood and Peritoneal Fluid Depends on the Site of Sampling

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## 1. Introduction

The concentration of steroid hormones in arteries varies according to the site of blood sampling. The hormone concentration is higher in the ovarian and testicular arteries than in the aorta resulting in a high impact on the target organs, opening a route for local hormonal regulation between organs. Local application of drugs may induce a potential method for semi-specific treatments. Vaginal application of hormones will therefore induce relatively higher concentrations in the uterus and urinary bladder area than a peripheral application. Likewise, nasal application will induce a higher relative concentration in brain arterial blood than peripheral application. This is due to local counter-current transfer between venous and arterial blood, and between the lymphatic and arterial vessels. Similarly, the concentration of steroids in peritoneal fluid varies according to the site of sampling.

## 2. The third way of humoral communication: local counter-current transfer

Humoral communication between cells can be either through local diffusion in the interstitial fluid between neighbouring cells or through the vascular system. The present paper will discuss a third possibility that is part of the vascular distribution. The paper will concentrate on local communication between organs belonging to the reproductive system and steroid hormones, but will also touch other organs (the adrenal, the brain and the peritoneal cavity) where local transfer of steroids seem to be involved in the physiological regulation.

McCracken et al. (1972) initiated the hormonal transfer investigations in the female. The anatomical structure had, however, been known for hundreds of years (Blancardi 1687, published in 1739). Ginther (1967) described the functional importance of a close connection between the ovarian artery and veins. The work involving steroid transfer in males was started by Jacks and Setchell (1973) and Einer-Jensen (1974). The documentation comes from investigations in several animal species as well as in man (see

Einer-Jensen et al., 1989; see Krzymowski, 1990; see Einer-Jensen and Hunter, 2005). Despite the anatomical differences between the species (one ovulation versus 10-20 ovulations, large uterine body and small uterine horns versus small uterine body and large horns), the picture of transfer is similar.

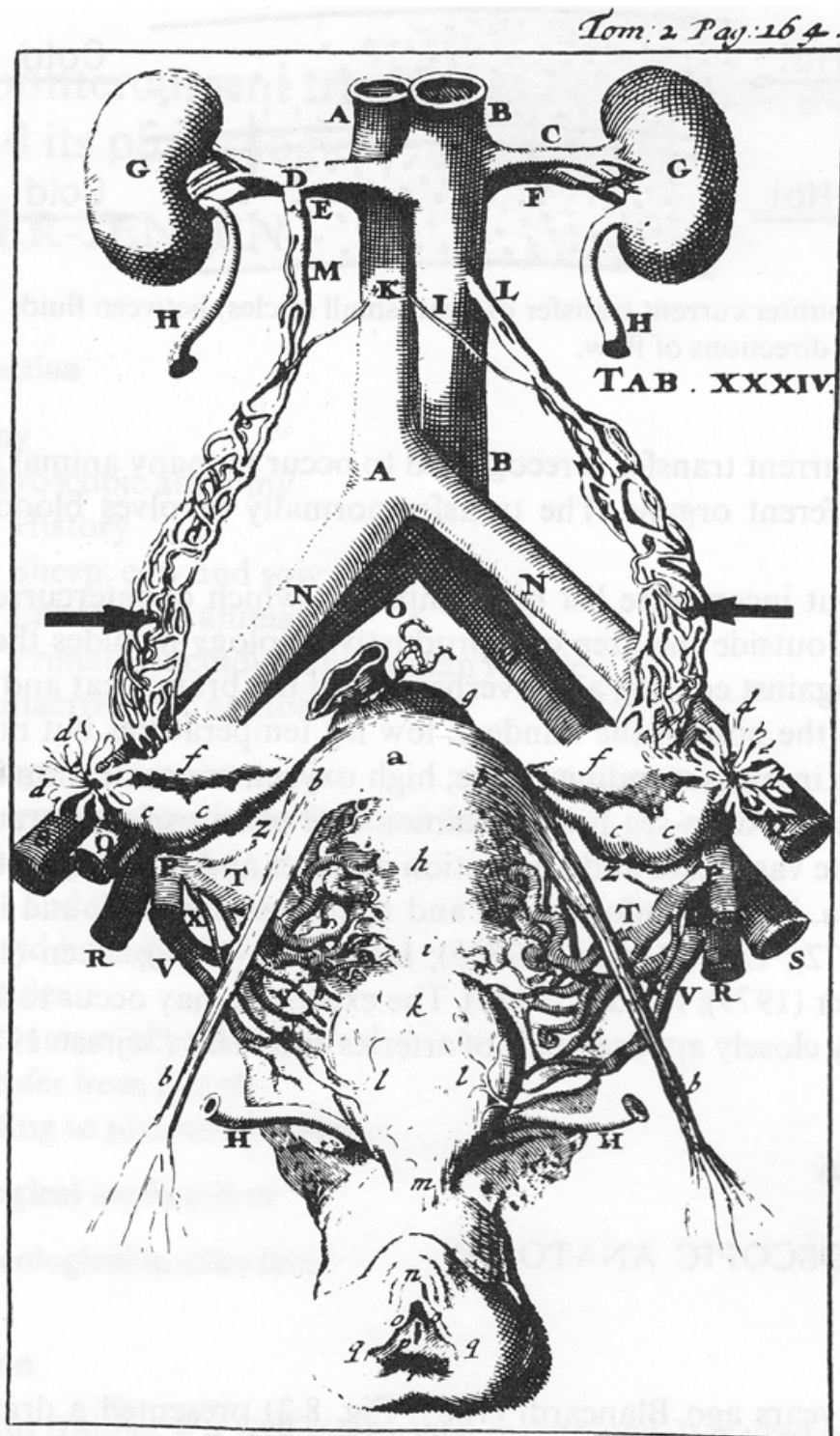


Fig. 1. The human genital organs and their vascular supply. The plexus formed by the ovarian artery and vein can be seen (arrows). (From Blancardi 1687).

Signal substances such as hormones produced in an organ will diffuse to the surrounding lymph and blood capillaries. Thus the signal substance will be present in the content of local lymph and blood vessels removing fluid and blood from the organ. The concentration will, of course, be high here compared to the peripheral fluids since no dilution has taken place (Einer-Jensen and Hunter, 2005).

In some hormone producing organs, the vessels removing the fluid from the organ are very intimately arranged with the artery supplying the organ. This is the case for steroid producing organs such as the gonads in both male and female. It is well known that the temperature in the extra-abdominal testis is a few degrees Centigrade lower than the general body temperature due to cooling through the scrotal wall and maintenance of the temperature gradient by counter-current transfer of heat energy. The transfer is expected to take place between the venous plexus (the Pampiniform plexus) and the convoluted testicular artery. The efficacy of the heat transfer is very high, close to 100% (Glad Sørensen et al., 1991), thus the cooling through the scrotal wall can be kept at a low level – which will diminish the waste of energy from the body. In most mammals, the testis is an organ positioned outside the abdomen, but even in animals with intra-abdominal testes the close apposition between the vessels is found, e.g. in small whales (Einer-Jensen, pers. com.). This strongly suggests that cooling is not the only reason for the vascular arrangement

The ovaries are always positioned in the abdomen and one would not expect temperature gradients within their tissues. The vessels to and from the ovary are closely apposed in a way similar to the male, indicating the potential for of a transfer system. However, the temperature of the pre-ovulatory follicles tends to be lower than deep body temperature (Hunter and Einer-Jensen, 2005; Hunter et al., 2006). Heat “consuming” proteins induce lower temperature and the temperature decrease is maintained by a very local heat-exchange mechanism in the vessels to and from the follicle.

### 3. Counter-current exchange

When blood or lymph flows through arteries, and veins and lymph vessels, and the vessels are in close contact, the flow can be described as counter-current flow.

Counter-current exchange along with Concurrent exchange comprise the mechanisms used to transfer some property of a fluid from one flowing current of fluid to another across a semipermeable membrane or thermally-conductive material between them. The property transferred could be heat, concentration of a chemical substance, or others. Counter-current exchange is a key concept in chemical engineering thermodynamics and manufacturing processes, for example in extracting sucrose from sugar beet roots. (Wikipedia, the figure below is also from Wikipedia).

The present authors expect the transfer to be passive; no active transfer mechanisms have been detected or proposed (to the best knowledge of the authors). The laws of physics, the respective rates of flow, the diffusion distance between the vessels, the chemical nature of the substances, especially the lipophilicity, will determine the rate of exchange. In general, a system will transfer heat at almost 100% (Glad Sørensen et al., 1991), whereas the exchange of tritiated water may be 20%, and the rate of steroid hormone transfer a few per cent.

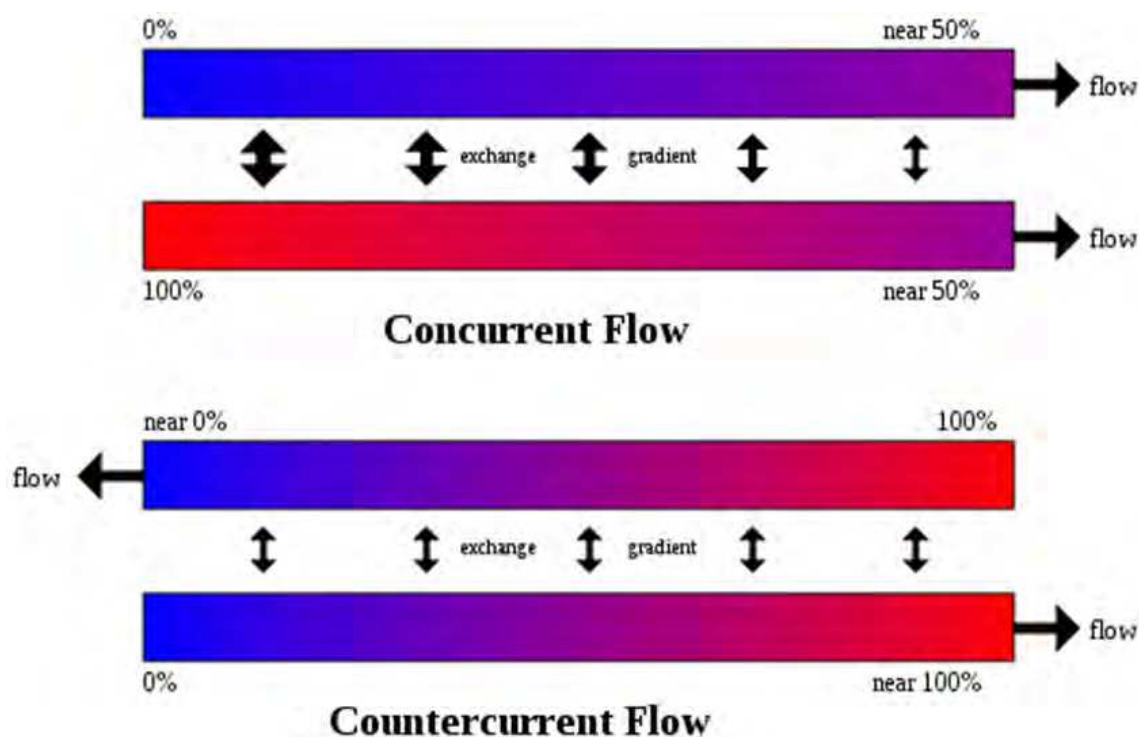


Fig. 2.

Many of the first experiments evaluating the transfer were performed with radioactive gases ( $^{133}\text{Xenon}$  and  $^{85}\text{Krypton}$ ). The efficacy of the transfer is similar to that of tritiated water. The advantage of using gas was the lack of recirculation since more than 95% of the gas is cleared during the first passage.

Even a limited transfer of steroids may have a marked physiological impact. Only non-protein bound steroids are biologically active. The hormone transferred will reach the arterial blood as free hormone and, because the binding takes some time (seconds), the steroid may reach the capillaries before it is bound to the plasma proteins (Einer-Jensen, 1984, 1989).

#### 4. Steroid transferred from the gonads will reach the epididymis and the Fallopian tube

Like heat energy, substances may be transferred in areas with a close connection between lymph vessels, veins and arteries. The gonads are typical examples. The close connection between the winding testicular artery and the Pampiniform plexus is well known. It is not, however common knowledge that the blood supply to the first part of the epididymis also originates from the testicular artery. Thus, the epididymis is involved in the local transfer system and transfer of steroids will act to stimulate the epididymis more than indicated by the content of testosterone in peripheral blood. An intramuscular injection of testosterone may produce a high peripheral concentration of the hormone and produce a strong negative feedback on the pituitary gland. However, it will not produce the concentration difference between the blood in the testicular artery and any other arterial sample.

In the female, the arterial supply to the Fallopian tube and the proximal part of the uterus originates from the ovarian artery. Any hormone in or transferred to the ovarian artery will also reach the tube and part of uterus (Stefańczyk-Krzyszowska et al., 1998; Einer-Jensen et al., 2002; Cicinelli et al., 2004a). The ovarian production of individual steroids is cyclic and the amount of hormone transferred will therefore fluctuate (Cicinelli et al., 2004c). The increased production of oestradiol shortly before ovulation and of progesterone in the days after ovulation may be especially important, since transfer to the blood supply of the Fallopian tube and proximal part of uterus will influence tissue function. The transfer has been documented in both experimental animals and in man. The border between the blood supply from the uterine and tubal arteries shifts during the ovulatory cycle in man, probably due to the local vasodilatory effect of oestrogens in the tubal artery (Cicinelli et al., 2004b; Cicinelli et al., 2005).

Cooling of the vagina induces a temperature fall in the vesica and corpus of uterus but not the tubal part, probably through a counter-current transfer mechanism (Einer-Jensen et al., 2001a). Application of steroids in the vagina will induce a semi-selective effect in the vesica and uterus (Cicinelli et al., 2001). Cycle dependent variations in transfer of  $^{133}\text{Xenon}$  from vagina to uterus was found in rats (Zhao and Einer-Jensen, 1998).

## 5. Other organs may also have a local transfer mechanism

An important steroid producing gland, the adrenal, does not have the external artery-veins complex needed for a counter-current transfer. It is, however, known that glycolytic steroids potentiate the production of adrenalin. It is tempting to think that a local exchange mechanism exists within the adrenal gland. There is some anatomical evidence, but the hypothesis has not been documented sufficiently to exclude doubt (Einer-Jensen and Carter, 1995).

Local counter-current transfer between the brain blood vessels has been found in experimental animals (Krzyszowski, 1992; Einer-Jensen and Larsen, 2000a and b; Einer-Jensen et al., 2001b; Einer-Jensen et al., 2002). The brain is (probably) not a steroid producing organ, but some neurons have steroid receptors. Nonetheless, the effect on the brain may be semi-selective when treated with nasal application of steroids as based on the following knowledge. When animals exercise intensively, the body temperature tends to increase. The brain is the first body organ to be damaged after a rather small increase of 3-5° Centigrade. Nature has developed a brain cooling mechanism. Large airflows through the nose will cool the nasal mucous membrane and the capillary blood. The venous blood will leave the head either through a superficial or a deep vein before reaching the jugular vein, the route being decided by an autoregulated mechanism. The higher the temperature, the more blood will reach the deeper vein. This vein is at one point in close connection with the carotid. In some animals, an arterial plexus (Rete Mirabile) is formed by the carotid creating a very effective transfer system which decreases the temperature of the carotid blood and therefore of the brain. Transfer of steroid hormones has been found in experiments involving nasal application in isolated, perfused heads from pigs (Skipor et al., 2003). The transfer mechanism may also be present in man.

## 6. The importance of high progesterone concentrations in peritoneal fluid

The peritoneal cavity, its lining membrane and fluids are active participants in local regulation of the reproductive processes. In women, peritoneal fluid was collected during

abdominal surgery by means of cotton swaps in nine women all with an active corpus luteum. Several samples were collected during the same operation (over the active corpus luteum, over the opposite ovary, at the right left and right paracolic gutter and at the pouch of Douglas). Progesterone concentrations close to the corpus luteum were 4 times (range 1.4 – 9.2) higher than in the other peritoneal samples and, on average, 5 times higher than in the systemic blood (Cicinelli et al., 2009). Progesterone would be expected to enter the peritoneal cavity locally (close to the corpus luteum). The authors know of no similar investigations in farm or experimental animals. One may speculate on the physiological importance:

Nonetheless, female genital tissues and their mesenteries are bathed in fluid with an elevated concentration of steroid hormones and, in many species, peritoneal fluid also enters the Fallopian tube ostium around the time of ovulation. This is principally due to the ab-ovarian beat of the cilia on the inner surface of the fimbriated infundibulum. In addition, evidence from pigs indicates that vital dyes irrigated onto the mesometrium and mesosalpinx enter the lymphatic vessels bordering the genital tract of oestrous animals (Hunter, 2011). There is little doubt that steroid hormones would do likewise, eventually influencing the activity of the endosalpinx and its secretions at a time when gametes and/or embryos could be present in the lumen.

The contralateral ovary is bathed in the high progesterone-containing fluid, which may influence follicular development. Other steroids such as oestrogens may behave comparably. Although alternating ovulation between the two ovaries is far from obligatory, signal transfer via the peritoneal fluid may have an influence on such a phenomenon (Hunter et al., 2007).

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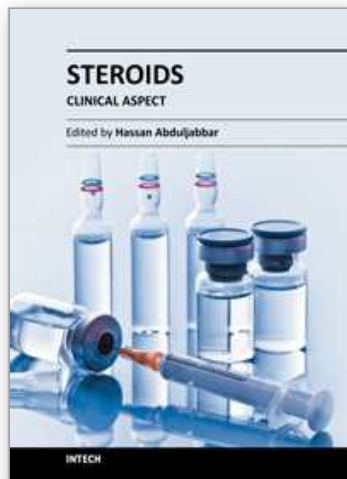
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