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From Classical to Molecular Physiology and back again

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From classical to molecular physiology and back again

N. Einer-Jensen¹, H. F. R. Hunter²

Combining classical organ physiology with cellular and molecular approaches would create a symbiosis. Local effects due to local counter-current transfer of signal substances are underestimated. The authors have included suggestions for future experimental evaluation of these points.

This essay is an attempt to document the potential benefits if traditional organ physiological science is revitalised and combined with cellular and molecular physiology. This should create a symbiotic effect. Suggestions taken mainly from reproductive physiology are mentioned, as are possible benefits, not least if applied in clinical situations. These include a) gamete and embryo culture systems with computerised control of specific temperature shifts, b) establishment of a very early pregnancy factor in women, c) using procedures of local counter-current brain cooling in hyperthermic emergencies, and d) applying nasal or rectal counter-current physiology in therapeutic situations. **J Reproduktionsmed Endokrinol 2014; 11 (5–6): 280–5.**

Key words: counter-current transfer, hormones, blood vessels, local application, local effects

■ Introduction

The authors are no longer young and started working on experimental studies in physiology soon after the unravelling of DNA and invention of the electronic library. In those days, physiology was mainly in vivo and in vitro organ physiology, and research tried to describe the interaction between cells and organs [1]. During our careers, we have seen the development of cellular, biochemical and molecular physiology. The new disciplines are certainly successful and have produced dramatic results and major steps forward, while traditional physiology has starved – it seems to be out of fashion. Nonetheless, there has been development of modern electronic equipment, improved quality of experimental animals and procedures of anaesthesia etc., yet these are still not fully utilized. Clinical pharmacology investigations financed by industry are common, while basic clinical physiological research has suffered. As a result, references in the present article tend to be historic.

The paragraphs that follow concern physiological integration between different organ systems, such as the importance of the cardio-vascular system for organ function and organ interaction. It is much more than a simple transfer of a substance from A to B. Attempts will be

made to pin-point research results which could not have been created in test tubes alone. We will also suggest areas in need of more information and further research in domestic animals and humans. Most examples are taken from reproductive physiology since this is the research field of the authors. Without doubt, comparable examples could be taken from other areas.

The authors do not want to downgrade the importance of any type of biochemical or molecular physiology research and knowledge, but rather wish to strengthen an understanding of the interactive aspects of physiology. Test tube physiology may be suitable to describe the function of an *E. coli* bacterium but it is insufficient to describe the function of a mammalian organism. The suggestion is to use the best of both worlds by reinvestigating classical physiology and combining it with the latest cellular and molecular techniques to obtain new knowledge. Such symbiotic studies represent a way forward.

Young scientists perform literature searches with a computer. One consequence of this approach is that scientific activities and reports older than the rather recent computer age are overlooked or reinvented. This fact of modern life seems unavoidable. Young people never

do as told. Mature scientists may diminish the loss or damage by publishing review articles in good journals (e.g. [2, 3]). This will transfer old knowledge to the present databases.

Evolution of mammalian organisms has taken millions of years; the many special arrangements so developed have a purpose. There are of course differences between species, but also many similar mechanisms and likewise different mechanisms to achieve the same physiological goal. In most aspects, man seems to behave as a typical mammal. As a consequence, we may be able to answer some parts of the following questions, but further development of knowledge should keep future generations of physiologists usefully occupied and intellectually stimulated.

■ Integration between the Circulatory System and Organs of the Reproductive-Endocrine Systems

Humoral regulation is a transfer of regulatory substances from one cell (group of cells or whole organs) to another system of cells. “Regulatory substances” covers a broad range of substances, including traditional hormones, prostaglandins, and regulatory peptides. Three types of humoral distribution will be mentioned,

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the third point being the main topic of this article:

1. Diffusion between neighbouring cells. A signal substance may diffuse to an adjacent cell through the extracellular fluid. This mode of action is termed paracrine. The maximum distance is probably of the order of 10 μ , otherwise the substance will diffuse into a capillary and the potential local effect will be abolished. Transmitter substances in the nervous system may be placed in this group as a special case with a closed diffusion space.
2. There is a high density of capillaries in every organ. The diffusion distance between a cell and a capillary is minute. When locally produced molecules diffuse in the extracellular space, they will, with a high probability, diffuse through a capillary wall into the lumen and be carried away. During the next passage of a capillary, such molecules may diffuse through the wall and extracellular space into a cell and perform an appropriate regulation. This mode of action is endocrine and represents traditional endocrinology.
3. Vessels to and from an organ, and even within an organ, may be anatomically very close and form a counter-current transfer system. This offers a local redistribution system that creates increased concentrations of locally-produced substances in the neighbouring artery compared with the aortic concentration. This increased concentration may have a local effect on other cell groups in the actual organ or in other organs supplied from the same local artery. This mode of action could be called counter-current endocrine and is a common but frequently overlooked mechanism.

■ Basic Rules underlying Exchange from the Circulatory System to and from Organs

The vascular system is not a passive set of tubes. Rather, it is a highly developed, dynamic, and exceedingly complicated system, which influences the transfer of substances and where many of the substances being transferred have an impact on the function of the exchange system itself.

Diffusion in and out of blood vessels is mainly a passive process. Small molecules diffuse more effectively than larger ones, but even substances with a molecular weight of 500 Daltons or more may pass. Proteins will only pass to a minute degree. Lipophilic substances diffuse more effectively than hydrophilic substances of the same molecular weight. A low blood velocity in capillaries will facilitate equilibrium of substances between extracellular fluid and plasma. Excess fluid in the extracellular space (oedema) will delay diffusion to and from the capillaries and may disrupt normal capillary flow; substances will not be transferred properly.

Many substances are bound effectively to plasma proteins (a single albumin and diverse globulins); close to 100% binding is common. Only the non-bound fraction is physiologically active. When a hormone diffuses from the production site into the venous blood, it is not protein-bound. It remains free in the blood for a limited period (seconds) before becoming bound; an equilibrium was not reached in bovine plasma even after 10 sec [4]. When a substance is transferred from venous to arterial blood through the walls of the vessels, it arrives unbound. If the binding takes just a few seconds, the free hormone will reach the capillaries before binding. A small percentage of unbound substance will therefore increase the total of free hormone substantially whereas the increase in total concentration will be small. Locally transferred hormones may thus have a huge impact. Plasma binding kinetics under in vivo conditions remains a critical but almost overlooked topic.

Total blood flow through an organ may differ from the total capillary flow due to the presence of shunts. Functional arterio-venous anastomoses doubling the total blood flow are present, for example, in sheep ovaries without corpora lutea [5]. The reason is not obvious.

Despite their low rate of flow, the lymphatic vessels are part of the local transfer system as the hormone concentrations are very high [6, 7].

■ Questions Demonstrating the Limitations of Knowledge in Physiological Science

Why is the Temperature of the Testis and Epididymis lower than Body Temperature?

It is basic physiological knowledge that testicular temperature is 1–2°C or more below deep body temperature in mammalian species with scrotal testes. The cooler testicular venous blood is in close contact with the artery in the Pampiniform plexus and cools the arterial blood [8]. The heat transfer is close to 100% effective, thus keeping the heat loss needed through the scrotum to a minimum [9]. The head of the epididymis is supplied from the testicular artery and therefore has a low temperature. The low temperature in scrotal mammals is thought to be essential for sperm maturation, including both nuclear and membranous changes, and for functioning as a cool storage site for sperm before ejaculation. These presumptions may be correct and indeed essential, but very large mammals like whales and elephants have testes in the abdomen. The reasons for a low temperature in scrotal mammals have not been clarified, although a possible reduction in the incidence of germ-line mutations is frequently mentioned.

What is the Importance of Intra-Testicular and Testicular-Epididymal Signals?

One may postulate that cooling is just a side effect of hormonal redistribution. It is known that peptides and steroids are transferred to the testicular arterial blood in the Pampiniform plexus [10, 11]. Since the hormones are of testicular origin, they are recirculated to the testis and epididymis, thus creating a higher tissue concentration and essential effect locally. The increase in total hormonal content may be limited, but the hormones add significantly to the non-protein bound fraction for a brief period. Very few experiments have taken this into account.

Local transfer of testosterone in primates has been found by several groups of scientists [12, 13], but we still need information about changes in the testis induced by local hormone transfer. Local peptides may be produced and transferred. They may be difficult to measure

in peripheral blood samples due to dilution, although it could be possible to develop molecular probes to detect the levels in local samples. This would be an example of combining traditional physiology and molecular biology. Detection of peptides transferred via the local vascular system would add to our understanding of the regulation of sperm development. A testosterone binding protein in rete testis fluid was once thought to be essential for the transport of testosterone from testis to epididymis, but it may be of less importance due to the local vascular supply of the hormone.

It could be tempting to stimulate testicular or epididymal function through appropriate intramuscular testosterone injections. The peripheral testosterone concentration in blood may increase. However, the overall testicular production would decrease due to decreased stimulation with gonadotrophins caused by negative feedback from the peripheral injection. In addition, the local influence of counter-current transfer of testosterone could be abolished.

Why is the Temperature of large Graafian Follicles lower than in the rest of the Ovary?

The close apposition between the ovarian vessels in man was observed long ago [14]. Such intimacy indicates a counter-current mechanism, the presence of which was confirmed more than 300 years later [15, 16]. Many animal experiments in several species have also documented counter-current transfer [17].

Large pre-ovulatory follicles may be one or two degrees Centigrade cooler than the rest of the ovarian tissues [18, 19]. Nature has developed a local cooling system for pre-ovulatory follicles within a complicated organ positioned deep in the abdomen. The cooling may be important for the development process of the gamete or for the follicular tissues, but we do not know why or how. It is unlikely that evolution of such complicated processes involving both male and female gametes does not have a purpose. Fertility work involving follicle or oocyte culture could be performed at an appropriate reduced temperature although, in reality, subtle changes in temperature may be required. A computerized temperature control program should provide a way forward in this dynamic sphere.

Cooling of the large follicles may be a “side effect”, since all known vascular networks exchanging heat energy also transfer substances. Such local transfer of regulatory substances may create a not-yet-investigated local environment. This is an area where traditional animal experiments and molecular physiology together may clarify a long-standing conundrum.

What is the Significance of Intra-Ovarian Signals?

The adult ovary is an organ with diverse tissue types (follicles, corpora lutea, corpora albicantia, interstitial cells) and a cyclic function. Small follicles grow to medium size and some of them are stimulated to become mature, others to degenerate. Follicular growth is influenced by larger follicles and corpora lutea. There is every reason to believe that much of the ovarian regulation is local through local diffusion between neighbouring cells or through exchange between the ovarian vein and arterial blood of steroids and peptides. Mid-size follicles may be stimulated or inhibited by hormones from one or several large follicles. Local recirculation of progesterone from one or multiple corpora lutea may also regulate follicular growth. The fine-tuning of stimulation versus degeneration as well as the selection of the large “successful” follicles are not fully understood. Ovulations tend to shift between the ovaries in species with a single ovulation (the shift is not obligatory) but the tendency to alternation indicates that a one-sided regulation is involved. The field is open for investigation. In this context, a regulatory influence of germ cells should not be overlooked. Indeed, one of the authors has proposed that the oocyte acts as a centrally-located computer, programming and integrating conversations with ovarian somatic cells [20].

What is the Importance of Local Signals from the Ovary to the Fallopian Tube and Uterus?

The Fallopian tube receives the eggs and sperm, and fertilization occurs here. The young embryo(s) are maintained in the tube for some days (2–7 days), depending on species. The tube is a highly developed organ, much more than a simple conduit. Sperm transport and control of their numbers in the Fallopian tube are tightly regulated processes, as is move-

ment of the fertilized eggs (embryos) stepwise through the tube. Nutrition of a developing embryo is made available through secretory processes in the tube. Immunological suppression may occur since the embryos contain foreign proteins from the male genes. Signals derived from the ovary prepare the tube for a developing embryo [21, 22]. A branch of the ovarian artery supplies the Fallopian tube. Ovarian hormonal signals transferred in the vascular plexus will reach the tube locally. In mono-ovulatory animals and man, progesterone and oestrogens will reach the ipsilateral tube in “higher than normal” concentrations due to local transfer. Since the function of the tube is hormone-dependent, a local impact must be expected – and the hormonal changes are not measurable in peripheral blood. The morphology and function of the Fallopian tube on the ovulatory and contralateral sides should be compared during the ovulatory cycle in man. Any difference between the two tubes would strongly support ipsilateral mechanisms. It is improbable that progesterone and oestrogens are the only regulatory substances. Signal peptides may be expected as well as prostaglandins. Here again is a rich field for investigation combining in vivo trials with molecular techniques.

The ipsilateral aspect is documented in man [23, 24]. During the follicular and luteal phases, the border from either the uterine or ovarian arterial supply is moving in the ipsilateral side of blood supply during each ovulatory cycle. The ovulatory side is “preparing” the utero-tubal junctional region to receive the developing embryo through oestrogen secretion and later through progesterone secretion, both hormones being transferred unilaterally to the ovarian and thus tubal arterial blood. Observations suggest that miscarriage is less likely if the embryo implants in the ipsilateral fundus, again supporting the unilateral aspect. It is surprising that assisted fertility work is as successful as it is when considering our limited knowledge of early events in the primate uterus.

What is the Purpose of Local Signals from the Fallopian Tube and Uterus to the Ovary?

The ovarian veins drain the ovary and Fallopian tube and also parts of the uterus. Uterine blood supply may be an im-

portant factor in the regulation of the oestrous cycle [25]. This is a region in which arterial supply and venous return are not identical. In cows, sheep and several other species, PGF2 α is secreted from the uterus late in the oestrous cycle if fertilization fails or if eggs are retained in the Fallopian tube or embryos fail to implant – this is a non-pregnant signal inducing degeneration of the corpus luteum. Counter-current transfer of prostaglandin takes place in the ovarian vein-arterial plexus, the concentration in peripheral blood being hardly measurable due to metabolism of the hormone during the first pulmonary passage [26]. The same mechanism is not present in man, where a positive pregnancy stimulus (hCG, human Chorionic Gonadotrophin) is the accepted means of maintaining corpus luteum function. hCG is measurable in peripheral blood a week after conception, and commercially available urine assay kits will confirm conception after a missed menstrual period. hCG is probably too large a molecule to be transferred in the vascular plexus and an active transfer mechanism has so far not been documented. There is some indication that degeneration of the corpus luteum is prevented before the hCG level is significantly increased.

Hormone-containing intra-uterine devices (IUDs) are documented to be effective in preventing pregnancies, whilst at the same time diminishing side effects of IUDs such as spotting and menstrual bleeding volume. Observations indicate that they also have an effect on ovarian function (which could involve local transfer mechanisms).

Concerning signals from the uterus to the ovaries, there remain outstanding questions. For example, at the end of the luteal phase in pigs, there is controversy as to the mechanism of establishing pregnancy. In the presence of embryos, the uterine luteolysin PGF2 α is said to be internalised into the uterine lumen (exocrine secretion) rather than entering the uterine veins [27]. However, results from another laboratory using the pig model show that high titres of PGF2 α can indeed enter the uterine veins at the time of establishment of pregnancy (Days 13–16). The explanation proposed here was that luteotrophins from the many elongated conceptuses overcome the influence of uterine luteolysin

and permit establishment of the corpora lutea of pregnancy [28]. Further studies are needed to reconcile these differences. A potent local impact of multiple viable conceptuses should not be overlooked.

How soon does a Woman know she is Pregnant?

Many years ago, an Australian group postulated the presence of an “early pregnancy factor” (EPF) in serum [29]. The work was controversial because, in the beginning, it was difficult to repeat the Rosette test in other laboratories. Nonetheless, later immunological investigations supported the idea. The putative factor was found in pregnant women [30]. This, together with the suspicion that hCG may on occasions be produced a few days too late to promote survival of the corpus luteum, make more work around EPF much needed. The present authors postulate that the young embryo secretes a “pregnancy signal” in minute concentrations which is amplified by the neighbouring suspension of follicular cells [31]. The signal is detected by the endosalpinx and induces a larger production of the “real” early pregnancy signal. Molecular biology should be applied in suitable animal experiments to test this hypothesis. The EPF may, especially during the first days of a pregnancy, be difficult to measure in peripheral blood due to dilution. It may also be difficult to investigate the topic in man for ethical reasons, but it is potentially of considerable importance and could be performed using in vitro culture material.

Only 15–30% of the implanted embryos survive to give viable foetuses. This estimate is based on the assumption that most delayed menstruations are associated with early abortions. Vaginal progesterone treatment following egg transfer seems to increase the pregnancy rate to the normal range, but treatment with EPF, if it ever becomes available, may improve the outcome. Women sometimes describe “being sure” of their pregnancy a few days after conception, but a clinical trial around the issue is missing. A key trial could involve weekly blood samples from “just married women” lacking any contraception. hCG, EPF, and progesterone concentrations should be correlated with the subjective experiences of the women (when did you feel pregnant?).

Why is the Adrenal Gland Producing both Adrenalin and Corticosteroids?

The adrenal gland is a morphologically unusual combination: the cortex producing corticosteroids develops from mesoderm and the adrenalin producing medulla originates from ectoderm, combination of distinct tissues also exists in the pituitary gland. A probable explanation for this arrangement is that adrenalin producing tissues benefit from the close contact with the corticoid producing tissue [32]. It has been suggested that local transfer of corticoids from the small veins to the adrenal artery takes place and facilitates adrenalin production. Medication with corticoids will suppress the cortical production of hormones and this may influence adrenalin production. This possibility appears not to have been investigated with modern techniques.

What is the Purpose of a Cooling Mechanism to the Brain?

The survival of a mammal is threatened if the body temperature increases by 5° or 6° C; the first organ to be damaged is the brain. Running (fight or escape), fever and environmental heat stress may thus be life-threatening. A brain cooling mechanism has been documented in ruminants including camels, likewise in pigs and rats [33]. A cooling mechanism has also been postulated in the horse and man. Respiratory air cools the nasal cavity and therefore the nasal venous blood. Heat energy is exchanged between this blood and carotid blood in the plexus, decreasing the temperature by several degrees Centigrade in carotid blood. Increased respiration due to running or heat stress will increase the cooling effect. Auto-regulation prevents cooling if the brain temperature is normal or low; the blood will be redirected from the deep veins to superficial veins before reaching the jugular veins.

The mechanism has not been fully documented in man. In clinical studies, pressure and temperature probes are used in hypothermic patients, but the brain cooling thesis cannot be tested in this group of patients as the cooling mechanism is shut down in the hypothermic patient by an auto-regulatory mechanism. Weis et al. [34] have suggested a new method for temperature measurements in man based on Magnetic Resonance Spectroscopy

Imaging (MRSI). We suggest a pre-hospital investigation on intubated, potential or actual hyperthermic patients: flush the nasal cavity in intubated patients with air or oxygen before arrival at the hospital. One logical consequence is that brain damage should be less extensive.

Does a Local Hormonal Exchange System exist in the Brain?

The short answer is “yes”. Steroid transfer from nasal vein blood or the nasal cavity has been demonstrated in isolated, perfused pig heads [35]. Transfer of several substances has also been found from the nasal cavity in rats [36]. It should be possible to treat patients by way of nasal application to obtain higher brain arterial concentrations than indicated by peripheral blood samples; one may call it a favourable therapeutic ratio. The topic is under-explored, and human trials and better animal models are needed. The clinical possibilities are considerable.

Has the brain vascular transfer system developed to favour brain cooling or for signal substance transfer or both? Why have comparable transfer mechanisms of hormones evolved in the brain, the testis and the ovary? The physiological advantages must be significant. Could molecular studies give guidance here? Regulation of temperature is critical for nuclear, cytoplasmic and membrane function.

Are hormones distributed by the Peritoneal Fluid?

The peritoneal cavity is not passive, and its ability to combat infections is well known. However, the possible involvement of the peritoneum in distribution of hormones is seldom appreciated [37]. Man is predominately mono-ovulatory. In each cycle, the ovary producing the dominant follicle and corpus luteum creates a unilateral hormonal sphere influencing the function of the nearby organs (Fallopian tube, tip of uterus) [38]. The local hormonal environment is mainly created by local transfer of hormones between the blood and lymph vessels, and also by post-ovulatory leakage from the ruptured follicles which have elevated steroid concentrations in the coagulated follicular fluid. Local concentration differences in steroid hormones have been found in peritoneal fluid, and peritoneal fluid is in contact with the endosalpinx. Pre-ovulatory oestrogens and post-ovu-

latory progesterone in peritoneal fluid may influence diverse functions of the Fallopian tube. Peritoneal fluid may therefore prove part of the explanation for a local regulation.

Hormones in peritoneal fluid may include not only those derived from the ovaries, but also from the intestines, its mesenteries and associated deposits of adipose tissue such as leptin. In this regard, post-operative surgical adhesions developing between the uterus and intestines in pigs induce maintenance of the corpora lutea, an observation corroborated by suturing together 15–20 cm portions of corresponding uterine and intestine tissues [Léglise PC, Hunter RHF, 1968, unpublished observations].

Why is Drug Administration via the Nose, Oral Cavity, Rectum, and Vagina not yet universally accepted when enhanced local Effects can result from such Treatment?

The short answer is: lack of knowledge and little discussion in the medical school curriculum.

There are many advantages in these special routes of administration. However, interest in such routes is limited and few investigations have been made. There may even be a built-in negative bias: patients and doctors do not like it, it is a nuisance; both groups want oral pills or injections. Rectal or vaginal treatment used to be quite common but it gradually went out of fashion. This was before the distinct benefits of local drug administration were documented. Doctors and veterinarians introduced long-acting antibiotics and sulphur pills, oil suspension or implants into the uterus or rectum. The dose was smaller than for general treatment (penicillin was expensive in those days) and, especially in ruminants, the effect on the stomach microflora was less dramatic. Few treatments survived: progesterone (gestagen) containing “vagitories”, the treatment seemed successful in preventing early abortions after embryo transplantation; and sublingual application of nitroglycerine against angina pectoris. Vaginal application of oestrogens may also be useful to treat incontinence, since local transfer of substances takes place from the vagina to the uterus and bladder. The underlying rationale is that the first-pass liver metabo-

lism is avoided and a local favourable therapeutic ratio induced.

Counter-current transfer mechanisms add a new argument for local treatment, and the following comments will indicate the possibilities:

1. Intubated individuals with a high body or brain temperature should anticipate less brain damage if air is blown into the nasal cavities to cool the brain arterial blood. Clearly, this will not work at low body temperatures, but it does offer a safe and easily applied pre-hospital tool.
2. Drugs in nasal sprays may be locally transferred to brain arterial blood, and this partly specific treatment would favour the CNS compared to the peripheral nervous system. The system works in some animal species and possibly also in man. The documentation remains weak and further studies would be valuable.
3. Oral deposition of drugs has a special use at present: nitroglycerine under the tongue to enhance cardiac circulation. This is a proven quick and effective treatment – one may think of other possibilities.
4. Rectal administration has also a proven history, but patients tend to dislike the method. A first pass of the liver is avoided. The vascular supply to the distal 5–10 cm of rectum indicates that local transfer to the uterus and bladder may take place. In gynaecological cases, the rectum may be as useful in this respect as the vagina. In the male, rectal administration could be used for local treatment of bladder and prostate problems, but systematic investigations are needed.
5. Vaginal administration may be useful under specific circumstances. At present it is the most widely used application exploiting the advantages of a local counter-current transfer system. It is probably often used without knowledge of the local transfer. Vaginal administration of small doses of oestrogens (pills glued to the vaginal wall) tends to diminish incontinence in mid-aged women. Administration of progesterone after embryo transfer seems effective in preventing early abortion. Vaginal introduction of prostaglandin is used after administration of anti-gestagens in early pregnancy to induce uterine contractions and abortion.

Conclusion

The authors believe that studies combining classical organ physiology with cellular and molecular approaches would create a symbiosis that should increase our present knowledge dramatically. Furthermore, we believe that local effects due to local counter-current transfer of signal substances are underestimated and should always be included when discussing regulation of any organ function. The authors have included various suggestions for future experimental evaluation of these points.

Conflicts of Interest

Both authors contributed to the manuscript. Neither has any conflicts of interest.

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