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Review Article

Bloodless Circulatory Systems Including Axonal Transport and Eye Therapy Through Medicating the Toe

Rupasinha A. D. C. S.[1*] and Pathirana W[2]

[1]Research and Development Center, Link Natural Products (PVT) Ltd, Malinda, Kapugoda, Sri Lanka.

[2]Formerly at Department of Pharmacology and Pharmacy, Faculty of Medicine, University of Colombo, Kynsey Road, Colombo 08, Sri Lanka.

*Corresponding author: *chanadcsr@yahoo.co.in*

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ABSTRACT

A number of vital circulatory systems operate in the body which are devoid of blood. Each of these systems operate in isolation. This article intends to treat these bloodless circulatory systems as one whole new physiological entity so that they receive due attention. They carryout most functions of blood other than those related to erythrocytes. Unique among these is the neuron axonal transport of biological materials, now known to transport drugs. Treating eye diseases in *Ayurveda* through medication of the big toe of the foot for millennia appeared as an impossibility. Under this review it was possible to trace the probable axonal connecting pathway from big toe to the eyes. Strange enough, in this almost six-foot pathway, the drug molecules have to pass through only four biological cells except for 4-5 inches within the brain.

Key words: Axon microtubules; Kinesin; Dynein; *Padabhyang;* Cortical homunculus; Cerebral dorsal stream; Romberg's test; Aqueous humor; Lymph; Cerebrospinal fluid; Bloodless circulatory systems

INTRODUCTION

In the healthy human body, fluid is distributed between intracellular and extracellular compartments.(1) The most abundant extracellular fluid is interstitial fluid and it is occupying the space between cells.(2) The main intravascular body fluid is the blood plasma, which flows in the arteries and veins. Other extracellular body fluids that occur in lesser amounts are lymph, cerebrospinal fluid, the aqueous humor of the eye, and synovial fluid.

The main objective of this review article is to conceptualize the bloodless circulatory systems (BSCS) with novel drug delivery potential. These systems are quite intricate to simply explain under conventional drug absorption, distribution, metabolism and elimination (ADME) as applied to blood circulatory system.

Healthcare personnel have a general understanding about these bloodless circulatory systems (BSCS), under the

subjects of anatomy and physiology more as a passing mention rather than as a concept. A number of these fascinating systems are operating in the human body and in higher animals. The article intends presenting the fundamental basis in establishing the BSCS as a new physiology entity with their drug delivery potential. Emerging out of the systemic blood circulatory system through a molecular filtration process these systems circulate in loops and return back, except axoplasmic circulation in nerve axons which is an intricate independent system. These systems consist of 100% fluid media as against the blood circulatory system which is a 45% solid suspension of erythrocytes. The proposed systems already play a role in drug distribution inherent to them but without the grip of our deliberate efforts. Intricate details related to the subject could be found in articles, images, animations and videos in Google search under the key scientific terms spread across the article.

Four major BSCS include the lymphatic system, cerebrospinal fluid circulation, ocular circulatory system, and the nerve axonal circulation involving axoplasma and micro-tubules. The last one is identified as the underlying drug transport mechanism in *Ayurveda* therapy where certain eye diseases are treated by applying drugs on the big toe of the foot.(3)

Oral liver bypass carbamazepine delivery through the lymphatic circulation had been successfully attempted in a research project at the University of Colombo.(4,5) Following administration, certain drugs diffuse through cerebrospinal fluid and through the ocular circulatory system though mostly as an unintended side event. In the ocular circulatory system, the process operates counter-productively by washing off instilled drugs from the eye. When the intraocular fluid discharge from the eyes is blocked, it leads to pressure built up resulting in glaucoma. The nerve axoplasma circulatory system, neglected until recently has come under a flurry of research activity presently. These systems are quite intricate to simply explain under conventional drug absorption, distribution, metabolism and elimination (ADME) as applied to blood circulatory system. As for the BSCS it may be a matter of circumventing, retarding or enhancing one or more of the ADME stages of a given drug. There is good scope for physical manipulations and of course, surgical interventions too.

LYMPHATIC CIRCULATORY SYSTEM

Background: Any anatomical figure displaying the lymphatic vessels in the human body would indicate how widespread these vessels are. Lymph capillaries are more profusely intertwined alongside the finer capillary tufts of the blood circulatory system, an arrangement that facilitates reabsorption of interstitial fluid from the tissues leading to formation of lymph. The lymph circulation is unidirectional from the periphery of the body towards the heart. Two major lymph vessels, the right lymphatic duct, and the thoracic duct enter the blood circulation at the right subclavian and left subclavian veins discharging the lymph into the blood circulatory system (Figure 1). (6, 7)

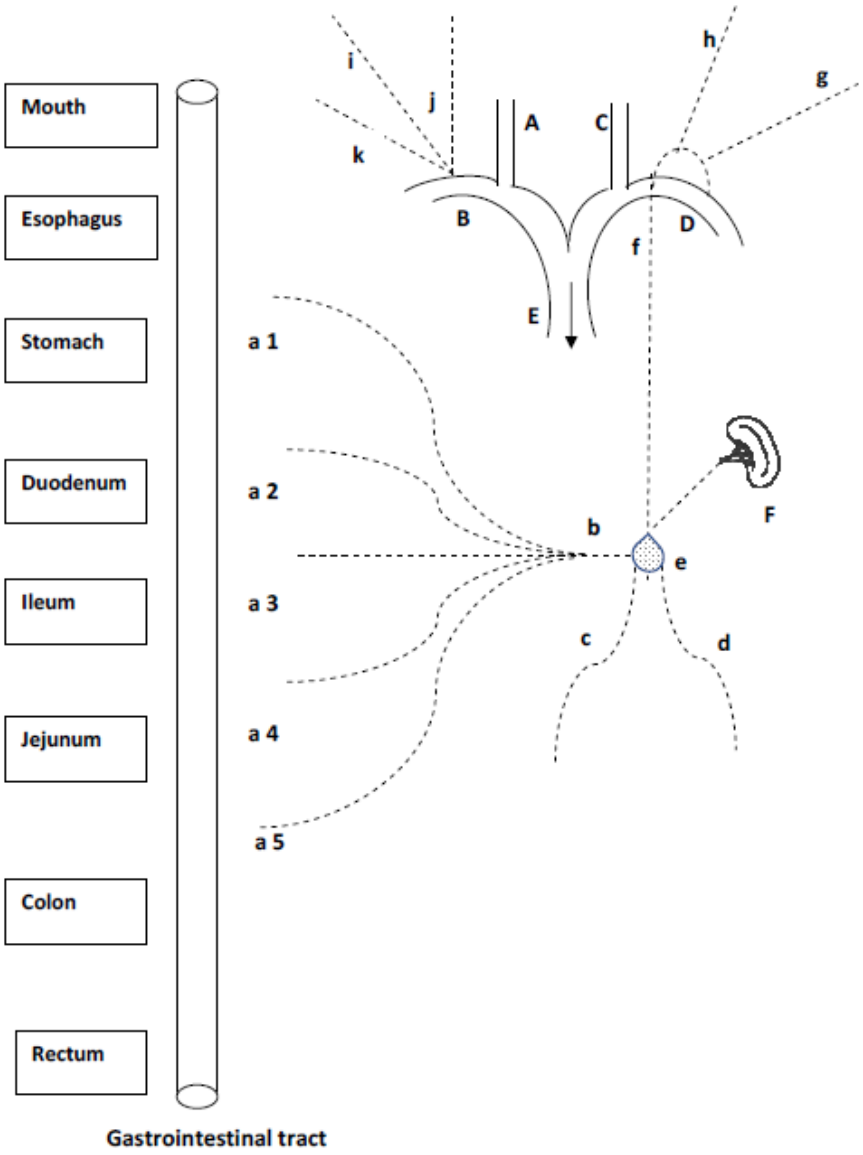

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Figure 1: The major lymphatic vessels displaying gastro-intestinal drainage into circulatory system bypassing liver. Fully diagrammatic, not to scale,

a1-a5: Lymphatic vessels originating in gastro-intestinal tract from stomach to colon, b. Intestinal lymph trunk, c. Right lumbar lymph trunk, d. Left lumbar lymph trunk, e. Cisterna chyli, f. Thoracic duct (Left lymphatic duct), g. Left subclavian lymph trunk, h. Left jugular lymph trunk, i. Right lymphatic duct, j. Right jugular lymph trunk, k. Right subclavian lymph trunk, A. Right jugular vein, B. Right subclavian vein C. Left jugular vein, D. Left subclavian vein, E. Superior vena cava and F. Spleen.

The major lymph vessel involved in the long chain fatty acid absorption from the intestines is the intestinal lymph trunk. The long chain fatty acids are trapped in chylomicrons and find their way in to and pass through the lymph trunk. It joins with the thoracic duct in a unique arrangement to bypass the liver conveying the fatty acids directly into blood circulation.(8) The major structures of the lymphatic circulatory system include the lacteal capillaries of the intestinal mucous membrane, Payer's patches of the intestines, terminal lymph capillaries in other parts of the body, lymph sacs, lymph nodes, intestinal

lymph trunk, right lymphatic duct, thoracic duct, tonsils, spleen, thymus and the vermiform appendix.(9) Composition of lymph is determined by the molecular filtration of extracellular fluid and is related to the composition of plasma.(10) The lymphatic fluid is pumped by peristaltic action (intrinsic pumping) of some of the lymph vessels. In other lymph vessels, the transport mechanism (extrinsic pumping) results from intermittent squeezing by the relative motion of, or pressure change in surrounding tissues such as, breathing action of the chest and the presence of valves preventing backward flow of lymph.(11)

The most significant aspect of drug delivery by lymph circulation is the possibility of diverting oral drug absorption bypassing the liver.(12) The advantages are the avoidance of first pass metabolism and minimizing the liver toxicity of drugs. The generation and the presence of lymphocytes in the lymphatic system and the prospect of these turning in to cancerous lymphomas is the greatest health concern related to the lymphatic system.(13)

Current applications: The lymphatic system has not received the attention of the formulation scientists until recently. It has been left to function much in the same way as it was before the advent of modern drug delivery technologies. This system conveys absorbed long chain fatty acids together with vitamin A following a meal. It is well established that certain fat-soluble drugs are absorbed through lymphatic pathway. Certain fat-soluble drug molecules, macromolecules and protein drugs including insulin have been formulated to deliver through intestinal lymphatics following oral administration.(14) These processes are mediated through assembly into chylomicrons, the discharge of these into blood stream that peaks around the 50th minute following consumption of a fatty meal.(15) Attempts are being made on transdermal drug absorption through lymphatics with the use of hyaluronic acid as an absorption enhancer.(16)

Research: No known commercially available oral medication is designed to be absorbed and conveyed through the lymphatics at present. In a research study involving rats and human volunteers, diazepam and carbamazepine had been successfully orally administered to absorb bypassing the liver conveying through the lymphatics into blood circulation.(4, 5)

As an excessive intra-ocular pressure relief measure in glaucoma, laser drilling of tiny canals through the clogged trabecular structure had been undertaken (trabeculectomy). This facilitates discharge of aqueous humor out of the eye from anterior chamber reducing pressure in order to prevent blindness.(17) The trabecular structure is located at the angle between the iris and the cornea. The surgically constructed canals then discharge the fluid into the Canal of Schlemm that runs around outside the irido-corneal angle of the eye. The finding of lymphatics in the eye, and their role in aqueous humor drainage represents a novel therapeutic target for glaucoma therapies.(18)

Most of the anticancer drugs are administered as IV infusions due to poor oral bioavailability, poor aqueous solubility, high P-glycoprotein (P-gp) effluxing and macro size of drug molecules. Intestinal lymphatic transport of drug delivery has been recognized as a potential route of oral anticancer drugs as it bypasses liver first pass metabolism and also due to their high lipophilicity and macro size of drug

molecules. The lymphatics have the potential to play a major role in anticancer treatment as the spread of cancer is much earlier in lymphatics than the vascular system. Because of this, administration of chemotherapy via the lymphatic absorption as a new concept for the prevention and treatment of metastatic lymph nodes give added advantages over existing IV and oral chemotherapy.(19)

A review article deals extensively on lymphatic delivery of orally administered drugs. Multiple formulation approaches have been developed to enhance the lymphatic transport of drugs and animal models have been used in these experiments. Most drugs that are destroyed by the enzymes in the liver could be delivered through the lymphatic absorption route to great advantage.(20)

CEREBROSPINAL FLUID CIRCULATION

Background: In the common parlance, little reference is made to the circulatory aspect of the cerebrospinal fluid (CSF). The CSF is in constant circulation within and around the brain. Also leaving the skull at the base, it circulates down to the lower end of spinal cord at vertebrae L1-L2 and further down into the subarachnoid space representing sacra1 vertebra S2.(21) In this way, a thin layer of CSF surrounds the entire brain and the spinal cord. The lumber puncture is performed inserting a needle into the subarachnoid space at L3-L5 to avoid injury to the spinal cord.(21) CSF is secreted at the choroid plexus and is present within the central nervous system (CNS), in the four ventricles of the brain and in the central canal of the spinal cord. The major component of the CSF is water (99%) and remaining 1% consisting of proteins, ions, neurotransmitters, and glucose.(22) Production of CSF is a two-stage process and in the first stage plasma is passively filtered from the fenestrated capillary endothelium into the choroidal interstitial space. In the second stage ultrafiltration happens across the choroidal epithelium into the ventricular spaces.(22) Driving force for the CSF flow is through the ventricular system, assisted in part by ciliated ependyma which beat in synchrony. Arterial capillaries that generate CSF in the choroid plexuses in the brain ventricles are mainly responsible for the pressure gradient that promotes the circulation of the fluid.(22)

In the average adult human, there is roughly 140 mL of CSF circulating at any given moment. In the human brain, the CSF circulation rate is quite slow and excreted in to blood every 4-5 hours or 4-5 times per day.(23) From the drug diffusion point of view, it can be considered a static layer of fluid since equilibration of drug distribution of most drugs peaks within 1-2 hours. Drug elimination down to ineffective concentration occurs in 6-8 hours. This fact has contributed to the recent successful experiments on transcranial brain targeted drug delivery. Here drug molecules diffuse through the scalp into the brain along the emissary veins, through the CSF layer and the meninges covering the brain.(24, 25, 26)

Neuroanatomy related to CSF circulation: The meninges covering the brain consist of three layers, the dura mater, arachnoid mater, and the pia mater in an exterior to interior direction. The dura mater has two layers, periosteal layer abutting the skull and the deeper meningeal layer.(27) Between the two dural layers lies the venous sinuses which drain blood from the brain into the internal jugular vein.(28) The next inner layer of the meninges is the arachnoid mater. Underneath this layer lies the subarachnoid space

internally lined by the innermost layer, the pia mater that tightly envelops the surface of the brain.(27) The last two meningeal layers together with subarachnoid space extend down the vertebral column enveloping the spinal cord. The subarachnoid space extends all around the brain and the spinal cord and contains the CSF.(27) CSF generation points are the choroid plexuses, located in the two lateral ventricles and in the fourth ventricle of the brain.(23) In the brain ventricles, the fluid passes through connecting ducts and foramen, finding its way out near the base of the brain escaping into subarachnoid space surrounding the brain and the spinal cord (Figure 2). The CSF leaves the fourth ventricle into the central canal of the spinal cord through medial aperture (Foramen of Magendie) and into the subarachnoid space through the two lateral apertures (Foramina of Luschka). Thereafter the fluid flows down the spinal cord and rises all around the brain in an upward direction finally escaping at the top of the brain through arachnoid granulation into venous sinuses in the dura mater.(21)

Arachnoid granulations or the villi are small superficial projections of the dura mater into the venous sinuses through which CSF is finally discharged in to sagittal sinus and thereafter into the internal jugular vein (Figure 2).(22, 28) The innermost pia mater lines all the superficial structures of the brain, sulci, gyri, fissures separating lobes of the brain, cisterns and the Virchow-Robin spaces representing a structure somewhat like the surface of a cauliflower.(27) This structural feature vastly increases the surface area of the brain surface which is in contact with the pia mater that is bathed in CSF. Increased surface area in turn promotes drug diffusion from CSF into the brain.

A unique setup is found in the optic nerve, which is surrounded by the meninges, the subarachnoid space with the CSF surrounding it almost to the very base of the eyeball similar to the brain.(27) In this sense, the eyeball almost sits on the brain. In fact, embryologically origin of the innermost part of the eye is common to that of the brain.(29) Similar set up extends up to the bony labyrinth of the inner ear which is in intimate association with the auditory nerve.(30) It is the close association of these two organs to the CSF compartment that facilitate any infection of these organs spreading into the meninges and the brain which is always viewed as a clinical concern.(31, 32) This anatomical set up may be responsible for some of the adverse effects of certain toxins and drugs (methyl alcohol, streptomycin etc.) on these two cranial nerves.(33, 34)

The brain ventricles consist of two lateral ventricles lying upper most somewhat horizontally with 3rd and the 4th ventricles lying below connected through ducts and foramen. The overall ventricular structure carries two anterior, one posterior, and two inferior horns. The 3rd and 4th ventricles lying one below the other are connected by the Aqueduct of Sylvius.(22, 28)

Current applications: Epidural, intracisternal, intrathecal, spinal and intracerebroventricular injections are intended for local action or to be diffused

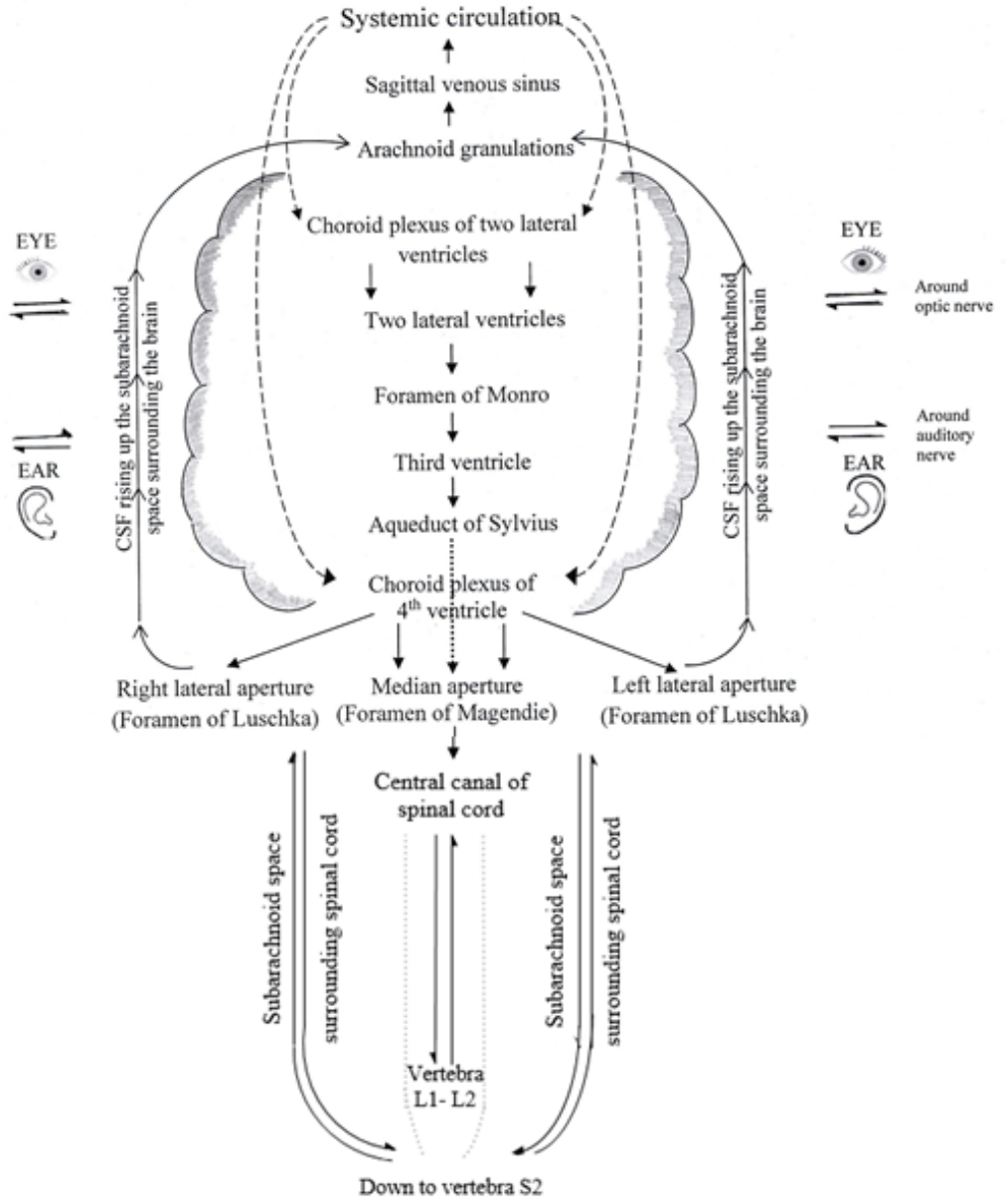

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Figure 2: Flow chart for the cerebrospinal fluid (CSF) generation and circulation pathways

Blood circulation ----------►

Bloodless circulation of CSF ——————►

Arrow pathway runs below the text ·····►

throughout the CSF.(35) Following the injection of a drug, it moves through the CSF flow tracks, and is absorbed into the peripheral bloodstream across the arachnoid villi to enter the general circulation.(23) Some of these injections carry highly specialized drug substances including genetic materials, proteins, enzymes etc. and mostly require services of a specialist formulation pharmacist to avoid the addition of

excipients.(35) Intrathecal drug delivery of baclofen injection/infusion, morphine, gentamicin etc. is currently approved in the UK.(35)

Some of the *Ayurvedic* massages over the vertebral column may be intended to convey herbal medicinal substances to the central nervous system through CSF of the spinal cord.(36)

Research: Diazepam and methadone solutions in sesame oil had been administered by applying on the scalp of rats and human volunteers in brain targeted drug delivery experiments. Drugs were expected to be conveyed by emissary veins in to dural sinuses and thereafter diffuse through meninges and CSF layer into the brain. The results show that brain targeting across CSF layer is possible.(24,25,26) Such a transportation is favored by the extremely slow rate of 4-5 changes of CSF in 24 hours giving ample time for drug diffusion. There are reports indicating that drugs absorbed into CSF find their way into the systemic blood stream at a rate resembling that of a slow intravenous injection.(23)

THE OCULAR CIRCULATORY SYSTEM

Background: This is the smallest of the bloodless circulatory systems. The fluid flow path is less than 4 cm and is essentially confined to within the anterior part or cavity of the eyeball lying in front of the lens. Because of the potential for the loss of sight, this system carries much significance. The cornea and the lens of the eye are devoid of blood vessels and lymphatics.(37) Therefore, these tissues are outside the immune system, an arrangement that greatly facilitate corneal transplants without the need for elaborate tests such as tissue typing.(37) These tissues depend on nutrition supplied by the aqueous humor which is discharged into the posterior chamber of the eye through the ciliary body and flows between the lens and the iris.(38) The freshly generated aqueous humor converge on the pupil, flows out of it into the anterior chamber and spreads in a reverse direction over the iris in a 360^0 direction in the shape of a mushroom (Figure 3).(17, 38) The respiration is directly from the air which is in contact with the cornea. The contact lenses interfere with this respiratory process and certain complications are possible during long term use.(39)

After collecting metabolic waste, the fluid then passes through the trebacular mesh lying at the irido-corneal angle of the eye leaving the anterior chamber into the ring-shaped Canal of Schlemm.(38) This wash down mechanism is the reason why eye drops have to be administered four times a day in order to provide the required therapeutic concentration. The blockade of the Canal of Schlemm to any degree leads to a rise in intraocular pressure leading to glaucoma.(38) Anterior and the posterior chambers together constitute the ‘anterior cavity’ and the larger space containing the vitreous humor constitute the ‘posterior cavity’, which are the two cavities lying anteriorly and posteriorly to the lens (Figure 3).(40) Posterior chamber should not be confused with the posterior cavity which does not belong to the circulatory system. A light ray thus enters the eye passing the structures in the order, cornea, anterior chamber, pupil, posterior chamber, lens, vitreous humor and retina.(40)

Though not exactly a circulatory system, there is the tear duct in each eye which is responsible for the draining out of tears as well as eye drops into the vestibule of the nose.

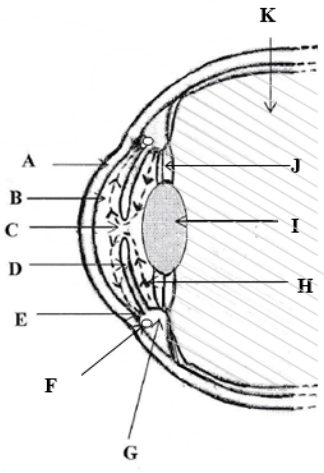

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Figure 3: Longitudinal section through anterior portion of the eye for the demonstration of bloodless aqueous humor circulation pathway

A: Cornea, B: Anterior chamber, C: Pupil, D: Iris, E: Trabecular mesh, F: Canal of Schlemn, G: Cilliary body, H: Posterior chamber, I: Lens, J: Suspensory ligament, K: Vitreous humor (Posterior cavity), B+H: (Anterior cavity).

--------▶Direction of aqueous humor flow

The tear duct drains out any excess fluid from the Cul de Sac of the eye, which is the potential space between the surface of the eye and the eye lids (Figure 4).(41) The tear gland duct, Cul de Sac and the tear duct of the nose taken together could be viewed as a closed ducting system when the eyes are closed but is open to atmosphere when the eye lids are open. The tear duct is a kind of a natural fistula. It is common knowledge that following application of eye drops, after few minutes bitter taste of certain drugs could be felt in the mouth. Long term administration of certain eye drops results in throat irritation.(42) This is because the tear duct connecting medial corner of the eye with the nose making it possible for the drugs to diffuse into the systemic circulation via the highly vascularized nasopharyngeal route.(42)

Current applications: The more fastidious eye drops manufacturers indicate measures against the loss of medication through tear duct in their product information leaflets. The instruction is to keep pressing medial corner of the eye (puncta compression) in order to retard drainage of the medication through tear duct providing longer time for the drug to diffuse across cornea into drug receptor sites.(42)

Research: As a surgical relief measure in glaucoma, laser drilling microsurgery could be performed as described under Research subsection of **Lymphatic Circulatory System.** One of the most sort after research area for the last few decades is the attempt to apply insulin drops or spray in order to deliver insulin through the eye.(43, 44)

In a research study, it has been successfully attempted to deliver Tetramethylpyrazine hydrochloride in to rats through ocular pathway targeting brain disorders.(45)

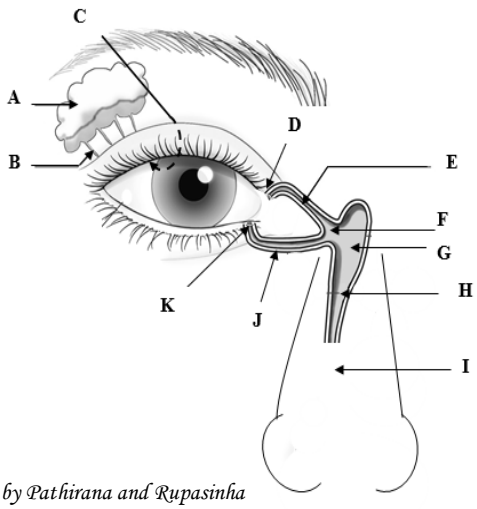

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Figure 4: Diagrammatic representation of the naso-lachrimal duct (tear duct) system of right-side eye

A: Tear gland, B: Tear gland ducts, C: Cul de Sac, D: Superior punctum, E: Superior lachrimal canal, F: Common canaliculus, G: Lachrimal sac, H: Naso-lachrimal duct, I: Vestibule of nose, J: Inferior lachrimal canal, K: Inferior punctum.

It is suggested that ocular administration is a promising alternative route for the administration of drugs for brain therapy as this pathway is noninvasive, permits the rapid onset of therapeutic effects and avoids first-pass hepatic metabolism.(45)

NERVE AXON MICROTUBULAR CIRCULATION

Background: The nervous system of the human body with all its ramifications may have a wider distribution than the blood circulatory system. The circulatory or the transport function of the nerve axons had eluded the scientists until recently. For decades, the author was fascinated and wondered about the possible mechanism behind the reported *Ayurveda* treatment of certain eye diseases by applying medicines on the big toe of the foot.(3) Equally curious was the folklore practice among the villagers in the belief that bad effects resulting from wading in water leads to catarrhal conditions especially in children. In the bygone days wading in water was viewed as a cause of catarrh. A reference that is remotely related to this mechanism could be found in which it speaks about reflex constriction of blood vessels in the nose.(46, 47) This shows some close connection between toes and the eyes despite the extreme distance between their anatomical locations. Anatomy of the blood circulatory system does not indicate any specific vessels connecting the two sites.

The first plausible anatomical feature here is that the one meter long sciatic nerve runs all the way down to sole of foot starting from the spinal cord at L4 to S3 segments of the vertebral column. Sciatic nerve consists of the axons of single neurons (or a single biological cell) bundled together lengthwise which represents the lower motor neuron.(48) From the spinal cord another single neuron, which is the upper motor neuron completes the connection to the motor cortex of the brain.(49) Hence an entire height of a man from head to foot is connected by only two neurons. The eye or more specifically the retina is connected to the visual cortex in the occipital region of the brain also through two neurons. The first neuron takes the visual sensory pathway to the lateral geniculate nucleus from where a second neuron connects it with the visual cortex.(50) A striking feature here is that at both ends of the axonal pathway that is being traced, the outer most sensory surfaces are just two neurons away from the brain. These two segments involve one synapse each.

Despite the extreme linear distance of about seventy inches on two segments described so far, only four neurons (or four biological cells) are involved in connecting the eye to the big toe. This leaves to account for less than five inches between the motor and visual cortical centers which will be explained later.

The nerves are composed of short dendrite neurons confined to within the brain and long axon neurons connecting the other parts of the body lying outside the brain.(51) Running through the axons (diameter 0.1-1.5μm) are the bundles of micro-tubules formed by alpha and beta tubulin heterodimer profilaments 1-10 mm long, mostly 13 in number, each tubule being 25 nm in diameter. Unlike blood vessels the microtubules are not permanent structures often assembling and separating the building blocks of these tubules.(52) Through these many biological substances such as neurotransmitters are transported from cell body to end synapse that may be one meter apart.(51)

Axons are wrapped around by several layers in the formation of the nerve trunks one of which is the endoneurium. Within the

endoneurium individual nerve fibers (composed of several axons) are surrounded by the endoneurial fluid which is the equivalent of CSF of the CNS.(53) Although lying outside the axon, this fluid too may play a part in nerve mediated transport of drugs.(54, 55)

The transport of material down the axon is called axoplasmic transport and it is established that the nerve axons constitute a widely distributed unique circulatory system.(51) It has been reported that the speed of axoplasmic circulation is comparatively slow at a rate of 1 - 400 mm/day.(51, 56) Various types of cargo are transported through the axoplasma.(51, 56) This is an indication that the onset of action in the eye following administration through the toe is bound to take time. It is widely reported that most agents are transported through the axons mediated by chemical motors. The two major chemical motors are the proteins Kinesin that moves cargo away (anterograde) from the cell body towards synapse (lipid, protein, mitochondria, vesicles) and Dynein that moves substances towards (retrograde) the cell body.(51, 56) A drug molecule picked up at the nerve terminal in the big toe will only have to cross two neurons and one synapse in the segment under consideration to reach the brain. It has been found that hundreds of drugs have been conveyed through the axon route following intramuscular administration. Some have been found to be effective at $1/300^{th}$ the normal dose.(57) Nerve impulses and axonal transport are two independent functions of the nerve axons. The axonal transport mechanism should be common to both sensory and motor neurons.

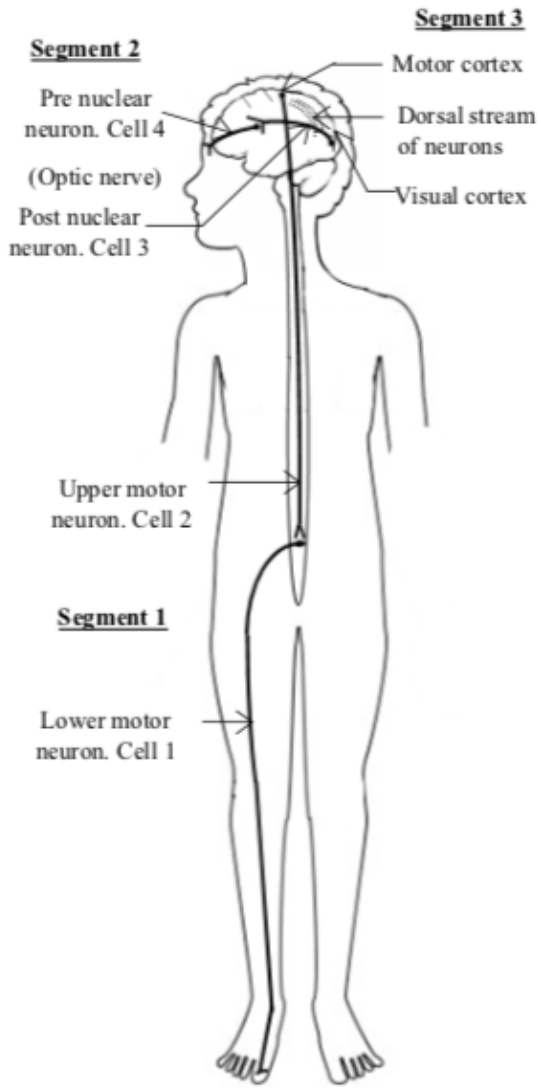
Thick skin histology: The nature of the dosage design, technique of application, and drug diffusion through the unusually thick skin of the sole of foot were the other areas that had to be understood. A probable unique histological feature of the sole of foot may exist that distinguishes it from the rest of the skin.(58) The sole has a much thicker skin. In other parts of the body, blood vessels reach the skin surface at the same level and nearly in the same density as the nerve terminals. Therefore, any drug administered dermally through general skin will be quickly absorbed by the circulatory system that has an overwhelmingly larger circulatory rate depriving absorption by the nerve terminals. In the case of the thick-skinned sole of foot, the density of nerve endings appears to be greater than that of the capillaries. Further the nerve terminals penetrate towards the surface of the sole whereas blood supply terminates at deeper layers of the skin. There are four types of cutaneous mechanoreceptors named Pacinian corpuscles, Ruffini corpuscles, Merkel's disks, and Meissner's corpuscles distributed in the sole of the foot skin.(59, 60) The absence of hair follicles in the sole would mean the absence of skin appendages such as sebaceous glands that has a rich supply with tufts of blood capillaries. The absence of skin appendages drastically reduces the skin surface area. Therefore, unlike the rest of the skin, the histological features of the sole of foot show that the nerve terminals have a comparative advantage over the blood vessels in exposing them for drug absorption. It is this abundance of nerve supply that provides for swift reflex withdrawal of foot from the smallest prick before the object reaches the blood vessels preventing bleeding.(60) This explains the basis of medicated foot massage in *Ayurveda* system of medicine in certain central nervous system diseases and applying medications to the big toe in treating certain eye diseases.

Toe to eye axon tubular pathway: A probable nerve axon transport pathway connecting the big toe with the eye can be traced as follows. A good knowledge in the anatomy of the nervous system, cerebral cortex, the neurons, dendrites, nerve axons, axon microtubules and the microtubule transport chemical motors serves as the basis in tracing this pathway. A Google search under 'cortical homunculus' (small person) will show the cortical areas representing the toes. The two neurons, meaning two biological cell connecting path from the motor cortex of the brain to the big toe of the foot represents the movement of the lower limbs (Figure 5). Similarly, the visual senses of the eyes are connected to the visual cortex through optic nerve which also consists of two neurons.

Completion of the five-inch gap between the motor and visual cortical centers is through the 'dorsal stream' of interconnecting third segment of neurons of the brain identified in this study.(61) These three segments constitute the possible big toe to eye diffusion pathway for drugs. As for the synapses interrupting the continuity of axon microtubules, it must be assumed that the drug is discharged from distant neuron and absorbed by the proximal neuron at the synapse. A synapse could be well adopted to such a process as evident by its activity with respect to release and reabsorption of neurotransmitter acetylcholine.

Romberg's test in tracing sole of foot to eye axon pathway: A person's orientation of sitting, standing or lying is basically monitored by numerous proprioceptors widely distributed in muscles, tendons and joints throughout the body.(62) However, there are significant in puts from two other sources providing enhanced proprioception. These are the vestibular sensory inputs of the ears and more significantly the visual sensory inputs.(63) During certain pathological condition in the brain with deterioration of proprioception or vestibular inputs, the patient rely heavily on the visual pathway inputs to keep his balance.(64) Two sensory pathways coordinating the same function is an indication that their nerve pathways are connected. In the Romberg's test, the patient is asked to stand and close the eyes cutting off the visual inputs on which he now relies on for sustaining the posture.(65) Romberg's test is considered positive if there is significant imbalance with the eyes closed or the imbalance significantly worsens on closing the eyes.(65) It has been reported that blind subjects deprived of visual pathway inputs rely more on vestibular and somatosensory feedback for locomotion control than normal sighted people.(66) These are the indications that the visual nerve pathways are connected to proprioceptors of the lower extremities. In turn, this supports the proposed toe to eye three segment neuron theory and that axonal micro-tubular drug delivery from the toe to the eye is a possibility.

In the traditional *Ayurveda* therapy, drug is bandaged to the big toe which is expected to have an anatomical specificity to the nerve pathway to the eye.(3,67,68) Some of the Indigenous and *Ayurvedic* medical practitioners associated with foot medication treatment in Sri Lanka are Dr. Janaka Hulugalla, medicated shoemaker from Bibile, traditional practitioner Wijesinghe Wedamahattaya at Lankaramaya road, Anuradhapura (oral communication with K de Costa, 10th April 2020) and an *Ayurvedic* doctor at *Ayurveda* Research Center, Government of Sri Lanka, Navinna, Maharagama.



Drawn by Pathirana and Rupasinha

Figure 5: Diagrammatic representation of four cell (neuron) pathway from big toe to eye through cerebral dorsal stream.

For diseases in the left eye mediation is applied on the big toe of the right foot and vice versa. This accounts for the crossing of half the optic nerve fibers from each eye to the opposite side at the optic chiasm in the brain.(69)

A summary of drug administration in a patient who was cured of poor vision and able to see without spectacles for the last 20 years is as follows. A small portion of ground medicinal leaves was placed on the big toe nail. This may be to retard the rate of absorption. Cover medication with a piece of banana or betel leaf and wrap it around the toe with a bandage. Medication made to diffuse around the toe facilitating absorption. Hold it for 6-8 hours, remove it and take a bath. Following day at the exact time apply the same portion same way slightly moistened with warm water. Repeat process for one month and visit practitioner for a fresh portion. End of one-year patient was able to see without spectacles (oral communication with K de Costa, 10th April 2020).

The sciatic nerve has diverse branches of sensory nerve terminals distally with the branch median planter nerve supplying the big toe and a complex of nerve roots emerging from the spinal cord proximally.(70) It is beyond the scope of this article to trace the specific axon fibers originating from the big toe, ascend through the sciatic nerve and take a specific nerve root as they cross into the spinal cord and beyond up to the motor cortex. Most difficult would be the identification of specific dorsal stream group of neurons consisting of the third segment connecting the motor cortex with the visual cortex.

Current applications: It has been observed that tetanus resulting from injuries to areas rich in nerve supply such as fingers are more intense than from injuries to other fleshy areas of the body. This is because a greater concentration of nerves is present in these areas making it possible for more of the tetanus toxin to get conveyed to the brain along the nerve axon. Tetanus toxin reaches the central nerve system from a peripheral site of injury through retrograde axonal transport.(71, 72) Herpes zoster is another instance where the herpes virus is conveyed

to skin sites throwing up blisters in the chest wall most commonly through intercostal nerves and cranial nerves.(73) It is also suggested that the polio virus travel through the nerve axons to their sites of attack.(74) Hand, foot and mouth disease in children are known to undergo retrograde neuron axonal transport.(75) A confirmed case of drug diffusion based on microtubules is the axonal transport of the drug taxol.(76) In Sri Lanka, herbal medicated slippers are manufactured by Jeeva Sri Ayurveda aimed at drug absorption through sole of foot to the brain.(77)

Ayurveda perspective and *Padabhyang*: References to the neuronal pathway connecting the sole of foot with the eye are extremely rare. This may be due to lack of awareness among the scientists about the *Ayurveda Padabhyang* concept.(78) The least evident part of the anatomical segments thus far identified in this pathway is through the dorsal stream of neurons in the brain. The ventral stream of the brain is responsible for two of the most important co-ordinations. These include the co-ordination of the visual and auditory stimuli with the motor cortex facilitating the instantaneous reactions of the extremities to the incoming visual and auditory stimuli.(79) Damage to these two cortical nerve streams results in responses restricted only to the ability to see and hear but with the loss of ability for any coordinated response of the body, particularly those of the extremities. The medication of the eye through sole of foot or the big toe is mediated through this largely hidden ventral and the dorsal stream pathways essential for normal coordinated bodily activity. Central nervous system drugs could also be possibly conveyed through the *padabhyang* pathway by administering through the sole of foot.

Ayurvedic foot massage activates the acupoints present in foot. Vision related acupoint is in the lateral aspect of foot. When acupuncture stimulation is performed at the vision related acupoint in the lateral aspect of the foot, activation of occipital lobes was observed by using the Magnetic Resonance Imaging (MRI).(80)

Unusually thick dermis of the foot needs revolutionary formulation techniques and manipulative measures to facilitate migration of the drug molecules into the axon terminals. It may take several hours to reach optimal absorption. It was possible to collect a host of suggestive formulation ingredients. These include aloe vera (*Aloe barbadensis*), castor oil, ghee, mustard oil, sesame oil, olive oil and coconut oil. Aloe vera is said to have deep penetration property of up to the innermost layer of the skin.(81) However, this might encourage absorption of the medication into blood stream through capillaries lying in deeper skin layers.

Prior to treatment of any callous formation and excessively thick parts of the foot need to be rubbed off using pumice stone after softening the parts.(82) For the removal of callouses the recommended ingredients include licorice (*Glycyrrhiza glabra*), aloe vera (*Aloe barbadensis*), flaxseed oil, castor oil, vinegar, calendula (*Calendula officinalis*) and salt. Fresh aloe leaves to be split, applied on affected parts and left-over night. Castor oil need to be mixed with vinegar.(82) Haritaki (*Terminalia chebula*), common salt, bees wax, garlic (*Allium sativum*), cinnamon (*Cinnamomum verum*), black wall nut hulls (*Juglans nigra*), neem (*Azadirachta indica*) and copper oxide are the other ingredients mentioned in removing and cleaning the excessively thick skin prior to administration of the medication.

A research setup in tracing the scientific validity of *padabhyang* therapy could be on the following lines, first in animal models and then in human volunteers. A suitable formulation of a swiftly responding modern active ingredient could be prepared based in line with the principles of *Ayurveda* formulation techniques. It must be supported with the necessary inputs of modern formulation science. Changes to the diameter of pupils could be easily measured. The lengthy diffusion pathway of axon microtubules may take several days to reach and manifest response in the pupil. Some of the mydriatics that are suitable for the trials include atropine, phenylephrine and tropicamide.

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