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Cerebrospinal Fluid Absorptive Site of the Parasagittal Dura: a Cadaveric Study

BY

Richard John Fox

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of Master of Science

IN

Experimental Surgery

DEPARTMENT OF SURGERY

Edmonton, Alberta
Fall, 1995

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7640 70 Avenue
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With cordial regards,

Alan L. Shabo, M.D.
Clinical Professor of Ophthalmology
UCLA School of Medicine

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Dr. Richard J. Fox MD
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May 8, 1995

Dr. Joe G. Hollyfield
Editor-in-Chief, Experimental Eye Research
Cullen Eye Institute
Baylor College of Medicine
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U.S.A. 77030

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Editor, Brain
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London
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Table 1-2 - p-9

Figure 1-3 p-18

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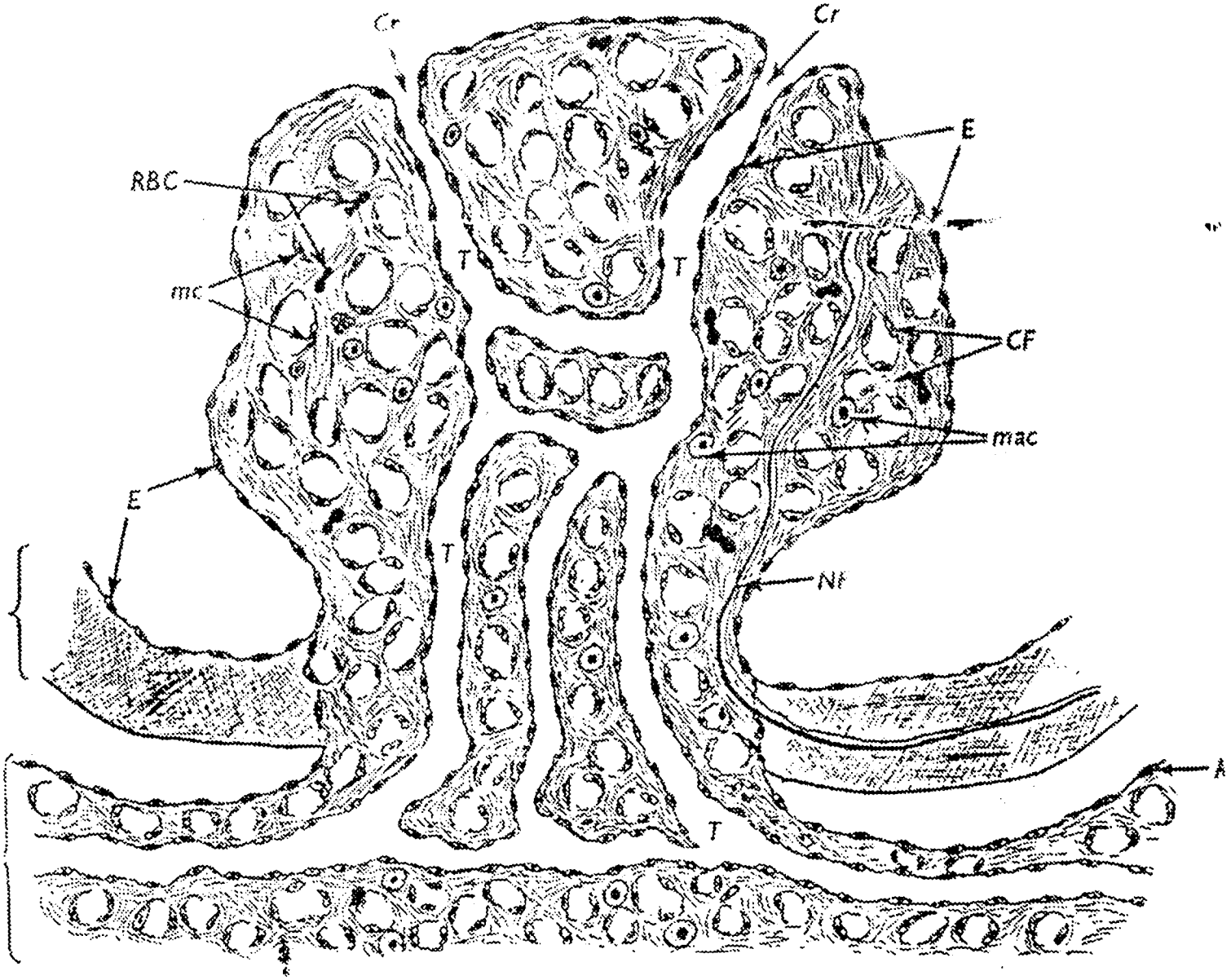
Figure 5 55



SAS, Subaraenoid space; *D*, dura mater; *A*, arachnoid membrane; *E*, endothelial cell; *T*, tubule; *mac*, macrophage cell; *mc*, mesothelial cell; *Cr*, crypt; *CF*, collagen fibres; *RBC*, red blood cell; *NF*, nerve fibre.

From Jayatilaka, 1965

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Dr. Richard J. Fox MD
7640 70 Avenue
Edmonton, Alberta
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May 9, 1995

Dr. Robert A. Fishman
Editor, Annals of Neurology
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Fig 1-2 - p 16

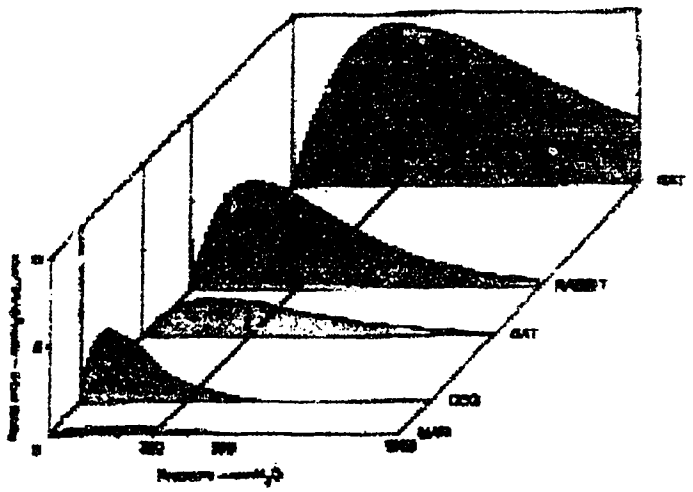

Fig 6. *Comparative plots of CSF sulphur variations as a function of pressure for various mammalian species. Pressure values for rat have been reduced by a factor of 10 to allow graphic comparison. Points on the curves represent the maximal sampling pressure tolerated for each species. Plots for cat and rabbit were obtained from data previously reported by other workers* [12, 18].

Dr. Richard J. Fox MD
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March 21, 1995

Thomas H. Milhorat, MD
Department of Neurosurgery
State University of New York
Health Science Center
450 Clarkson Avenue
Brooklyn, New York
11203

Dear Dr. Milhorat:

I am a Neurosurgical Resident at the University of Alberta in Edmonton, Canada. Currently, I am engaged in writing my Masters of Science thesis on the subject of the parasagittal dura and cerebrospinal fluid pathways. With your permission, I would like to include a diagram taken from your book entitled " Cerebrospinal Fluid and the Brain Edemas", Neuroscience Society of New York, 1987 (copy enclosed) as part of my thesis.

Your work has been most helpful in my studies.

Kindest Regards,

Richard J. Fox, MD

Approved, Fig 10, page 27
Thomas H. Milhorat MD

Good luck with your thesis!

Figure 1-1 p6

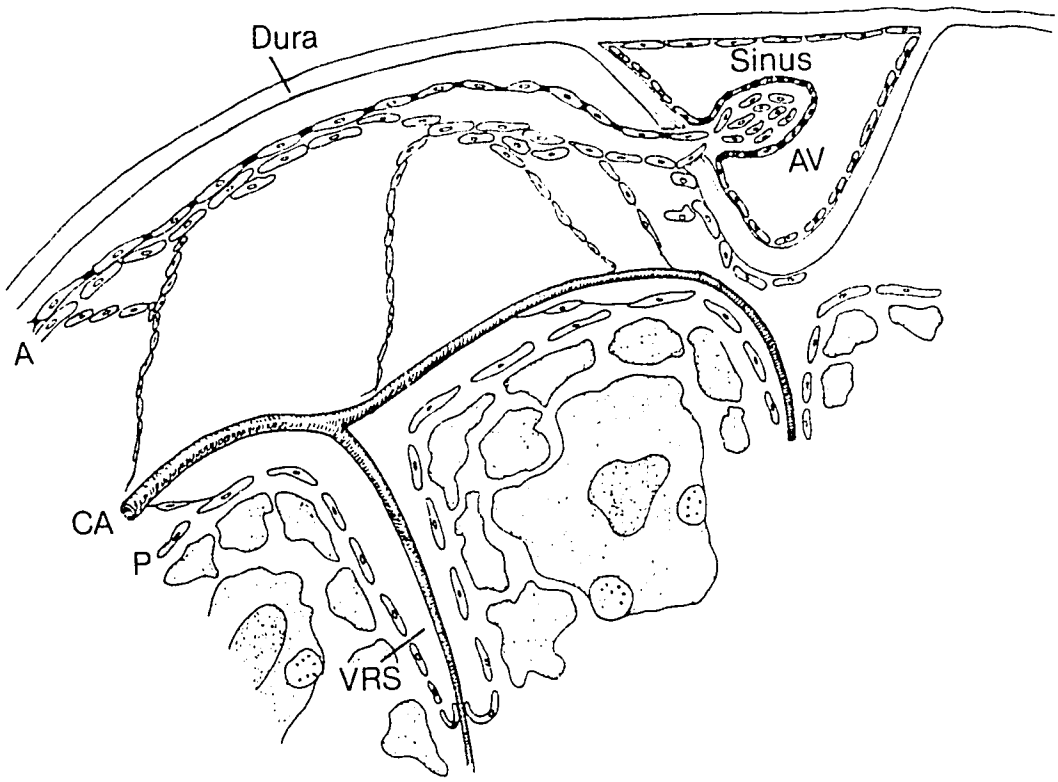

Figure 10: Subarachnoid space. Note that tight junctions join cells of outer layer of arachnoid and sinus endothelium overlying arachnoid villus. CA = cerebral artery, VRS = Virchow Robin space, P = pia, A = arachnoid, AV = arachnoid villus.

Dr. Richard J. Fox MD
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June 22, 1995

Dr. A. L. Shabo
Department of Anatomy and
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UCLA School of Medicine
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Dear Dr. Shabo:

I am a Neurosurgical Resident at the University of Alberta in Edmonton, Alberta, Canada. Currently, I am engaged in writing my Masters of Science thesis on the subject of parasagittal dura and cerebrospinal fluid pathways. With your permission, I would like to include in my thesis a diagram taken from **The Journal of Neurosurgery.** The article is entitled "the Morphology of the Arachnoid Viili: A Light and Electron Microscopic Study in the Monkey" and is found in Volume 29, Pages 451-463, 1968, Figure 1. A copy of the diagram is enclosed for your convenience. Permission to reproduce has already been obtained for the Journal of Neurosurgery and I am writing to Dr. Maxwell to obtain his consent also.

Kindest regards,

Richard J. Fox, M.D.

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NAME OF AUTHOR: Richard J. Fox

TITLE OF THESIS: Cerebrospinal Fluid Absorptive Site of the Parasagittal Dura: a Cadaveric Study

DEGREE: Master of Science

YEAR THIS DEGREE GRANTED: 1995

Richard J. Fox, MD
7640 70th Avenue
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Date: August 20, 1995

University of Alberta

Faculty of Graduate studies and Research

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Cerebrospinal Fluid Absorptive Site of the Parasagittal Dura: a Cadaveric Study** submitted by **Richard John Fox** in partial fulfillment of the requirements for the degree of Master of Science in Experimental Surgery.

K. E. Aronyk

Dr. K.E. Aronyk

Dr. K.C. Petruk

Dr. A.H. Walji

Date: 28 August 1995

This work is dedicated to my loving, patient, and supportive Wife, Roxanne, and to my late Father, John Dodge Fox, who's own love for science and knowledge helped me notice the uncommon in an otherwise common world.

Abstract

Cerebrospinal fluid (CSF) absorption occurs primarily via arachnoid granulations (AG) in the superior sagittal sinus (SSS) and lacunae laterales (LL) in parasagittal dura. Anatomic descriptions of this region suggest a network of intra-dural channels, but lack demonstrations of their extent and relationship to AG.

The SSS and parasagittal dura of 20 formalin-fixed adult cadavers, and 15 fresh autopsy specimens of ages 18 weeks gestation to 80 years were studied using light microscopy (LM), scanning and transmission electron microscopy (SEM, TEM), and corrosion casting. Intradural injections into the parasagittal region were performed in two formalin-fixed and four fresh autopsy adults using normal saline and corrosion casting medium.

Extensive, laterally-branching networks of intra-dural channels of 0.02 to 2.0 mm diameter were noted in all specimens. They connected to the SSS through regulary spaced trunks in its sidewall, or into LL, and extended up to 3 cm laterally. Their size and frequency increased with age. They were lined with endothelium similar to that of the LL and SSS, with positive factor VIII antibody staining and tight junctions. The LL were a coalescence of channels. The dural underside was trabeculated where these channels were abundant. AG were inserted between these trabeculae in sheets. In regions of dura where channels were sparse or absent, the dural underside was consistently smooth and lacked AG. The underlying cortical veins opened directly into the SSS, and were generally unrelated to the intradural channels.

Intra-dural parasagittal injections readily accessed the SSS via the parasagittal intradural channels with pressures of 0-20 cm water at an infusion rate of 1.5 mL/minute.

These channels appear to represent important pathways of CSF conduction to the SSS, and may represent a potential site for purely intracranial CSF diversion .

Acknowledgements

There are so many people at the University of Alberta whose expertise and enthusiastic interest have made this work possible. To begin with, Dr. K.E. Aronyk, my supervisor and mentor, has been the source of unending enthusiasm and support. Based on Dr. Aronyk's earlier work in Chicago, this project was undertaken in our lab in hopes of developing new ways of managing the problem of hydrocephalus—a problem which makes up a large and often unhappy segment of pediatric neurosurgical practice. It was under his keen eye for the new and unusual that our research took its course. For a remarkable experience this past year, I thank Dr. Aronyk. I must also thank Drs. K.C. Petruk, A.H. Walji, and B.W. Mielke for their helpful suggestions.

Ms. Maxine Farr-Jones, in her quiet, "behind the scenes" way, continues to be a key figure in the smooth running of the Neurosurgical laboratory (despite the often distractable thought processes of the Neurosurgeons and Residents!). Similarly, Mr. Alan Sarafinchan was instrumental in ensuring that we had full access to the Anatomy laboratory at the Medical School.

Dr. Ming Chen of the Medical/Dental Electron Microscopy laboratory and Mr. George Braybrook of the Geology Scanning Electron Microscopy laboratory provided excellent technical assistance and insightful suggestions which were key to the success of our work.

Finally, recognition must be given to Mr. Tom Turner for his remarkable ability to use photographic techniques to their fullest potential in recording our findings. Rebecca Aronyk, with similar painstaking attention to detail, provided us with illuminating graphic artwork to convey our interpretation of the anatomical structures we studied.

Funding for this work was generously provided by Division of Neurosurgery, Department of Surgery, University of Alberta.

Table of Contents

List of Tables

Chapter 1

List of Figures

Chapter 1

Chapter 2

List of Figures

Chapter 2 (continued)

Chapter 4

List of Abbreviations

ATP	Adenosine Triphosphate
AG	Arachnoid Granulation
CNS	Central Nervous System
CP	Choroid Plexus
CSF	Cerebrospinal Fluid
FGF	Fibroblast Growth Factor
ISF	Interstitial Fluid
LL	Lacunae Laterales
LM	Light Microscopy
MRI	Magnetic Resonance Imaging
NPH	Normal Pressure Hydrocephalus
PGI_2	Prostacyclin
SAS	Subarachnoid Space
SEM	Scanning Electron Microscopy
SSS	Superior Sagittal Sinus
TEM	Transmission Electron Microscopy
VIP	Vasoactive Intestinal Polypeptide

Chapter 1

The Anatomy and Physiology of the Cerebrospinal Fluid System

Introduction

Management of communicating and non-communicating hydrocephalus remains a significant problem. These conditions arise due to obstruction of flow of the cerebrospinal fluid (CSF) somewhere between its sites of production and absorption. Treatment using a simple bypass procedure —a CSF shunt— is an intuitive approach to dealing with the underlying defect. Though third-ventriculostomy procedures using ventriculoscopic technique have an important role in the management of selected cases of non-communicating hydrocephalus,[32] there remains a large population for whom the CSF shunt is the only currently available option. The ventriculoperitoneal shunt is currently the most widely used device for shunting CSF. Complications related to the length of ventriculoperitoneal shunt systems and the required valve mechanisms are well described.[32] Attempts have been made to devise intracranial bypasses in hope of overcoming some of these problems. Indeed, therein lies the essence of the third ventriculostomy procedure.

Our own interest in alternate approaches to CSF diversion initiated a closer inspection of the parasagittal dura and related arachnoid mater. The consistently spongy appearance of this region in post-mortem specimens has been likened by others to the trabecular meshwork in the anterior chamber of the eye, leading to the canal of Schlemm.[65, 126] Also, our preliminary observations of cadaveric meninges revealed that arachnoid granulations are found not only invaginating directly into a dural sinus or lateral lacune, but also more laterally, where no such obvious vascular receptacle resides. Our question of how CSF could travel from these lateral sites to a venous destination has led to closer examination of the parasagittal dura using various techniques.

A comprehensive review of the literature regarding all aspects of CSF anatomy and physiology has been the starting point for our investigations.

Historical Overview of CSF

Absorption of cerebrospinal fluid has been a focus of research at least since the time of Galen(130–200 A.D.), who proposed that CSF was a liquid carrier for the essential vapour of the brain, the psychic pneuma.[3, 124]Observations made on live animals indicated that CSF originated from the choroid plexus within the ventricles, and emptied over the base of the brain through an opening in the fourth ventricle. He described the pathway of drainage from the cranium via the cribriform plate into the nasopharynx. He also described pathways through a vascular plexus, the *rete mirabilis*, clustered around the infundibulum and draining to the palate. Galen was limited to animal studies (as human autopsy was illegal under Roman law), and thus did not realize this plexus was replaced in the human by what is now known as the circle of Willis. He also believed that air could enter the cribriform plate and mix with the fluid.[124]

Vesalius (1514 –1564) considered CSF to be a fluid, and pointed out that the plexus seen in the calf around the infundibulum was a circular network in humans (later known as the Circle of Willis).[15]

Harvey (1578 –1657), and his contemporary Thomas Willis (1621–1675) at Oxford in England, put forth that venous return was a potential for drainage of the cranial contents rather than the cribriform plate, and hypothesized that CSF thus might also be absorbed into the venous system. Also at Oxford, Richard Lower(1631–1691) through work with dye tracers, failed to demonstrate a significant CSF drainage pathway through the cribriform plate, and argued strongly that the only significant absorption of CSF was into the venous system.[15, 124]Albrecht von Haller (1708 –1777) considered that CSF was absorbed into veins, and any excess absorbed into the base of the skull and the spine. Fantoni (1738) was perhaps the first to conclude that CSF was absorbed into the venous blood of the superior sagittal sinus (SSS) via the granulations Pacchioni had described in 1701.[17, 124]

Key and Retzius in 1876 assembled a series of ideas of the previous hundred years to derive the first complete and authoritative description of CSF production, pathways, and absorption.[3, 124] Their experimental work on cadavers using gelatinous tracers was very exacting, with close attention paid to control of pressures of infusing tracers. They convincingly demonstrated the pathway of CSF flow across the arachnoid villi directly into the superior sagittal sinus, and their work remains a landmark in the field.[3, 132]

Investigations in the twentieth century are best considered in the context of our modern understanding of cerebrospinal fluid anatomy and physiology.

Role of The Cerebrospinal Fluid

The cerebrospinal fluid plays a multifaceted role in the central nervous system. It provides mechanical protection to the brain within the skull, and in early embryological development, may provide internal structural support. Perhaps more important to the daily functioning of the brain are the metabolic, neuroendocrine, fluid-homeostatic, and immunologic properties of CSF.

The brain essentially floats in its own CSF, both reducing its effective weight and providing a shock-absorbing environment. As Pacchioni described, the CSF in the subarachnoid space does provide a film of lubrication between the layers of the meninges, specifically the pia and the arachnoid mater.[17]

Normal development of the brain and cranium is dependent on adequate internal support provided by CSF.[84, 87, 104] It has been suggested that the Chiari II malformation represents a failure of this process. Observations of a murine model point to the failure of the transient closure of the primitive cavity in the CNS (the spinal neurocele), and likely the continued loss of CSF into the amniotic fluid *via* an open neural tube defect, as a cause for many of the characteristic anomalies of this disorder. Failure of the hindbrain to ad-

equately expand the posterior fossa may result in the observed cerebellar and brainstem herniation, the beaked tectum, and the cervical-medullary kink. Also, failure to distend the third and lateral ventricles may be the cause of gray matter heterotopias and fused thalami with a large massa intermedia.[87]

The CSF may be considered as a "sink" for metabolites and water produced by the brain. CSF in humans turns over its total volume four to five times each day, which provides a flushing system down the CSF absorptive pathways which are known to accommodate macromolecules.[102, 103] Within the parenchyma of the brain,Weed[131] identified a system of channel-like passages conducting interstitial fluid (ISF) of the brain either toward an ependymal surface or the perivascular channels and pial surface. These were later confirmed through ultrastructural studies.[23, 89] Such clefts are not the morphological equivalent of lymphatics elsewhere in the body as they possess no endothelial lining. **(Figure 1-1)** This parenchymal pathway for fluid and solutes does not involve a process of diffusion across intact plasma membranes, as evidenced by similar rates of movement of molecules with markedly differing molecular weights.[22, 23, 113] Metabolites produced by the brain move by bulk flow into the ventricular system down a pressure gradient; this can be experimentally modified to impair transfer of markers into the CSF at elevated ventricular pressures.[111] Solutes travel down a concentration gradient maintained by the dilutional effect of CSF production (sink action); this gradient can be neutralized by ventricular perfusion with the substance in question such that its CSF concentration reaches that of the serum. [23, 26, 106] The steady state CSF concentration of a substance injected intravenously can be increased with the use of acetazolamide, which decreases CSF production rate, thus lessening the sink effect.[13] There may be a component of absorption into parenchymal capillaries in certain pathologic states,[23, 111] but this remains to be quantified.

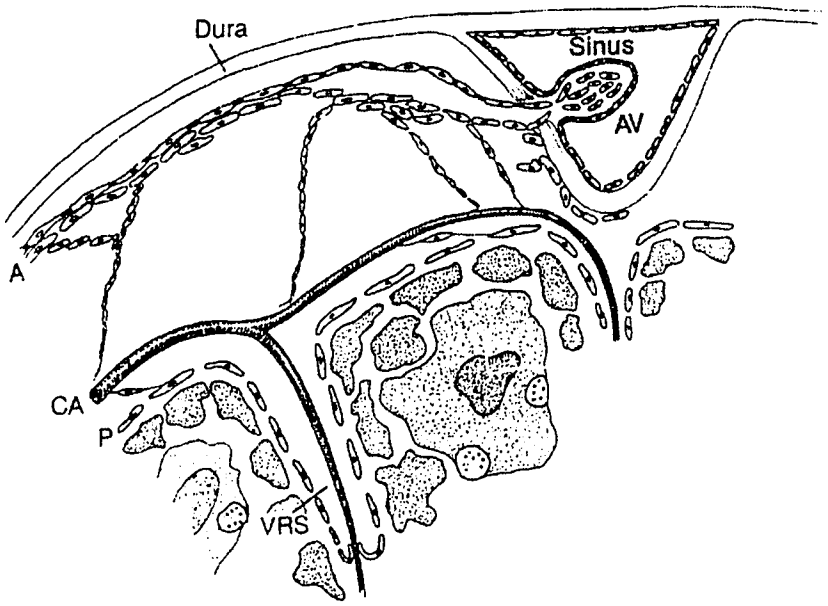
The ready exchange of solute and fluid between the brain parenchyma and the CSF also provides a mechanism for acutely maintaining cerebral water content despite variations in serum osmolality. The brain is made up of approximately 80% water, with the

Figure 1-1: the subarachnoid space and intraparenchymal clefts

A

Due to lack of copyright authorization, this diagram ofWeed's interpretation of the subarachnoid space has been omitted.

B



The descriptions of the subarachnoid space and the intraparenchymal clefts and perivascular spaces have changed little since Weed's description (A) in 1923 and modern descriptions such as Milhorat's (B)in 1987. The brain parenchyma contains open, unlined clefts which conduct CSF to the pial (shown) and ependymal surfaces. The leptomeninges is carried along with penetrating cortical vessels, forming invaginations of the subarachnoid space into the brain, known as the Virchow Robin spaces. Tight junctions are present along the outer aspect of the leptomeninges. With permission (A) The American Journal of Anatomy, 31:191-221, 1923, Figure 2,. and (B) Milhorat, TH, *Cerebrospinal Fluid and the Brain Edemas.* New York, Neuroscience Society of New York,1987, Figure 10, page 27.

extracellular fluid (ECF) representing some 15–20% of brain volume.[22, 31] White matter is much less dense than grey; the former can absorb up to approximately 10% water by weight, compared to only 1.5% by the latter.[31] Periventricular white matter edema is a commonly observed occurrence in the setting of hydrocephalus, in both acutely raised intracranial pressure,[70, 93, 94, 102, 103] and in "normal pressure" hydrocephalus[6, 66, 114] It has also been shown experimentally that fluid can flow across the ependyma to the interstitial space in a compensatory fashion. Intravascular infusion of mannitol or hypertonic sodium chloride solution into rats revealed prompt movement of CSF-born markers into parenchyma indicating that fluid shift from the subarachnoid space is a compensatory mechanism to prevent shrinkage of parenchymal cells.[108] Similarly, intraventricular infusion of hypotonic solutions results in increased brain water content, particularly in the periventricular white matter.[60] The capillary endothelium is not impermeable to ions, and flux of potassium, sodium, and chloride ions is important to the maintenance of brain volume. Cserr *et al* calculated that when the brain is dehydrated, most of the influx of water that accompanies sodium and chloride into the brain parenchyma comes from bulk flow from the CSF, and very little from plasma. In the case of potassium influx, most of the associated water volume arises by diffusion from the serum.[24]

The Nature of CSF

CSF is a clear colourless mixture of fluids released from the choroid plexus [132, 134] and the interstitium of the brain.[22, 102, 111] Its composition is similar to plasma except for a marked paucity of proteins. (table 1-1)

The Choroidal Component of CSF

The choroidal component of CSF is actively secreted from the choroid plexus (CP) through an ATPase-dependent process.[96, 117] At the surface of the CP, tight junctions at the apical ends of modified ependymal cells provide a selective blood-CSF barrier. The underlying core of the choroid plexus villi contain fenestrated capillaries, making the blood-brain barrier deficient here.[81, 89]

Table 1-1: comparison of cerebrospinal fluid and serum

With permission: Elsevier Science Publishing Co. Ltd., 1991, from *Principles of Neural Science*, Kandel ER, Schwartz JH and Jessell TM (eds), 1991, Table C-1, page 1053.

	CSF	Serum
Water content (%)	99	93
Protein (mg/dl)	35	7000
Glucose (mg/dl)	60	90
Osmolarity (mOsm/l)	295	295
Na+ (meq/l)	138	138
K+ (meq/l)	2.8	4.5
Ca++ (meq/l)	2.1	4.8
Mg++ (meq/l)	0.3	1.7
Cl - (meq/l)	119	102

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The rate of CSF production is essentially independent of intracranial pressure within physiologic range;[27, 81] however, with extreme intracranial hypertension, arterial perfusion pressure is overcome, and like the rest of the cranial contents, the choroid plexus is no longer perfused.

The reported opening pressure of the CSF in normal adult volunteers undergoing lumbar puncture is 11–14.4 mmHg;[1, 41] In neonates in whom no intracranial pathology is suspected, this value is reported to be 1.0–5.7 mmHg.[62]

CSF production rate varies significantly from species to species (table 1-2), and it increases somewhat with maturation. CSF production rate in children is reported as 0.18–0.6 ml/minute,[5] and in adults, 0.35 ml/min.[27] Human CSF renews itself approximately every 7 hours, based on a ventricular volume of approximately 140 ml,[67] and an average CSF production rate of 20 ml/hr as noted above. The rate of secretion may be significantly but transiently reduced with osmotic agents such as mannitol[117] and with acetazolamide or furosemide, which inhibit ATPase function.[27, 105, 117] These reductions, however, are transient. The effects of these agents demonstrate that the process of choroidal CSF production occurs across an intact membrane, and is an active process involving ATP. Injury to this membrane, (i.e. in the setting of ventriculitis), has been shown to decrease the rate of CSF

Table 1-2: values for CSF formation rate, CSF turnover,and resistance to absorption of CSF in several species.

Reproduced by permission from Oxford University Press from **Brain** 91:707-720, 1968,Table IV

Species	Formation ml/hr	Formation ml/min/g Chor. Plexus	Turnover %/hr	Resistance to Absorption cm/ml/min
Cat	0.9	0.38	24	390
Dog	3.1	0.59	23	224
Goat	9.8	.35	37	132
Calf	17.4	.36	—	123
Man	21.0	.18	23	13

formation. An experimental model in the rabbit demonstrated a drop of 50–66% of normal, with histologic evidence of choroid plexus epithelial damage without underlying vasculitis.[12]

There exists in the literature a body of evidence to suggest that the choroid plexus is subject to modulation of CSF secretion from the autonomic nervous system, as well as neurohumoural agents. Electrical stimulation of the superior cervical ganglion has been shown to significantly decrease the rate of CSF production.[58, 74, 76]It would appear that such a procedure in the setting of acute high pressure hydrocephalus has less effect than in chronic hydrocephalus. Lindvall reported a decrease of 18% in the rate of CSF production in rabbits with acute hydrocephalus through electrical stimulation of the superior cervical ganglia; this value increased to 39% in animals in the chronic stage. It was postulated that this was due to near maximal endogenous sympathetic tone in the acute phase, which then relaxed over time as other compensatory mechanisms came into play.[76]Similarly, sympathectomy results in a significant (33%) increase in the rate of CSF formation in rabbits after one week.[74]Qualitatively consistent results were found by radioimmunoassay of Na^+/K^+ ATPase enzyme function in a similar experimental setting in cats.[33] The autonomic effects are thought to be mediated through alpha-adrenergic receptors in the vascular smooth muscle cells, and beta-adrenergic receptors in the epithelium of the CP.[75] Other peptidergic nerves have been identified in the CP through immunohistochemistry and radioimmunoassay such as vasoactive intestinal polypeptide (VIP), neuropeptide Y, and peptide histidine isoleucine in the rat, pig, guinea pig, and rabbit.[95]Receptors for other neuropeptides such as melatonin and atrial and brain natriuretic peptides have also been described. A comprehensive review of this complex area has been recently published.[96]

CSF has also been shown to compete with ouabain (a cardiac glycoside) in direct inhibition of purified Na^+/K^+ ATPase *in vitro* .[51, 73]Also, the influx of K^+ is inhibited in red blood cells when placed in an extract of CSF, perhaps indicating that the K^+-driven ATPase is inhibited in this setting also.[51] Infusion of normal saline in humans results in increased

inhibition of Na^+/K^+ ATPase by CSF sampled 30 minutes after infusion. This effect was not observed following a simple glucose infusion.[50]

Experimental evidence of autonomic influence on CSF formation, and of CSF-borne neuromodulatory peptide control over electrolyte-pumping enzymes such as Na^+/K^+ ATPase provide further support for the concept of CSF as a buffer to maintain the homeostasis of the central nervous system despite acute changes in blood osmolality.

Extra-Choroidal Component of CSF

The above discussion has focused on the CSF produced by the choroid plexus. Our present day understanding of the significant non-choroidal source of CSF has stemmed from failure of a surgical procedure initially thought to be very soundly based. An intuitive treatment of hydrocephalus evolved in the early part of the century which involved destruction or removal of what was believed to be the only source of CSF. Choroid plexus coagulation was first performed in 1910 by Espinasse in Chicago.[47] A more aggressive procedure, choroid plexectomy, was first performed by Dandy in 1918.[118] This latter technique, based on a single successful procedure on a dog[89] was associated with high operative mortality (3 of 4 infants in the original series), as it required total drainage of the ventricles so that the choroid plexus could be removed; this resulted in severe shock.[118] The procedure was abandoned after other surgeons experienced similar tragic outcomes in the 1940s.[118] Choroid plexus cauterization, however, has lingered in the background. In the 1990s, it has been performed using modern ventriculoscopic techniques; Griffith and Jamjoom report 52% long-term cure.[47] A famous report by Milhorat of a child with persistent hydrocephalus following bilateral choroid plexectomy strongly suggested an extrachoroidal source of CSF.[90] However, it was not clear if the surgical procedure resulted in increased loss of proteinaceous fluid into the subarachnoid space (SAS), resulting in the hydrocephalus. Subsequent CSF

production rate was measured at five years and found to be normal.[92] The reasons behind this are crucial to the understanding of extrachoroidal production of CSF. The surgical procedure does not include removal of the choroid plexus in the third and fourth ventricles; this residual tissue may be sufficient to produce normal amounts of CSF, particularly if it is subject to a compensatory increase in production. Such compensation has not been demonstrated to the author's knowledge.

Another possible reason for failure of choroid plexectomy is that a significant component of the total CSF is produced by the interstitium of the brain [22, 89, 102, 111] The finding by Brightman that the brain parenchyma possesses an open system of clefts which conduct fluid toward the cortical surface as well as the ependymal linings was critical to the understanding of extrachoroidal CSF production. Since the brain does not possess true lymphatics, the concept of this "brain lymph" was not well accepted until these interstitial pathways were convincingly demonstrated.[14, 22, 23] The exact fraction of the CSF pool contributed to by interstitial sources remains to be established. This is not likely a consistent, or even measurable amount, as it may be subject to change from time to time in the individual, and certainly so after any structural intervention in a laboratory or clinical setting. However, it is generally accepted that the maximal decrease in CSF production following choroid plexectomy is approximately 40%.[89]

MORPHOLOGY OF THE CSF PATHWAYS

Overview

The choroidal component of CSF travels from its origin at the choroidal surface, mixing with the interstitial fluid which has transgressed the ependyma, through the ventricular system and exits via the paired foramina of Luschka and the midline foramen of Magendie.[114]Once in the SAS of the cisterna magna, it circulates in and out of the intrathecal space within the vertebral canal, through the basal cisterns, and over the cerebral convexities toward the sagittal sinus.[114]There may be specific or preferential CSF pathways within the subarachnoid space.[4] It has been demonstrated in rats that a pathway exists in the subfrontal SAS heading directly toward the cribriform plate.[139] Fluid is also contributed to the CSF pool from interstitial fluid spilling onto the pial surface from the perivascular, and in particular, periarteriolar spaces.[23]

MRI Studies

In the past few years, technology has provided us with a completely new window on CSF flow by way of Magnetic Resonance Imaging (MRI), and in particular, Cine-MRI. Several groups have reported common findings. Specifically, CSF has a pulsatile flow which most closely resembles the arterial pulse wave form.[59]CSF flow through the various intracranial compartments is not synchronous. The first movement following the R wave in the cardiac gated cycle is seen in the posterior basal cisterns and the upper cervical canal. Subsequently, flow is seen in the anterior basal cisterns. Flow through the cerebral aqueduct and the foramina of Monroe is last to occur, and is almost synchronous.[34, 35, 38, 72, 97, 109, 119, 122]

Th ability of MRI to detect changes in local CSF flow may prove it to be a useful diagnostic tool in hydrocephalus. For example, using MRI, flow through the aqueduct has been demonstrated to be fastest in the setting of Normal Pressure Hydrocephalus (NPH), less so in acute hydrocephalus, and slowest in the setting of hydrocephalus *ex vacuo*.[11] Decrease in flow has been observed with this technique in various settings including communicating and non-communicating hydrocephalus, and in spinal canal compromise.[34, 72, 97, 109, 119] Flow within syringes has also been reported, which may be important to the understanding of the pathogenesis of this condition.[109]

CSF production rate has also been quantified using Cine-MR. Interestingly (and inexplicably), the formation rate was reported as a mean of 0.625 ml/minute—approximately double that reported generally in the literature using conventional techniques.[123]

CSF Absorptive Pathways

The focus of interest in CSF absorption has vacillated since approximately the turn of the century. The pathways considered significant in recent years include the arachnoid granulations, the perineural route with extracranial lymphatic involvement, brain parenchymal absorption, and a vascular route involving the circumventricular organs. Each of these has been extensively investigated in numerous animal models as well as in humans.

A: The Arachnoid Granulation

For the purposes of clarity, the term arachnoid "granulation" will be used henceforth in this paper (somewhat arbitrarily) to imply an exuberant arachnoid villus—one readily observable by the unaided eye, whereas inspection of an arachnoid "villus" requires magnification. As noted, the arachnoid granulation was first described in the literature by Pacchioni in 1701.[17, 124] His description at that time did not suggest that these structures were part of a

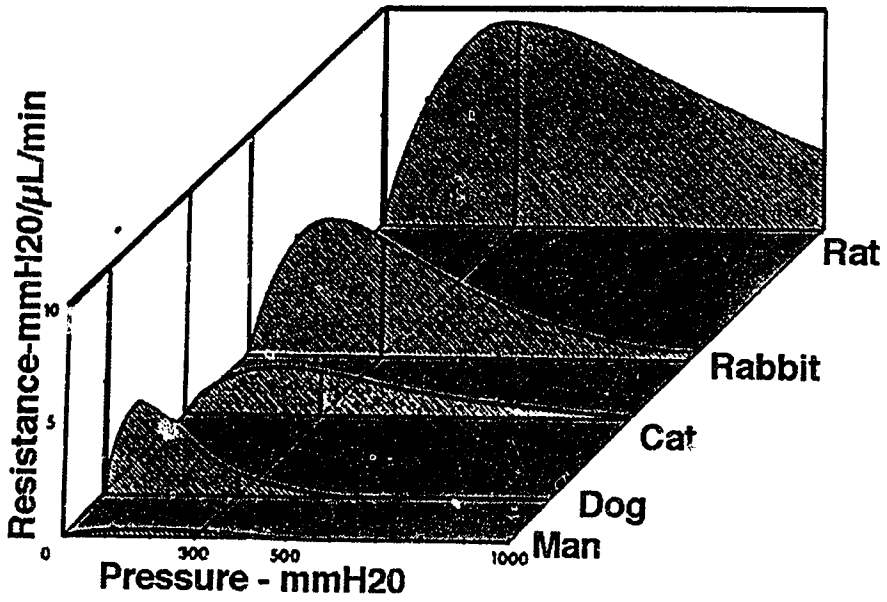
drainage pathway for CSF; rather, he suspected they were a site of fluid production, perhaps as a lubricant between the layers of the meninges.[17] Fantoni later proposed that these Pacchionian bodies were a site of CSF drainage into venous blood, and in particular the superior sagittal sinus.[3, 124]The work of Key and Retzius has been repeated, refined, and reconfirmed by numerous groups showing that indeed a pathway does exist from the subarachnoid space into the venous blood of the SSS through these herniations of arachnoidal tissue.[2, 20, 21, 28, 30, 120, 125-129, 131-133, 136, 138]Though there remains in the literature the occasional argument that arachnoid granulations are not the main site of CSF absorption,[18, 54, 80, 100]for the most part this concept is widely accepted. The debate continues however, as to the exact nature of the arachnoid villus, regarding both its own ultrastructural details and its relationship to recipient structures such as the SSS.

Arachnoid villi have been reported in humans as early as 35 weeks gestational age, and granulations by 39 weeks.[43] Development of granulations appears to continue throughout life. The few small granulations present in an infant in the SSS and precursors of the lacunae laterales evolve to a complex of macros opic structures housed in large lacunae in adults.[68, 98]Continued growth may lead to their becoming transdural,[112]and eroding depressions into the underside of the skull.[48]Primarily located along the superior sagittal sinus in a variety of animals as well as humans, granulations typically are found in the ostia of draining veins,[43, 68]and are found in greatest numbers carpeting the floors of lacunae laterales.[68, 98]They in fact occur along all the dural sinuses,[68, 131] the perineural veins of spinal nerve roots,[42, 137]and along middle meningeal veins.[68]

Common descriptions exist regarding the general structure of an arachnoid granulation. Weed's description of a meshwork of arachnoidal cells more dense than the arachnoid mater proper, invaginating into a venous sinus[131] has changed very little over the century. The concept of a continuous membrane overlying granulations was established by his work, and persisted until the 1960s. The concept of individual channels, lined with an endothelial membrane, and leading to the venous lumen, were proposed at this time.[61, 135] The idea that

the granulation was covered with a continuous membrane also found new support with ultrastructural studies showing the presence of vesicles in the endothelial layer.[120] The presence of nerve fibres in arachnoid granulations has been reported, though their significance remains ill-defined.[61, 130] Over the past twenty-five years, there have emerged two opinions regarding how CSF exits the SAS through the arachnoid granulation—ones supporting the open or the closed system of drainage. Each must explain a system which accommodates large pressure swings with postural changes in humans, tolerates the infusion of relatively large volumes of fluid into the SAS, and permits removal of large proteins along with CSF from the SAS. The remarkable ability of the human nervous system to absorb CSF with quite low outflow resistance, which falls with increasing outflow pressure (**figure 1-2**), demands explanation.

Figure 1-2: CSF outflow resistance in various mammalian species.



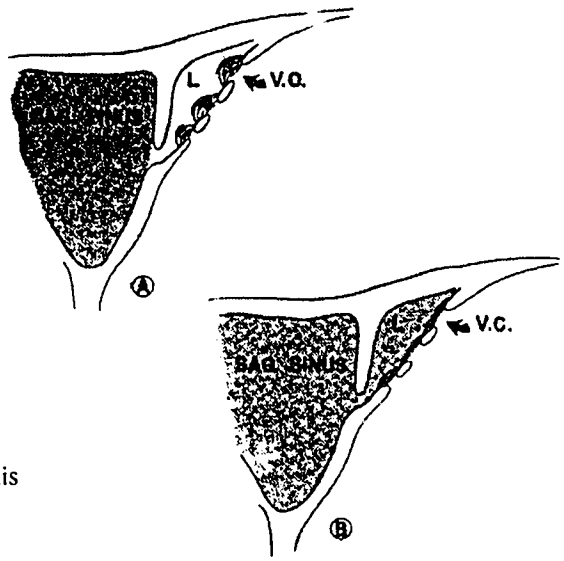
The CSF outflow resistance in man is significantly less than common laboratory mammals; however at least one common characteristic is evident.. Resistance to outflow decreases with increased outflow pressures. This favours an open system of CSF absorption. Note the rat resistances have been reduced by a factor of 10. Reprinted with permission from**Ann Neurol** 3:156-165, 1978, Figure 6.

The Open System

There is both anatomic and physiologic support for the concept of a physically open system of CSF drainage. Cushing conceived of the notion that CSF drained through a system of one-way valves at the arachnoid interface with the SSS. This idea was essentially a conceptual explanation for his observations that fluid would easily pass in large volumes from the SAS to the SSS, but blood was essentially blocked from travel in the opposite direction.[135]Also, in his work with effects of intracerebral compression using a mercury filled bladder, he noted that if the bladder ruptured, the mercury thus spilled into the SAS was recovered in the dural sinuses, jugular veins, and right heart, but not the cervical lymphatics.[132]However,Weed's work essentially dispelled Cushing's ideas. By injecting into the SAS a solution of potassium ferrocyanide and iron-ammonium citrate, (which resulted in a precipitation of Prussian blue granules), Weed demonstrated that the arachnoid villus was a blind-ended herniation of arachnoid mater, devoid of any valvular structure. Consequently, Cushing and most other contemporaries abandoned the open concept in favor of a process of diffusion across continuous membranes over the arachnoid granulation.

In 1960, Welch and Friedman revisited the question with experiments on the African Green Monkey. Having formalin fixed the specimens, small sections of the SSS were trapped between the ends of two cylinders, and lactated Ringer's solution infused across the membrane thus suspended. They found that the disc of membrane including arachnoid villi had an opening pressure of just under 25 mm of infusion fluid, that there existed a linear relationship of pressure and flow rate across the membrane, and that no back-flow of fluid from SSS to SAS occurred. They found no influence of osmotic force exerted by serum placed on the SSS-side of the disc, which argues against a continuous intervening membrane. Histological specimens indicated a "labyrinth of tubules" in the villi, leading from SAS to SSS. They interpreted this as an open system of channels of fixed diameter, with the property of

Figure 1-3: Welch and Friedman: One-way valvular system into the SSS



The concept of one-way valves at the interface of the arachnoid and the lacunae laterales explained the findings of highly compliant fluid transfer at this site. V.O. = valves open, V.C.=Valves closed. L= lateral lacune.Reprinted by permission of Oxford University Press from **Brain** LXXXIII:454-469, 1960, Figure 12.

a unidirectional valve system.[135] **(figure 1-3)** Electron microscopic examination of the SSS in 4 sheep by Jayatilaka in 1965 provided further support for this idea, with the interpretation of endothelial lined tubules existing within the core of the villus, opening directly into the SSS. [61] **(figure 1-4)** Subsequent studies with similar interpretations have since appeared.[45, 46] Upton *et al* reported small pores on the external apical surface of arachnoid granulations, leading to endothelial lined structures interpreted as venous. Also reported was a meshwork of channels within the collagen fibers of the villus core. This is similar to the description given by Jayatilaka.

Physiologically, an open system of absorption is supported. If the final step of CSF absorption included an intact endothelial membrane draped over the arachnoid villus, then one would expect that the rate of absorption would be affected by introducing osmotically active agents in either the SAS or the SSS. Davson *et al* demonstrated that the rate of CSF absorption is not affected by osmolality of CSF, whereas it is inversely proportional to its viscosity.[30] Significance of this finding is found through its contrast with the later work of Sahar *et al* , wherein the outermost layer of the choroid plexus, which by virtue of its tight

Figure 1-4: Drawing of sheep arachnoid granulation

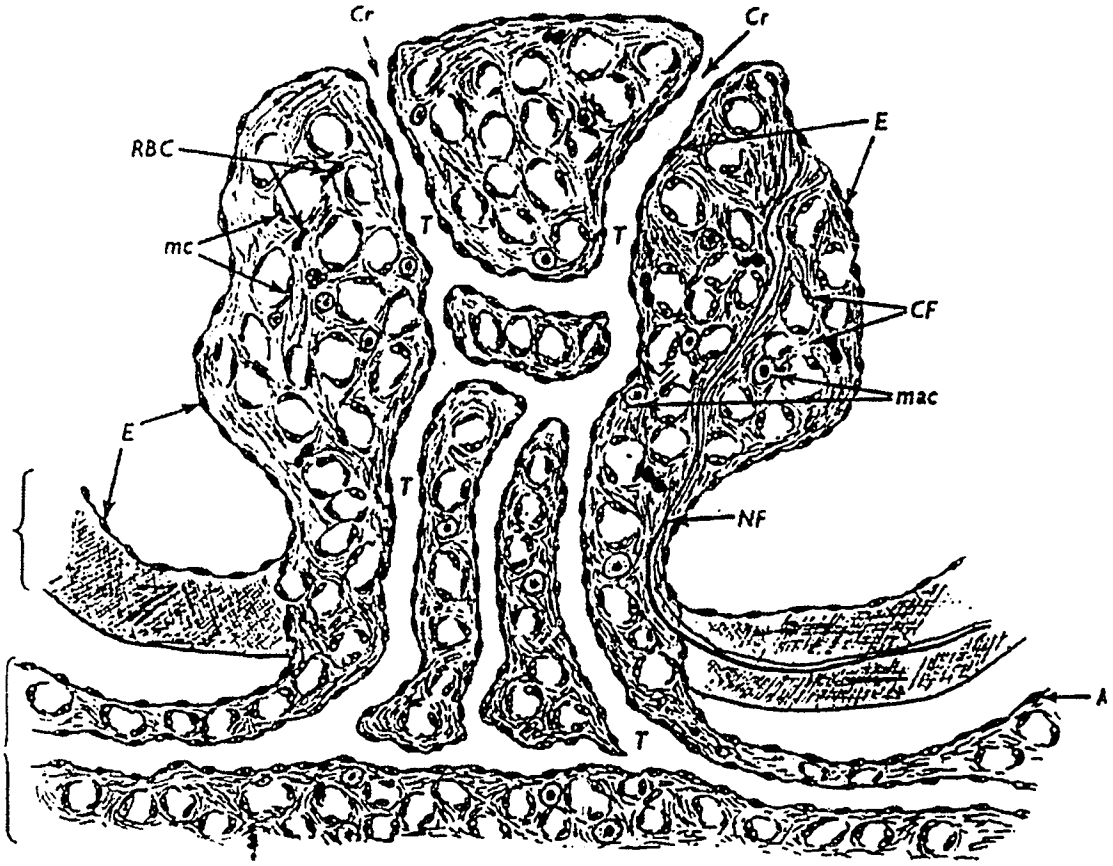


Fig. 14. *SAS*, Subarachnoid space; *D*, dura mater; *A*, arachnoid membrane; *E*, endothelial cell; *T*, tubule; *mac*, macrophage cell; *mc*, mesothelial cell; *Cr*, crypt; *CF*, collagen fibres; *RBC*, red blood cell; *NF*, nerve fibre.

Arachnoid granulation structure is proposed here to include a system of open endothelial-lined channels running through the core of the granulation, directly joining the subarachnoid space and the dural venous sinus. Reprinted with permission of Cambridge University Press: JayatilakaADP J Anat 99:635-649, 1965, Figure 14.

junctions, was found to respond markedly to osmotic agents by decreasing its rate of CSF secretion.[117]

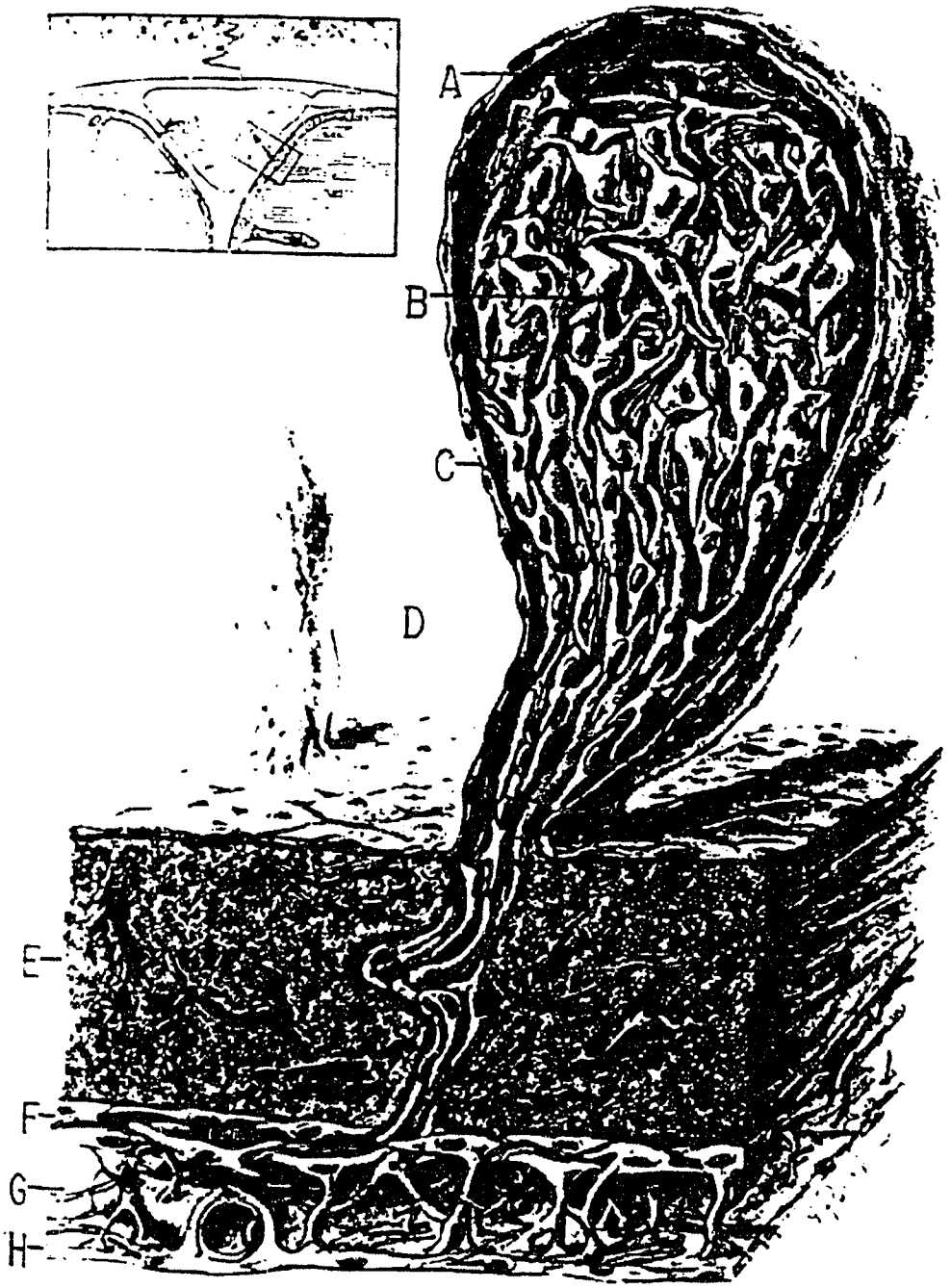
The Closed System

Weed's convincing tracer studies of the arachnoid granulations, failing to demonstrate Cushing's proposed valvular structures, supported the notion that the cerebrospinal fluid passed through a continuous endothelium to enter the SSS. Ultrastructural studies by Shabo *et al* indicated that the arachnoid granulation was indeed the main site of CSF drainage, through an intact endothelial layer.[120](**figure 1-5**) Alksne used intracisternal injections of horseradish peroxidase in dogs to trace the CSF pathway. His studies revealed a continuous layer of endothelium overlying the arachnoid villi in the SSS, with tight junctions uniformly present. Numerous vesicles described as micropinocytotic were noted in the endothelial cells, and felt to represent process whereby CSF is transferred from the arachnoid granulation to the SSS. No channels were identified through this layer.[2] Variations on these observations have been subsequently reported, including a mixture of pinocytosis and macrovacuolization,[28] and extensive work has been done showing a process of transcellular vacuolization resulting in transient transcellular channels.[125-128] The CSF system's ability to respond to sudden increases in pressure is perhaps explained better by a process of transcellular channels (transient or not), rather than a process of pinocytosis and exocytosis, or diffusion across an intact plasma membrane.

A Unifying Concept

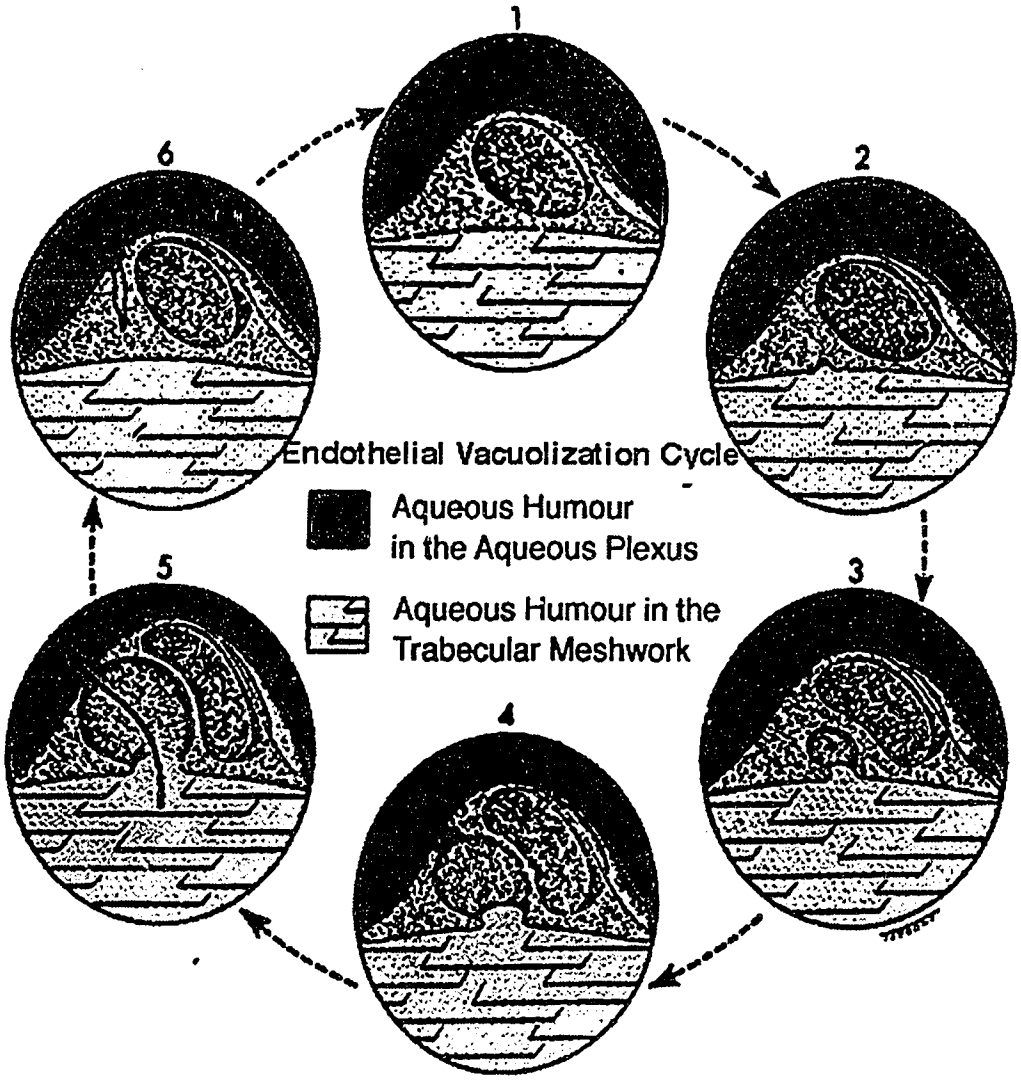
Perhaps the most convincing theory to date was developed by Tripathi and Tripathi in the early 1970s. Primarily interested in the physiology of aqueous humor drainage in the eye,[126, 128] this group performed transmission EM on SSS samples of monkeys, reporting the well recognized intracellular vacuoles in arachnoid granulations, but also noting that many of these empty inclusion bodies in the arachnoidal cells were in fact transcellular.

Figure 1-5: Shabo et al: Drawing of Rhesus monkey arachnoid villus



This detailed drawing depicts a continuous endothelial membrane draped over the arachnoid granulation which is projecting into the lumen of the SSS. D= sinus lumen, C= sinus endothelium,A= subendothelial space of villus, B= villus core consisting of meshwork of arachnoid cells and collagen, E= dural sinus wall. F= arachnoid cells, G = subarachnoid space, H=pia-arachnoid. Reprinted with permission:**J Neurosurg** 29:451-463, 1968, Figure 1.

Figure 1-6: endothelial transient transcellular channels



Tripathi described a process of transient transcellular channnels across the endothelium iining the CSF absorptive site, as well as that lining the canal of Schlemm in the eye (shown).With permission: **Exp Eye Res** suppl:65-116, 1977, Figure 17.

This was interpreted as transient trans-cellular channels, which could respond to changes in the CSF pressure from within. [125-128](**figure 1-6**) Excellent preservation of other intracellular structures, and similar findings with various techniques of preservation lend support to these findings being real as opposed to artifactual distractions. Of particular interest to the group was a finding in a single specimen which had suffered subarachnoid hemorrhage; they observed uptake of erythrocytes into these vacuoles. Levine *et al* performed perfusion/ fixation experiments on cynomolgus monkeys, keeping strict control on the SSS venous pressure and SAS pressure. He then performed SEM and TEM on tissue from the SSS wall, revealing 2 micron diameter pores in the apical surface of granulations and numerous intra- and trans-cellular vacuoles. By increasing the SAS pressure, thereby increasing CSF outflow, these structures became more numerous.[71] Findings of transcellular channels and endothelial pores have been reported in similar experiments on rats.[19]

The Gel Filtration Mechanism

Comparison has been made of the outflow pathways of CSF—that is the arachnoid-dural interface at the superior sagittal sinus—and the trabecular meshwork of the eye leading to the canal of Schlemm.[65, 128] The appearance of an arachnoid granulation and the trabecular tissue in the angle of the anterior chamber of the eye look very similar grossly, on light microscopy, and with transmission electron microscopy (TEM) and scanning electron microscopy (SEM). The ground substance within these structures has been studied in detail, revealing glycosaminoglycans (GAGs) to be the primary component.[64, 65, 86] A gel filtration mechanism for CSF through the arachnoid granulation has been put forth based on these findings. An intrinsic property of two of these substances—namely hyaluronic acid and chondroitin sulfate in the eye and CSF outflow pathways—is their ability to form a viscoelastic gel. Such a gel may serve a function of pressure regulation through a semi-permeable gel filtration system.[65] This concept would seem to support an otherwise open

pathway of drainage through the arachnoid layer to the venous blood, in keeping with the model of Tripathi or Jayatilaka.

B: Transependymal Absorption

Cserr demonstrated the pathways of interstial fluid into the lateral ventricles in the rat and rabbit,[22] and these were consistent with those noted by Milhorat several years earlier using a model of compensatory mechanisms in hydrocephalus, with the tracer traveling the opposite direction.[91] This same pathway has been noted elsewhere,[110] making a strong argument that indeed there is a pathway for flow of interstitial brain fluid into the ventricular system. There is also evidence of a change in capillary permeability in both grey and white matter in the setting of hydrocephalus in the rhesus monkey, which supports the compensatory mechanism of absorption via transependymal flow.[70] An interstitial pathway from the ventricles to subarachnoid vessels has been shown to exist in hydrocephalic mice.[85] However, the capacity of this pathway, particularly in humans, remains undefined. Functionally, it may be nothing more than a dead-end of interstitial brain edema.

Using animal models of hydrocephalus, many authors have demonstrated that there is uptake of CSF-borne tracer in the brain parenchyma and interstitium, as well as into the venous blood. However it is virtually impossible to assess the individual contribution to CSF absorption by arachnoid villi/granulations as compared to alternate intracranial pathways for the following reasons. Firstly, no hydrocephalus model can be perfect, meaning that CSF may continue to exit via the conventional subarachnoid pathways, and thus deliver tracer to venous blood in the "conventional" manner. It has been noted through isotope cisternography that even in the setting of supposedly complete ventricular obstruction, considerable subarachnoid flow still occurs, at a reduced rate.[52] Secondly, although it has been widely reported that CSF will flow across ependymal, pial, and choroidal surfaces,[40, 53, 54, 88, 89, 93, 94, 103, 115, 116] the relative amounts absorbed by each has yet to be calculated. This

may be impossible to do with any accuracy as the vascular bed varies between tissues, and thus the instantaneous tissue concentrations measured by conventional marker techniques may not represent true flux across the brain as a whole.

CSF absorption at the level of the spinal cord may represent a means of compensation in hydrocephalus in cats, where ligation of the spinal cord results in a decreased rate of absorption in a feline hydrocephalic model.[40] The significance of this in humans has not been demonstrated to the best of the author's knowledge.

C: Absorption by the Circumventricular Organs

The circumventricular organs are a unique site in the normal brain where a blood-CSF barrier exists in place of a deficient one between blood and brain. The choroid plexus may be included in this group of well vascularized structures, namely, the area postrema, neurohypophysis, vascular organ of the lamina terminalis, subforniceal organ, pineal gland, and median eminence. Several groups have demonstrated absorption of CSF tracers into venous blood in hydrocephalic models, with clear evidence of uptake into the circumventricular organs.[54-56]

Regarding the concept of CSF absorption via the choroid plexus (CP), Cserr argues that capillary plasma water loss in the CP to newly secreted CSF should result in Starling forces favouring absorption of interstitial fluid at the venular side of the plexus.[22] Brightman points out that the venous plexus vessels are fenestrated in the choroid plexus, as opposed to the tight junctions of the capillaries of brain parenchyma, and so could more readily absorb CSF.[14] Thus it should come as no surprise to learn that CSF is absorbed in part via the CP. [22, 56, 88] The relative contribution of this pathway to the total CSF absorption process remains to be quantified. Perhaps the ability of the circumventricular organs to sample the CSF, with its may chemical transmitters, provides a means of rapid communication between the CSF and blood.

D: Lymphatic Absorption

It has been shown by intracisternal tracer injection and cervical lymphatic cannulation studies in the rabbit that as much a 20–32% of CSF drainage may take place across perineural pathways, into cervical lymphatics.[9, 10] The morphology of the pathways in these reports seems consistent; the subarachnoid space extends along the cranial nerves (in particular, the olfactory tract) until their approximate site of exit from the cranium. The termination takes the form of a meshwork of channels leading openly to cervical lymphatic channels.[8-10]This Process represents a maximum of 13% of total CSF absorption in the cat,[9, 10]which may be explained on the basis of interspecies differences in olfactory tract caliber. Other groups have arrived at similar qualitative and quantitative results regarding CSF absorption along olfactory tracts,[13, 37, 39, 44, 63, 69, 77, 82, 107] optic nerves,[36, 82, 83, 121, 132] auditory pathways,[78] spinal nerves,[7, 13, 25, 29, 79, 137] and perivascular routes such as the carotid sheath.[10] Thus it would seem that there are unquestionably alternate pathways for CSF out of the cranium, but they vary significantly from species to species. Therefore in the human, one would not expect to find absorption through the nasal mucosa of the same magnitude as the rabbit, given the striking difference in the size of the olfactory tracts.

Anatomy of the Dura and Sinuses

Formation of the meninges

By day 35 of gestation, cells of mesodermal origin form a loose matrix around the neural tube, termed the meninx primitiva; this is the origin of the dura and arachnoid mater. The dura appears as an identifiable membrane of two layers by day 50, with the arachnoid thought to develop from its inner layer, which remains fused until day 140.[57] It has been

shown elsewhere that the arachnoid remains fused to the underside of the dura unless torn away by a pathologic process.[49] The dura's outer layer forms the periosteum of the inner table of the skull, and may contain osteoblasts and osteoclasts; the outer fibres of the dura may be calcified.[84] The inner dural layer is continuous with the spinal dura mater, and is a fibrous tissue containing fibroblasts and collagen in abundance.[8] The pia mater takes its origin from neural crest cells, and is closely adherent to the cortex.

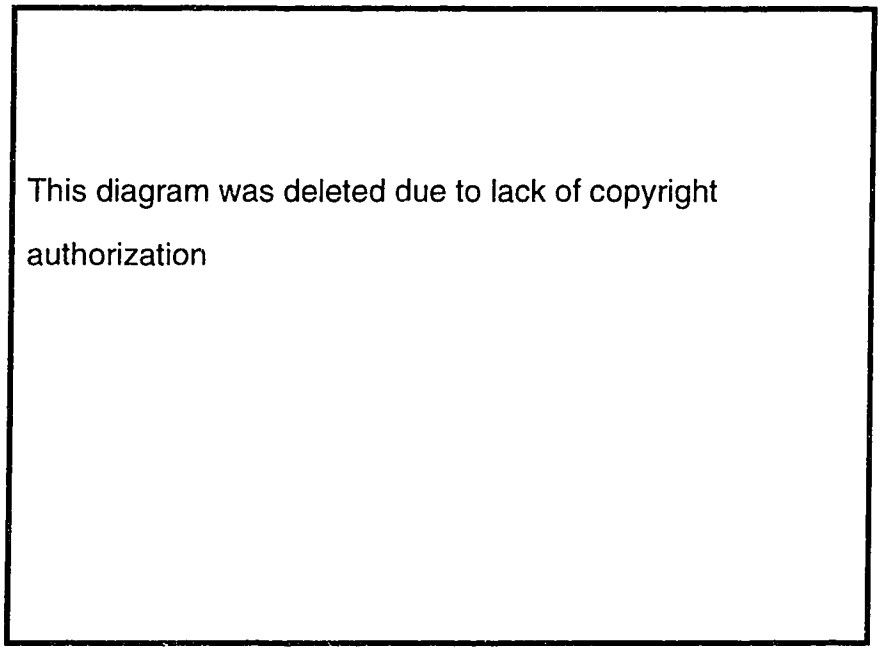
Blood supply

The cranial dura derives its blood supply from those vessels supplying the overlying skull.[32] The middle meningeal artery supplies much of the lateral surface of the dura; it is a branch of the maxillary artery, entering the cranial cavity through the foramen spinosum. Other blood supply to the dura comes from branches of the ophthalmic, cavernous segment of the internal carotid, occipital, and vertebral arteries. The parasagittal dura—the region of particular interest in our studies—is supplied only by the middle meningeal vessels.

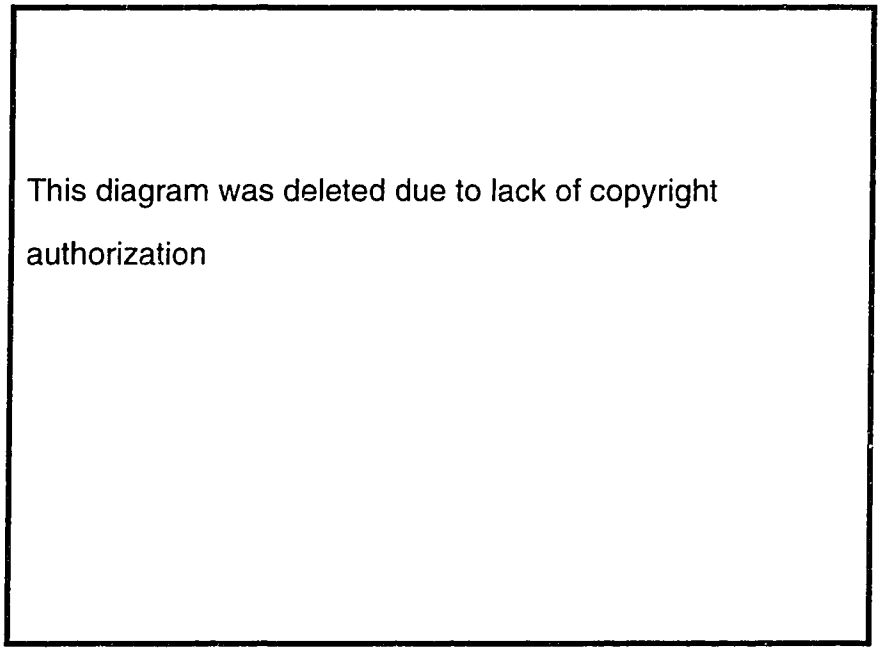
The primitive cranial venous system drains into the primary head sinus, with its paired anterior, middle, and posterior stems.[101](**figure 1-7**) Padget refers to middle meningeal sinuses, travelling in the outer layer of the dura, and veins in the inner layer, as forming the venous drainage of the dura. These vessels are embryonic derivatives of the anterior dural plexus, which also gives rise to the superficial cortical veins.[101] Three layers of veins in the dura have been described previously: a superficial group projecting superficially to form emissary veins, an intermediate group forming intradural veins, and a deep group forming the superficial cortical veins.[98] The middle meningeal vein develops from the middle dural stem. It courses superficially to an artery of the same name, and is compressed between dura and skull to become apparently doubled, split by the underlying artery. This vein may

Figure 1-7: development of the cranial venous system in Man

A



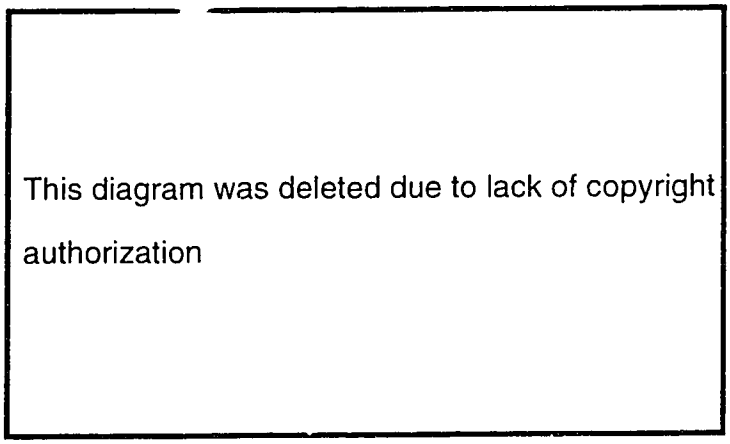
B



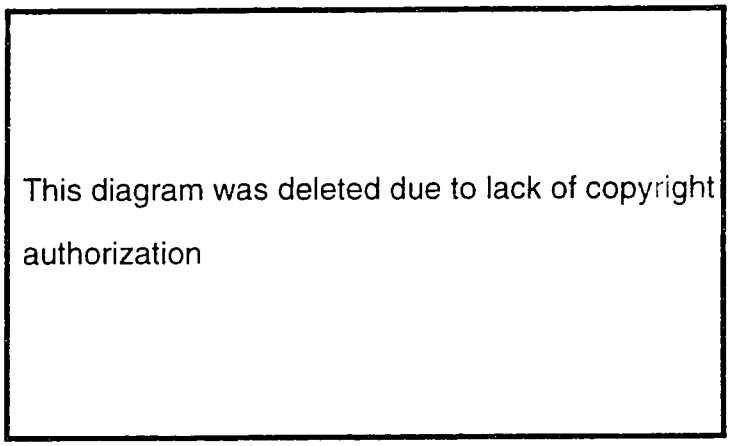
The cranial venous system includes the superficial cerebral veins and the sagittal sinus, both of which develop from the anterior segment of the primary head sinus. Padget refers to the outgrowths of the sinus giving rise to the superficial cortical veins, but no mention is made of an extensive parasagittal venous plexus. Included are the developmental stages of 10 mm crown-rump length (A), 80 mm (B), and adult configuration (C). (continued on next page)

Figure 1-7: development of the cranial venous system in Man (continued)

C



D



The adult configuration of the superior sagittal sinus with its attached superficial cortical veins is seen. (C) Detailed description of the anastamosis of the middle meningeal veins to the superior sagittal sinus is also shown. (D) In this dorsolateral epidural perspective, no description is given of a parasagittal venous complex, and the middle meningeal veins are shown anastamosing directly with the sagittal sinus.This represents the current understanding of the parasagittal dura, with the middle meningeal veins arborizing medially; with enlargement, these structures are described by Padget as coalescing to form the lacunae laterales.. With permission: **Am J Anat** 98:307-355, 1956, plates 1, 7.

also be referred to as a sinus, as it is no more than an endothelial lined tube in the most superficial layers of the dura.[101]

Superiorly, the middle meningeal sinus may connect with the SSS postnatally; it has been postulated that the lacunae laterales represent a coalescence of these middle meningeal sinuses.[101]The lacunae are connected via ostia into the SSS.[16, 99] Inferiorly, the middle meningeal vein or sinus may drain into a lateral wing of the cavernous sinus *via* the pro-otic sinus—an embryological structure representing this lateral extension to the cavernous sinus, passing laterally under the mandibular branch of the trigeminal nerve. The middle meningeal vein only rarely has partial drainage through the foramen spinosum, via the vein of Vesalius.[101]

Summary

The cerebrospinal fluid system is complex in terms of both anatomy and physiology. During early embryologic stages, it plays a supportive role from within to prevent collapse of the neural tube and subsequently of the ventricular system. Neuronal migration patterns may be affected by the configuration thus supported. The route of CSF out of the brain is neither singular nor simple. It may be safe to say that the majority of CSF flows out of the subarachnoid space through the arachnoid granulations situated in or near the SSS. An endothelial membrane covers the arachnoid granulations, but is probably discontinuous in places, due either to fixed channels of 1–2 microns diameter, or transiently forming transcellular pathways opening into the vascular channels against which the granulation is situated.

Management of obstruction to flow of CSF in the setting of hydrocephalus demands a bypass procedure of some kind. In the setting of a non-communicating hydrocephalus such as aqueductal stenosis, an intracerebral procedure such as a third ventriculostomy may

be indicated to bypass a restrictive cerebral aqueduct. In the setting of communicating hydrocephalus, bypassing the arachnoid granulations altogether and delivering CSF to venous blood through another route is needed. The ideal bypass procedure from a purely hydrostatic perspective would be entirely intracranial. For such a procedure to be effective, a means of introducing the CSF to venous blood in a near physiologic manner is required. Thus, further examination of the site where CSF is first introduced to the venous circulation —namely the parasagittal dura—is indicated.

Of particular interest is the observation in our preliminary studies, and in earlier literature[98] that by far, the most extensive arachnoid granulations occur in the lacunae laterales, as opposed to the sagittal sinus. Like the granulations themselves, the lacunae have been described (but not demonstrated) as developmental structures, present as a limited network of precursor channels in the infant, and becoming extensive and voluminous in the elderly.[68, 93] It is not known whether the lacunae form as a result of mechanical dissection of expanding granulations, or if they enlarge due to increased dural blood flow, with the granulations forming only as a parasitic process. If indeed the parasagittal dura does contain a network of channels which proliferate to become the lacunae laterales seen in adults, then this region of dura may have therapeutic implications if these structures can be utilized in a completely intracranial CSF diversion procedure.

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Chapter 2

The Cerebrospinal Fluid Absorptive Site of the Parasagittal Dura: A Cadaveric Study

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Introduction

Absorption of cerebrospinal fluid (CSF) into venous blood takes place largely across arachnoid granulations, which occur along the dural sinuses,[1, 3, 9, 13, 15, 22, 23] as well as along other venous structures on the craniospinal axis.[6, 26] Although the nature of arachnoid granulations has been exhaustively investigated, only limited descriptions are available regarding the anatomy of the dura in which they primarily reside. Anatomical descriptions of the dura mater dating from the late 1800s include the presence of lymphatic channels which were reported following intradural injection with Berlin Blue or India ink.[24] Weed later argued that the dura contained "unlined spaces between the dense strands of fibrous tissue", which could be "demonstrated by similar injections in any dense fibrous membrane".[24] Subsequently, a venous plexus alongside the superior sagittal sinus (SSS) was described in newborn infants,[13, 15] and in adults.[2, 15] Others have reported tributary veins running parallel to the SSS at their termination and fusing into sacs adjacent to the SSS thus forming the lacunae laterales.[8] Intradural lymphatics draining to the SSS have recently been described in European literature.[18] The present study describes the detailed anatomy of the parasagittal dura, and particularly the path of CSF from the arachnoid granulations to venous blood.

Materials and Methods

Part 1

Human dural specimens were studied from 10 adult formalin-fixed dissection cadavers and 10 fresh post mortem cadavers ranging in age from 18 weeks gestation to 80 years. Following removal of the calvaria, the middle half or two-thirds of the SSS was resected including the falx and a 3–4 cm margin of parasagittal dura. An effort was made to include the underlying arachnoid and some cortex without disturbing their anatomical relationships. Segments of unfixed dura were placed in a buffered solution of 10% formalin for 2–3 days prior to sectioning. Gross observations were made under a dissecting microscope. Segments of the sagittal sinus and parasagittal dura were embedded in paraffin wax and coronal sections taken for light microscopy (LM). Histologic sections were stained with Hematoxylin and Eosin, Ulex Europia, or factor VIII antibody.

Scanning electron microscopy (SEM) was used to examine the coronal and luminal surfaces of segments of SSS and parasagittal dura. With the coronal surfaces of the paraffin-embedded blocks cut smooth by the microtome for LM sections, specimens were then de-waxed in xylene, dehydrated in increasing concentrations of ethanol (50–100%), and dried using the critical point drying technique at 31° C with CO_2. Other unembedded segments were cut simply using a scalpel and similarly dehydrated and dried. Specimens were then sputter coated with gold (Edwards, Model S150B sputter coater) prior to viewing with SEM (Hitachi model S-2500 scanning electron microscope, Hitachi Corporation, Japan).

Part 2

A further 10 formalin-fixed dissection cadavers underwent corrosion casting[12, 14, 17, 27] of the SSS in the following manner. A burr hole was fashioned over the posterior SSS near torcular (confluence of sinuses), and the sinus opened. A size 8-French foley catheter with its tip remov[illegible]as inserted as far as possible [illegible] sinus anteriorly (10–15 cm). The sinus was flushed with large quantities of one–eighth Normal acetic acid to clear it of clot.[27] The catheter was then withdrawn to a point leaving only the balloon and distal tip in the sinus, and the balloon inflated. 8-10 ml of a casting medium was infused through the catheter using a syringe under gentle manual pressure. Casting mediums included either vinyl acetate (Carolina Biological), acrylic resin (GC company, Japan), or polyester resin (DOW chemical company). The SSS including part of the falx and the parasagittal dura together with arachnoid and some cortex was removed at least 24 hours later, and subjected to corrosion using 30-40 percent potassium hydroxide solution for several days with gentle agitation provided by a stirring plate. The resulting casts were cleaned under the dissecting microscope using a gentle water jet from a 27 gauge needle and syringe. Low magnification photography was used to record the gross specimens. Segments of the resin casts were then sputter–coated with gold and examined in further detail with SEM.

Part 3

Three to four segments of parasagittal dura from each of three fresh post mortem specimens were coronally sectioned and pre-fixed in 2.5% glutaraldehyde in cacodylate buffer (pH 7.2) at room temperature for 12 hours, followed by post-fixation in 1% OsO_4 for 1–3 hours. Following washing in distilled water, specimens were dehydrated in increasing concentrations of ethanol (5–100%), which was then replaced with propylene oxide. Embedding in Araldite CY212 mixture/propylene oxide for 1 hour and complete Araldite CY212

mixture overnight in a vacuum desiccator was followed by a 48 hour period at 60° C to allow for complete polymerization. Thick sections were made with a microtome, and stained with methylene blue. Areas of interest were identified with LM such that corresponding ultrathin (0.1 mm) sections could be made with an ultramicrotome. Specimens were studied using transmission electron microscopy (TEM) (Hitachi model H-7000, Hitachi Corporation, Japan).

Part 4

Intradural injections into the parasagittal region vinyl acetate or acrylic resin were performed in two formalin-fixed cadavers. In the supine position, the SSS was flushed with normal saline through burr holes over the sinus anterior to the coronal suture and over the torcular. Small parasagittal craniectomies were made at the coronal suture and near the mid-sagittal region bilaterally. Following exposure of the dura, a 20 gauge needle was inserted into the parasagittal dura superficially and parallel to the dura, at least 2 cm from the midline, for a distance of 3–5 mm toward the sinus. A Harvard pump was used to infuse normal saline coloured with methylene blue at rates of up to 1.5 ml per minute. An attached manometer monitored infusion pressure. When the infusate was seen to be flowing from the burr hole over the torcular, casting medium was substituted for the saline and injected by gentle manual pressure without pressure monitoring, thus forming a cast of the pathway taken by the fluid. After a period of 24 hours, the dura was removed and placed in 30% KOH for several days for corrosion.

Subsequently, five fresh post mortem adult specimens underwent similar procedures, with the dura harvested 10–20 minutes after injection. The specimens were allowed to cure in normal saline for 24 hours prior to corrosion in KOH.

Results

Gross

In newborn infants and fetuses (fresh post mortem), the medial edge of the membranous skull plates required cutting away from the thickened roof of the SSS, where they share a common origin with the dura. In specimens 2 years of age onwards to the sixth or seventh decade, the skull cap generally came away clearly from the dura. In more elderly specimens, the dura typically was adherent to the skull in patches, and trans-dural granulations were a common finding. It was difficult to ascertain if granulations were truly trans-dural in their undisturbed state, or if removal of the overlying bone simply unroofed them of a paper-thin layer of dura. Impressions were noted in the underside of the skull corresponding to these structures.

In adults (both formalin fixed and fresh post mortem), emanating from the roof of the SSS along its entire length were numerous small emissary veins. Upon opening the roof of the sinus longitudinally, numerous septae were seen along its walls, consistent with previous descriptions.[2] Obvious arachnoid granulations were identified along the walls of the SSS. These were discrete structures and ranged from only a few small (1–2 mm diameter) spherical ones in term infants to twenty or more multi-lobular collections in adults, particularly along the middle third of the SSS. They were less frequent anterior or posterior to this region. Numerous sidewall ostia, separate from and superiorly positioned to those of the cortical bridging veins were present along the sidewall of the sinus. In adult specimens, other ostia, which were larger in diameter, seemed to provide common openings to lacunae laterales and the termination of cortical bridging veins. In the newborn specimens, which

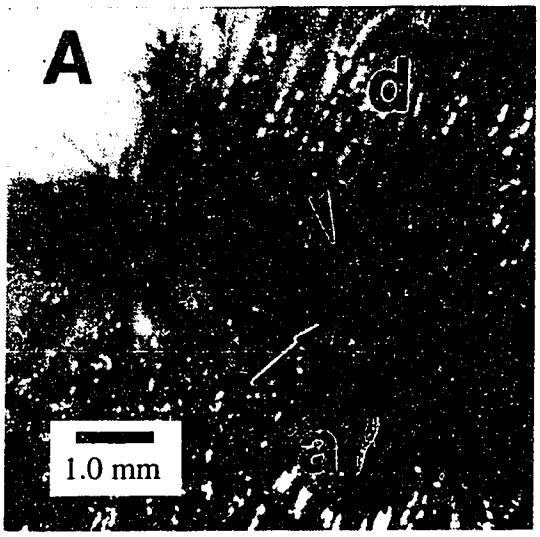
were nearly devoid of granulations, it was in these latter ostia that one could occasionally discover small granulations, similar to those reported previously.[6]

In specimens 2 years of age onward, lacunae laterales were identified along the middle third of the SSS and opened into the sinus through these sidewall ostia. In aged adult specimens, they often coalesced to form near–continuous cavities alongside the sinus. Exuberant granulations were present in all adult specimens within lacunae, essentially covering their floors, and increasing in size and number with age. Clotted blood was frequently present in lumen of the sinus, but was never observed in the lacunae, consistent with previous reports.[15]

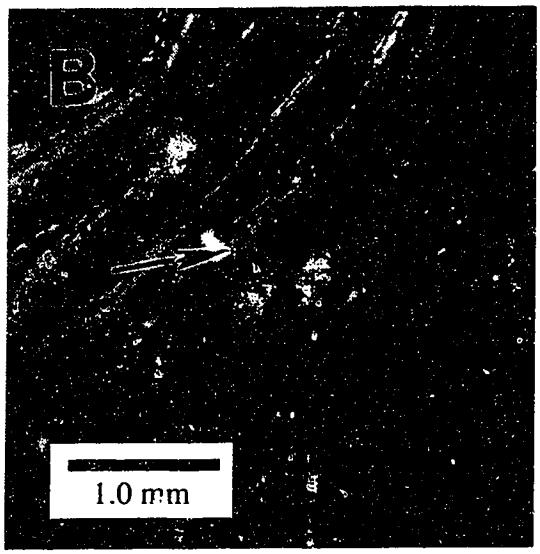
The underside of the dura displayed a varied texture(**Figure 1**). In the immediate parasagittal region and extending 1–2 cm down each side of the falx, the dura had a coarsely trabecular quality. This appearance occurred laterally in patches, either as extensions from more medial areas, or as discrete islands up to 3 cm from the midline. The arachnoid was adherent only at these trabeculated sites, by grossly apparent sheets of granulations herniating into the dura between the trabeculae (**Figure 2-1A**). Infant dura (**Figure 2-1C**) displayed less conspicuous trabeculations in the immediate parasagittal region, and by 2 years of age, these folds of dura had become similar in quality to adult specimens (**Figure 2-1B**), though less extensive.

The epidural aspect revealed transdural granulations in adult specimens, although it was impossible to determine if a thin layer of dura over the granulations had been torn away during removal of the skull cap. These transdural structures were present not only alongside the middle third segment of the SSS, but also in apparently isolated parasagittal islands. (**Figure 2-2A**) Unlike the granulations which entered directly into the SSS or lacunae, the connection between these granulations and any venous structures was not obvious to gross

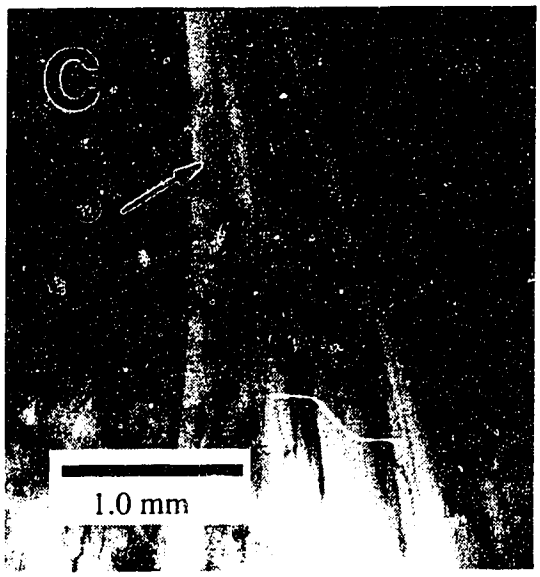
Figure 2-1: gross characteristics of the deep aspect of parasagittal dura



A: trabeculated appearance of the deep aspect of the parasagittal dura **(d)** in a 35 y.o. specimen as arachnoid **(a)** is stripped away in a medial direction, causing the granulations **(arrow)** to be avulsed from clefts **(arrowhead)** between the dural folds.



B: close up view of adult (35 y.o) parasagittal dural with arachnoid removed. SSS not included in picture but is oriented in transverse direction, inferiorly. The arachnoid granulations were invaginated into the deep crevices in the dura and held snugly in place with their necks held fast by the prominent dural trabeculae (arrow).



C: comparable view as B, seen in a term infant. The trabeculations are much less pronounced but easily identified (arrow). Arachnoid fell away easily in specimens of this age, and finding arachnoi granulations in the dura at this age was subsequently difficult.

examination. In thirty percent of fixed cadavers studied, grossly identifiable "isolated" granulations occurred adjacent to a prominent middle meningeal vein.(**Figure 2-2B**)

SEM

Coronal sections of SSS and parasagittal dura were examined as described (**Figure 2-3**). The dura immediately lateral the SSS was always relatively thick, ranging from 1–2 mm in newborns to 5 mm in adults. Within this thick area of dura were lacunae lateralis housing many granulations in adults. Numerous channels, cut at various angles,

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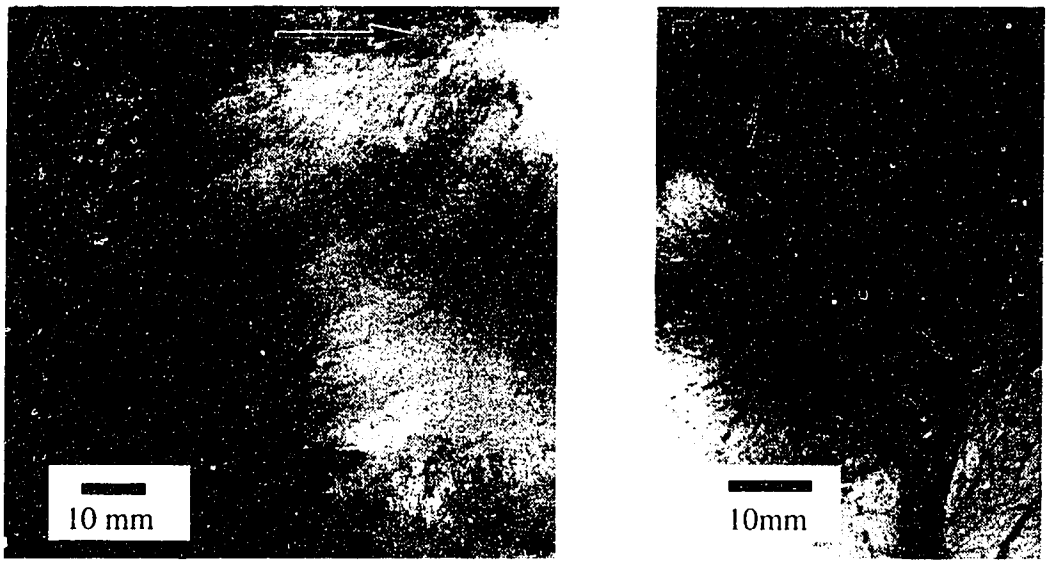
Figure 2-2: parasagittal arachnoid granulations unrelated to the sagittal sinus

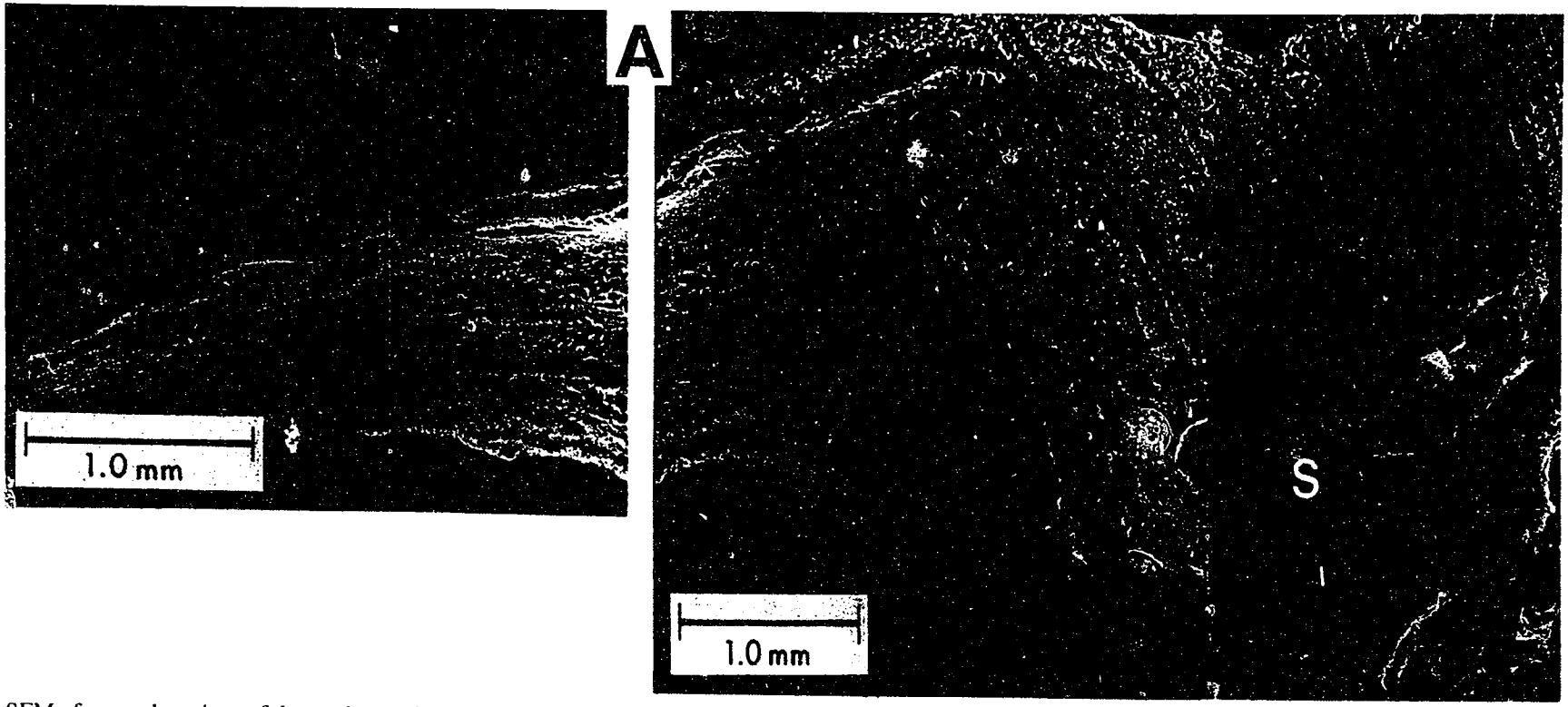


A: epidural view over the left frontal convexity in an elderly dissection cadaver with a lage area of dura through which numerous granulations have herniated. This site was not obviously connected to the SSS (**Arrow indicating orientation and direction of SSS**), or any other venous structure.

B: epidural view of aged dissection cadaver specimen showing the common finding of transdural granulations (**arrowheads**), adjacent to prominent middle meningeal veins (**arrows**).

were seen in this parasagittal region along the entire length of the SSS. Along the middle third segment, these channels appeared to enlarge and fuse to form lacunae in the adult specimens (**Figure 2-3E,F**). Lacunae were not seen in the pre-term infant specimens examined, but in those of 37 weeks gestation and greater, large channels were identified which could arguably be termed "early lacunae"(**Figure 2-3C**). The relationship of arachnoid villi to lacunae laterales is seen in **Figures 2-3 E,F and 2-4A**. The granulations project upwards toward these spaces and become intimately apposed to their endothelial lining. In segments of parasagittal dura without lacunae, villi were seen to protrude into dura, subjacent to the endothelial lined channels. (**Figure 2-3E**) The lining of the SSS, lacunae, and these channels was identical, having a quilted appearance of a continuous layer of endothelium. Pores of 1–2 microns diameter were seen at the perimeter of some endothelial cells overlying arachnoid granulations in the lacunae (**Figure 2-4B**).

Figure 2-3: SEM of coronal sections of dura at increasing ages



SEM of coronal sections of dura at increasing ages are seen on pages 53 - 58: **A- 18wks gestation; B- 27 wks gest.; C- 37 weeks gestation.; D- 2 yrs.; E- 67 yrs.; F- 70+ yrs**. Structures identified include the superior sagittal sinus (**S**), underlying arachnoid (**a**), arachnoid granulations (**g**), parasagittal intradural channels (**c**), which more medially become lacunae laterales (**L**). The parasagittal channels appear in increasing size and numbers with age. In image 'A', the large channel (**c**) lies near an ill-defined interface of dura and overlying forming skull primordia. It's exact nature— intradural or diploic —is not clear in this case, the latter seeming most likely. Seen at the left in image 'F' is an enlarged area indicated by the white box at the right; intradural channels were seen in adult specimens as continuations of lacunae. In adult specimens, granulations projected upwards into the substance of the dura to become intimately apposed to the intradural channels.

Figure 2-3 continued: SEM of coronal sections of dura at increasing ages

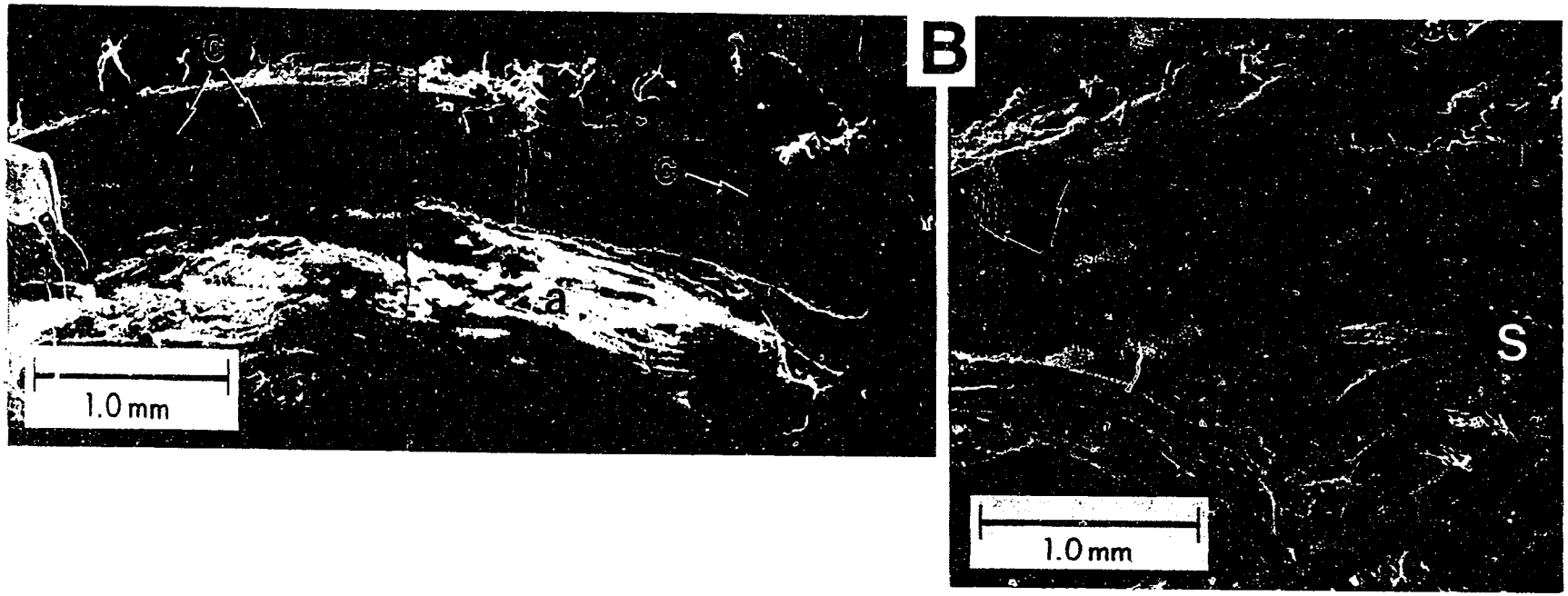


Figure 2-3 continued: SEM of coronal sections of dura at increasing ages

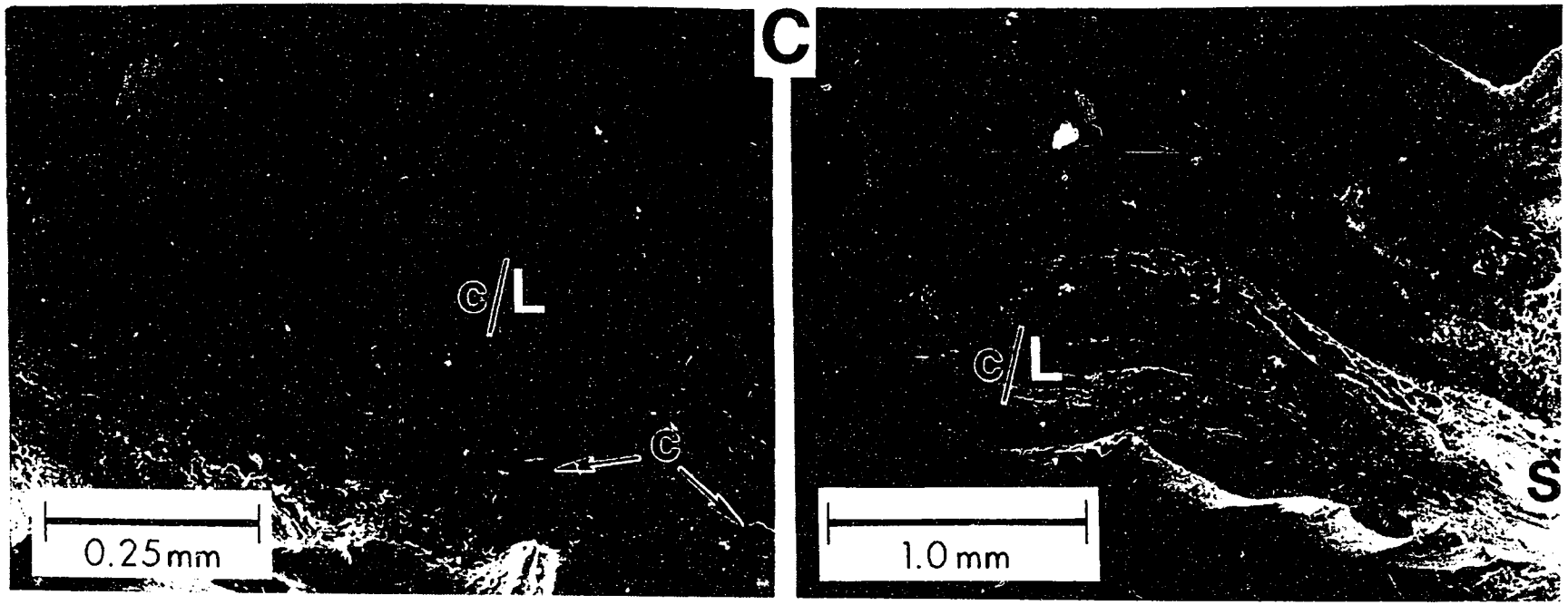


Figure 2-3 continued: SEM of coronal sections of dura at increasing ages

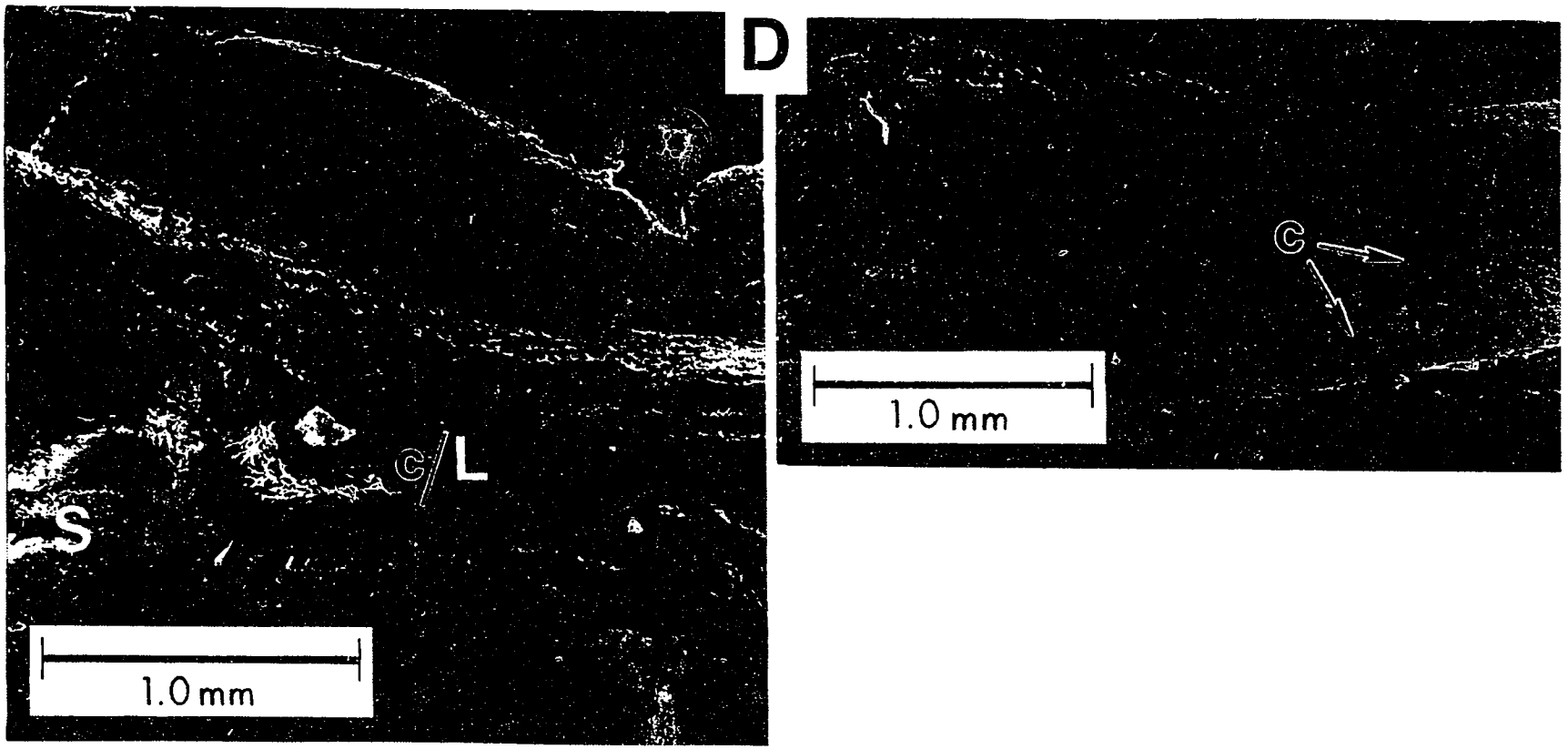


Figure 2-3 continued: SEM of coronal sections of dura at increasing ages

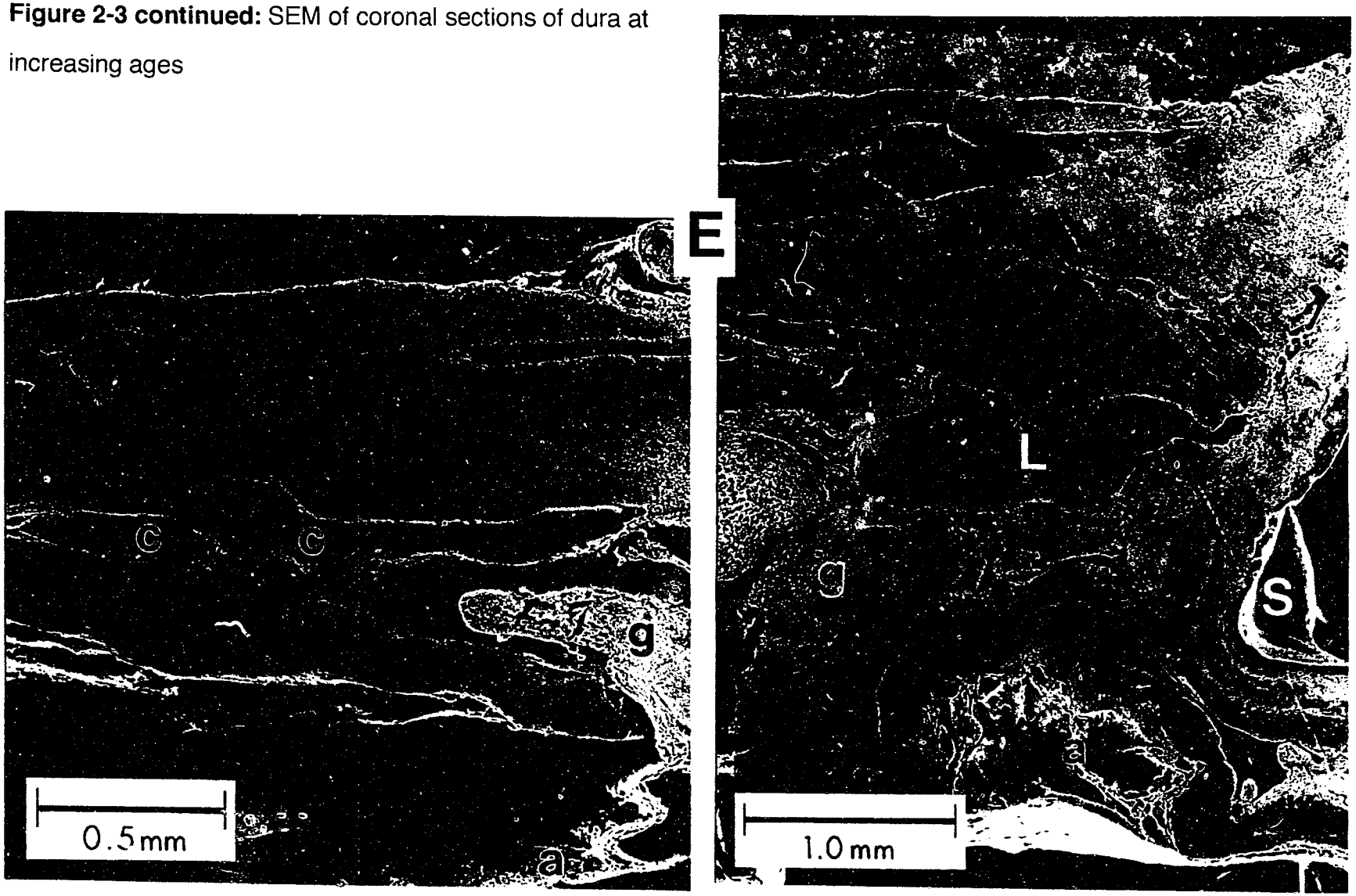


Figure 2-3 continued: SEM of coronal sections of dura at inc ing ages

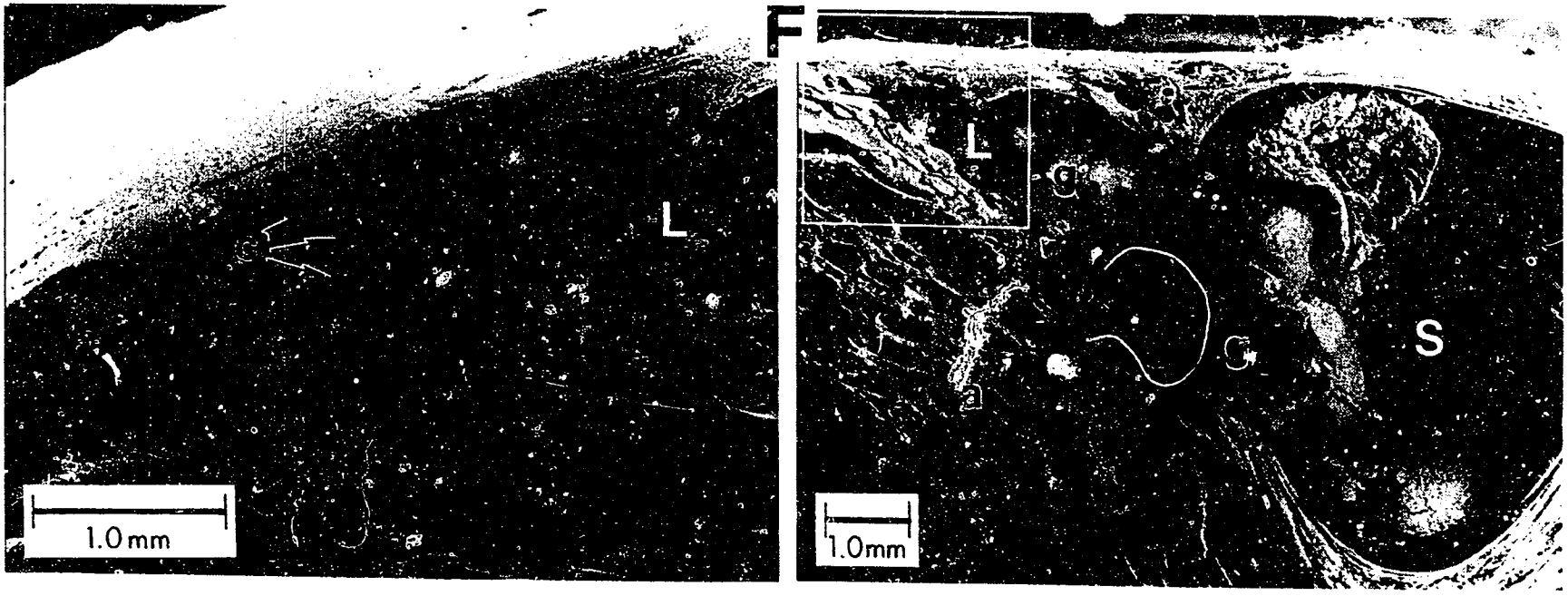
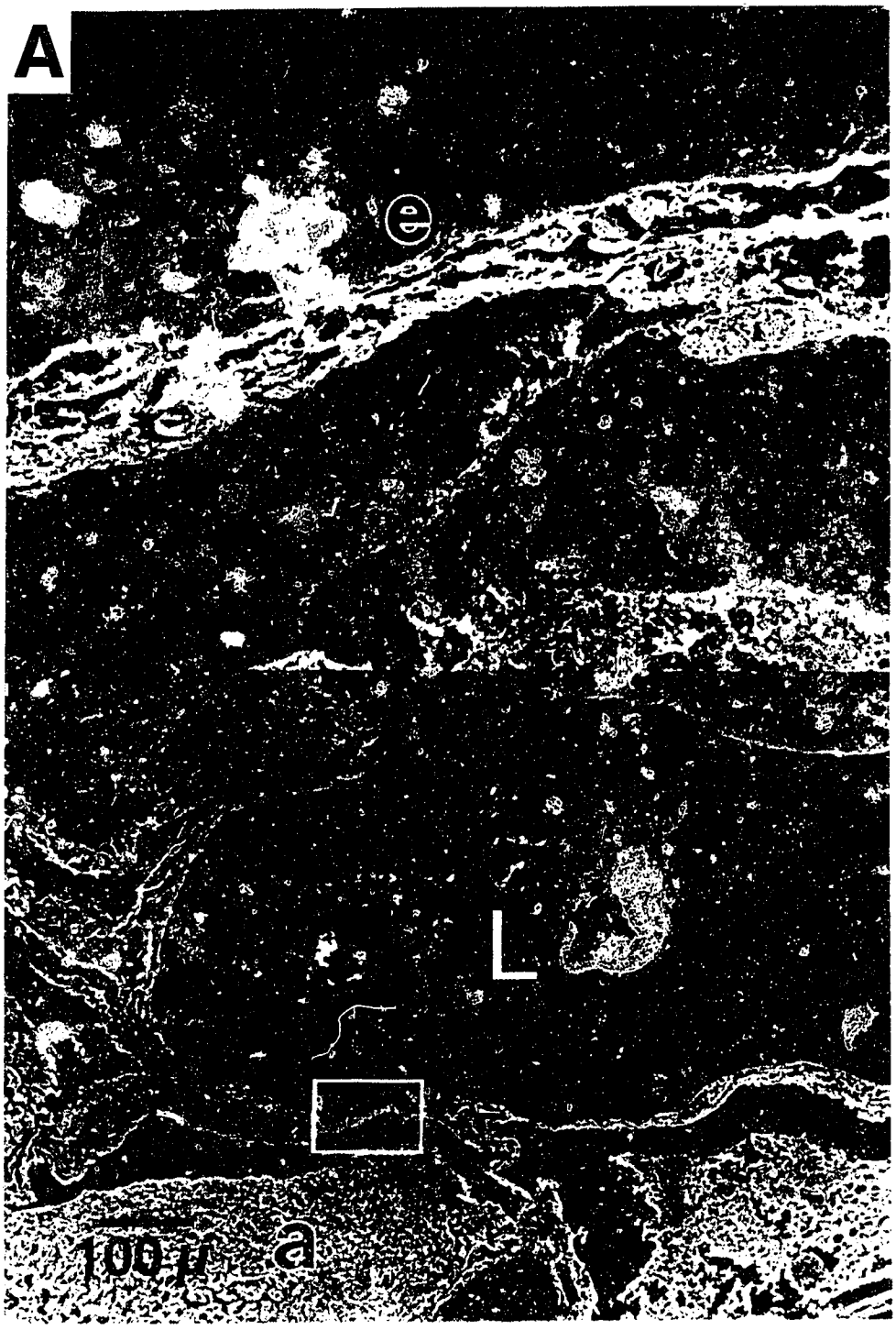
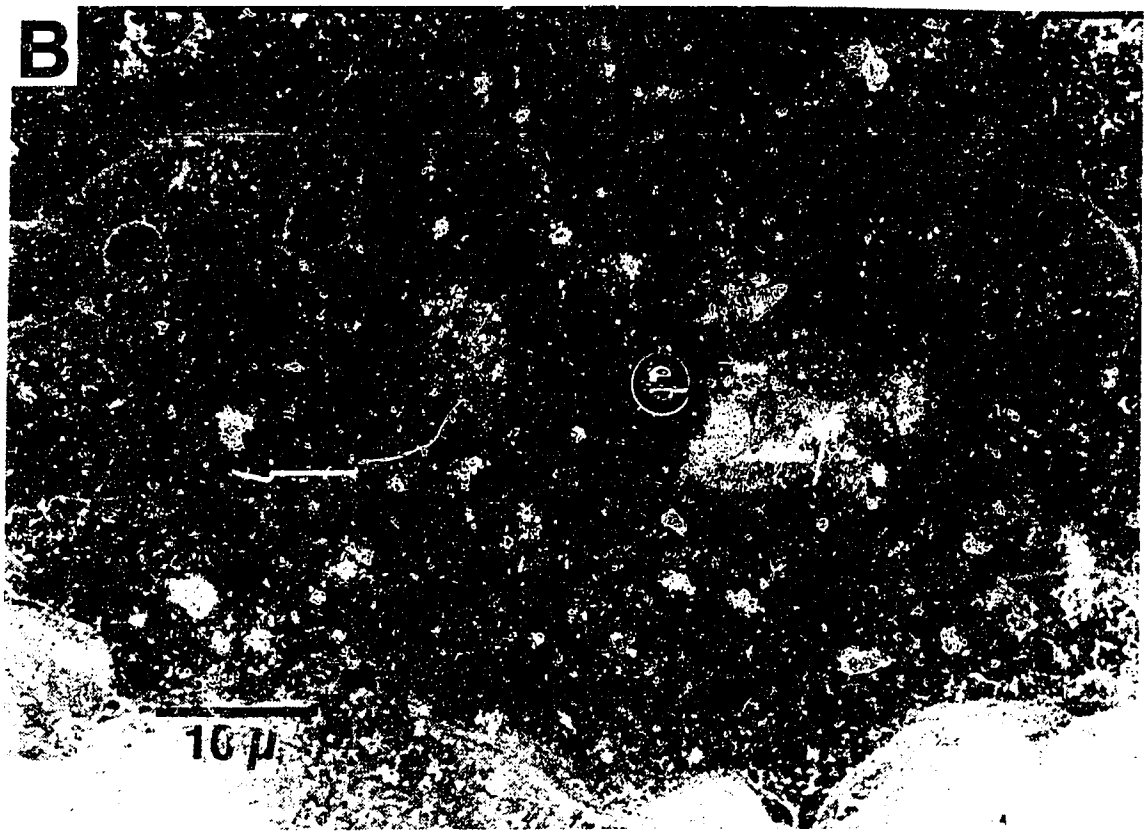


Figure 2-4: SEM of lining of parasagittal intradural channels



A: SEM of coronal segment of dura (see fig. 2-3E, right). Upper half of picture is enlagement (10X) of box in lower half.
The relationship of the underlying arachnoid granulation(**a**) to the lumen of a lacune (**L**) is shown. The intervening cleft is artifactual due to mechanical traction on the arachnoid during preparation, and tissue retraction with formalin fixation. Endothelial lining (e) of the lacune is evident, though detail is poorly seen at this oblique view.

Figure 2-4 continued: SEM of lining of parasagittal intradural channels



B: SEM of lining of a large parasagittal intradural channel, similar to those seen in figure 2-3E (left). The quilted appearance typical of endothelium (e) is seen. Though numerous artifactual tears are evident, with their jagged edges, pores of 1-2 microns diameter with smooth round magins were also observed (**arrow**), along cell borders.

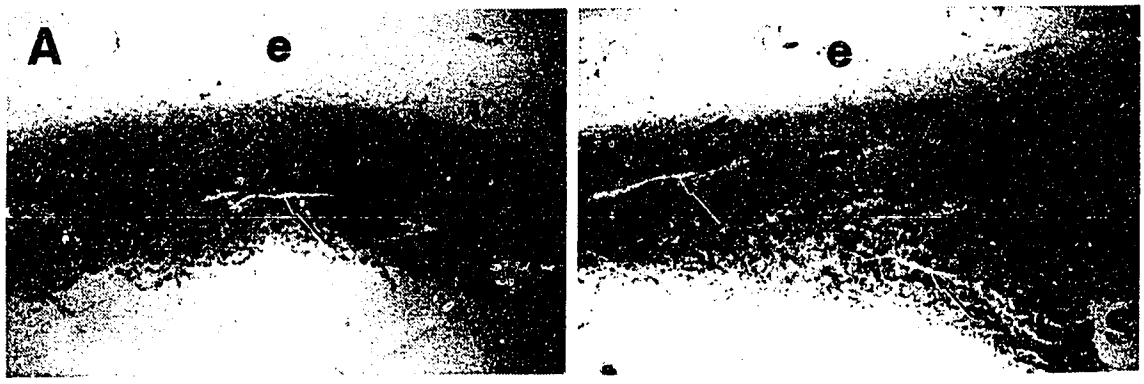
Histologic Sections

Histologic sections also revealed that the parasagittal dura contained endothelial lined channels which increased in size and frequency with age (**Figure 2-5**). The endothelial lining of the SSS, lacunae and the intradural channels stained positively with factor VIII antibody and Ulex Europ. These findings are consistent with the a vascular origin of this endothelium.

TEM

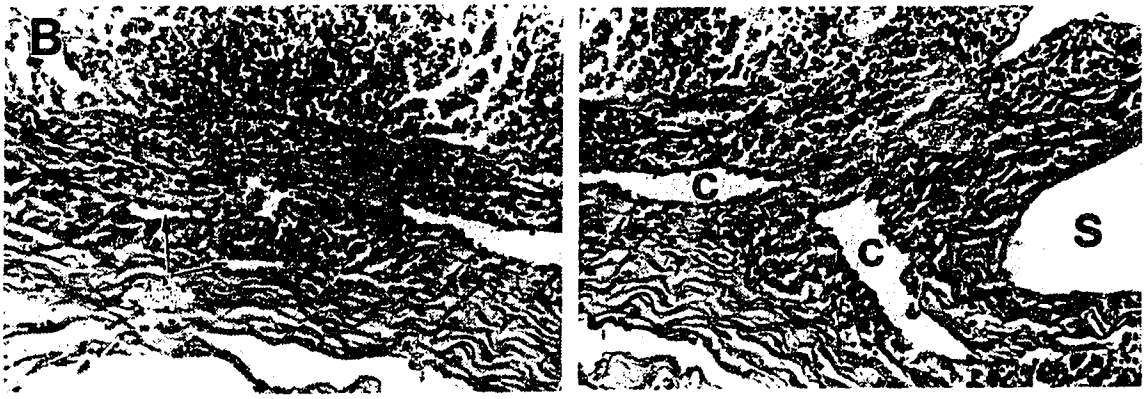
TEM was performed on multiple sections of parasagittal dura from three fresh post mortem adult specimens, looking specifically at the endothelial lining of the parasagittal intradural channels. Tight junctions were demonstrated consistently as was an underlying basement membrane.(**Figure 2-6**)

Figure 2-5: histologic sections of parasagittal dura at various ages



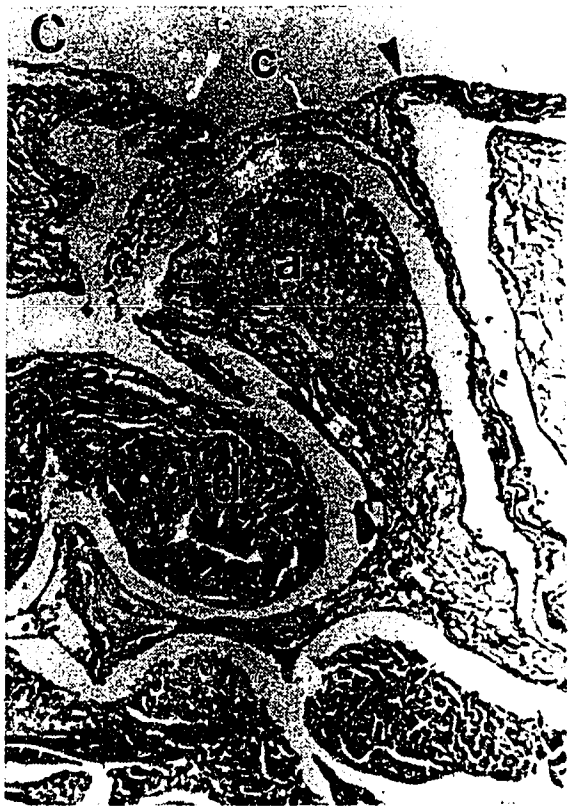
A:
At left, a coronal section of parasagittal dura approximately 15 mm from midline from 27 wk. gestation specimen with the epidural aspect (e) at top. Intradural channels are present, but of very small size (arrow). (H&E, 40X.)

At right, a more medial segment of dura including the sagittal sinus(S), again showing intradural channels, which at higher magnification are endothelial lined. They become larger and more numerous compared to more lateral sites. (H&E, 25X)



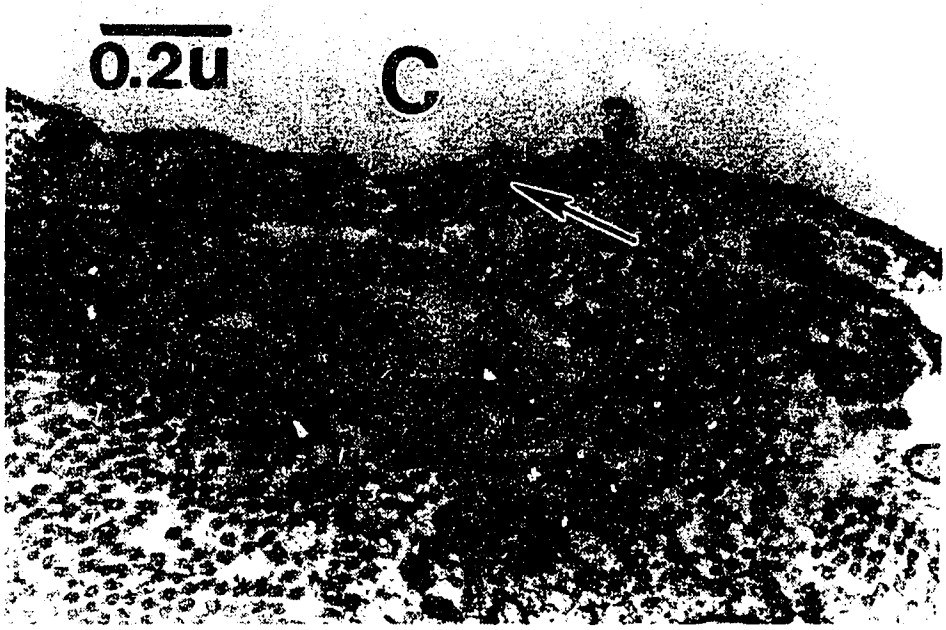
B:
Parasagittal coronal dural segments in a 37 wk. gestation specimen (left and right images overlap), showing sagittal sinus (S) at right, and intradural endothelial lined channels(c), becoming larger and more numerous with age as compared to A. (H&E, 100X)

Figure 2-5: histologic sections of parasagittal dura at increasing ages (continued)



C:
Parasagittal coronal dural segment in an aged adult specimen, similar to that seen in figure 2-3E (left). A large arachnoid granulation (**a**) has invaginated into the dura between dural trabeculae (**d**). A large channel(**c**) is separated from the granulation by an intervening endothelial layer (**arrowhead**) (as seen in figure 2-4B), applied to a connective tissue framework. (H&E, 68X)

Figure 2-6: TEM of endothelial lining of parasagittal intradural channel



TEM of endothelium lining an intradural channel (C) in an adult parasagittal dural section. Intact basal lamina (**arrowheads**) and macula adherens cell junction (**arrow**) are seen.

Corrosion Casting

Both vinyl acetate and acrylic or polyester resins provided detailed casts of a network of channels in the parasagittal dura. Though vinyl acetate did not reliably fill channels smaller than 0.1 mm, it provided a durable cast of the entire SSS and attached channels, as opposed to the detailed but extremely delicate resin casts obtained from acrylic resin.

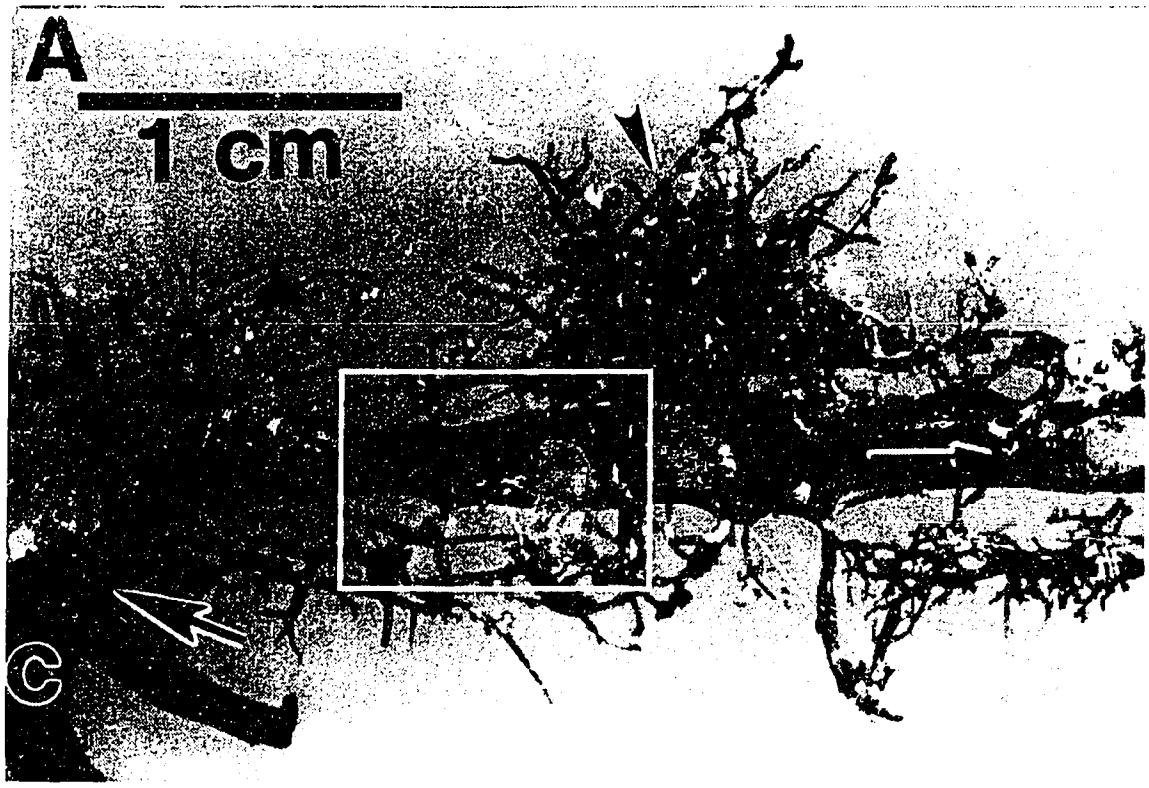
Vinyl acetate corrosion casting (**Figure 7**) revealed a dense network of channels stemming from regularly occuring ostia in the superolateral wall of the SSS, particularly along its anterior and middle thirds, and projecting laterally for up to 3 cm. Along the middle third of the SSS, lacunae laterales were seen as a dense plexus of these channels, at times coalescing into cavities, with an extensive network extending laterally from them. The midline emissary veins always followed a lateral course in the dura around the SSS prior to emptying into the same ostia as the parasagittal intradural channels.

[illegible]eal veins, however, were distinct from the intradural channels in that they were located on the surface of the dura, on a plane superficial to that of channels emanating from the SSS. Also,the branching pattern of the meningeal veins was opposite (i.e. arborizing medially) to that of the intradural channels (arborizing laterally).

The intradural channels were always most abundant where granulations were prolific, and sparse or absent where the dura was smooth and free of arachnoid invaginations. During the process of corrosion, the remains of granulations could be seen nestled in amongst the emerging casts of these channels. In adult specimens, there was an increase in size and number of channels making up the network as one progressed from anterior or posterior toward the middle third of the sinus.

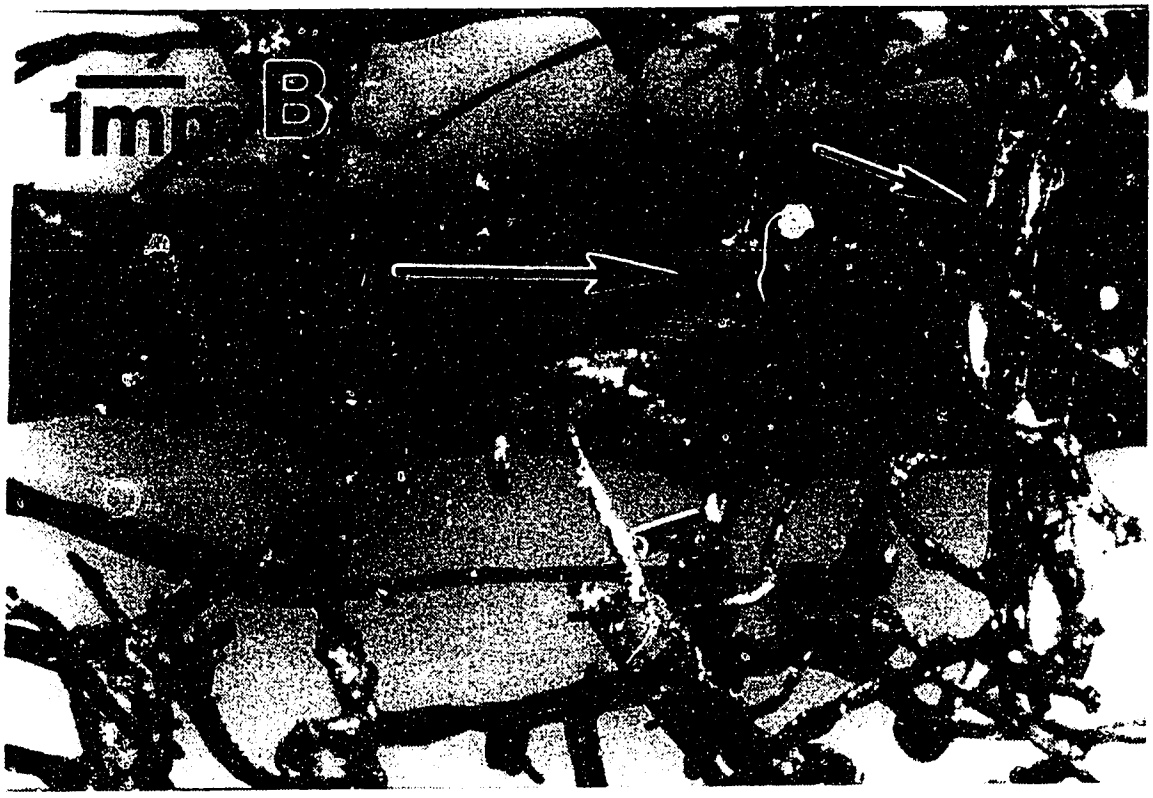
Close examination of the cortical bridging veins cast in the process revealed a general morphology consistent with previous descriptions.[2, 13, 15, 16, 27] The terminations of these veins occurred at the inferolateral margin of the sinus through their own ostia or ones shared by large lacunae. Cortical bridging veins were not seen to enter the lacunae, but rather, traveled beneath the lacunae on their way to the sinus. However, along segments of the bridging

Figure 2-7: corrosion casts of superior sagittal sinus



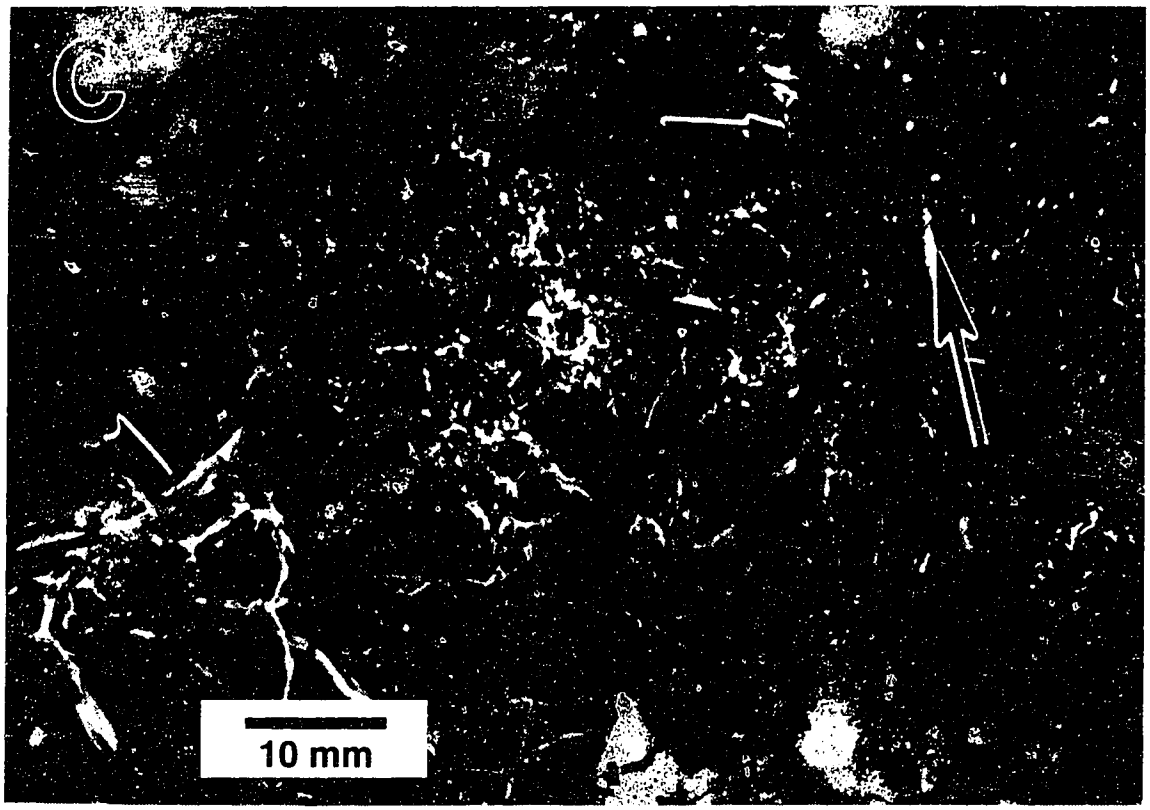
A:
Corrosion cast of the SSS from a formalin fixed aged cadaver viewed dorsally along the anterior third of the sinus. Vinyl acetate was back-filled into the sinus, filling the various connecting structures, including the anteriormost superficial cerebral vein(c), as well as numerous channels running within the substance of the dura. The intradural location of these latter structures is apparent during the process of corrosion. It can be seen in this specimen that the intradural channels run superficial to the cerebral bridging veins **(large arrow).** These channels are most abundant overlying the insertion sites of sheets of arachnoid granulations, and may begin to coalesce to form an early lacune**(arrowhead).** The direction of flow of the SSS is indicated **(small arrow).** White box indicates origin of Figure 2-7 B.

Figure 2-7: corrosion casts of superior sagittal sinus (continued)



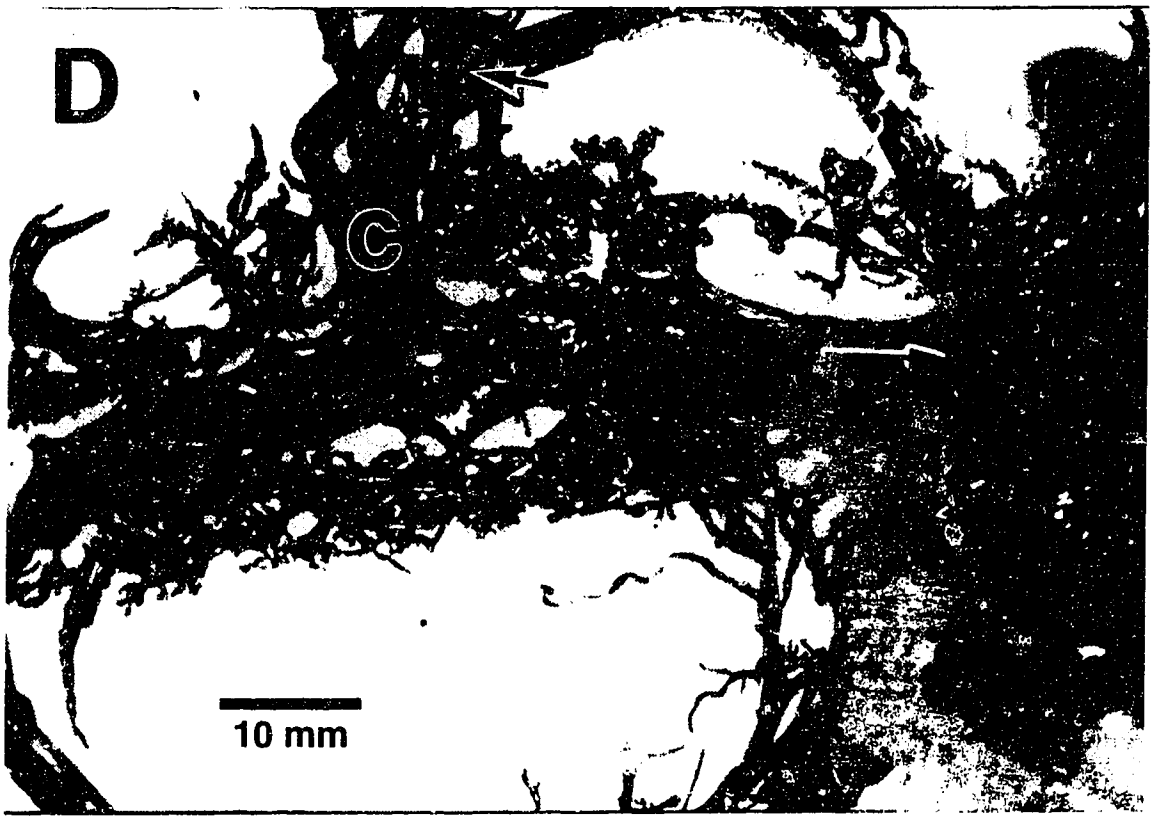
B:
Enlarged segment indicated by the white box in figure 2-7A. The intradural channels can be seen to enter the SSS through small, periodically spaced trunks(**arrowhead**). No evidence of a valvular structure was identified. Emissary veins entered the dura along the midline and coursed around the SSS withing the dura (**small arrow**), finally connecting to these same trunks. Direction of flow in the SSS indicated(**large arrow**).

Figure 2-7: corrosion casts of superior sagittal sinus (continued)



C:
Dorsal view of a vinyl acetate corrosion cast of specimen similar toA, but viewed along the mi[illegible]-th d segment of the SSS . An extremely complex network of channels are seen, and make up a system of lacunes. Laterally, middle meningeal veins anastamose with this network **(arrowhead).** Beneath this complex run the cerebral bridging veins **(large arrow)**, essentially uninvolved with the intradural channels. Direction of flow in the SSS is indicated **(small arrow).**

Figure 2-7: corrosion casts of superior sagittal sinus (continued)



D:
Specimen in C viewed farther arteriorly — similar in position to figure 2-7A. A cortical bridging vein is seen (**c**) giving off tiny branches into the dura (**short white arrow**).

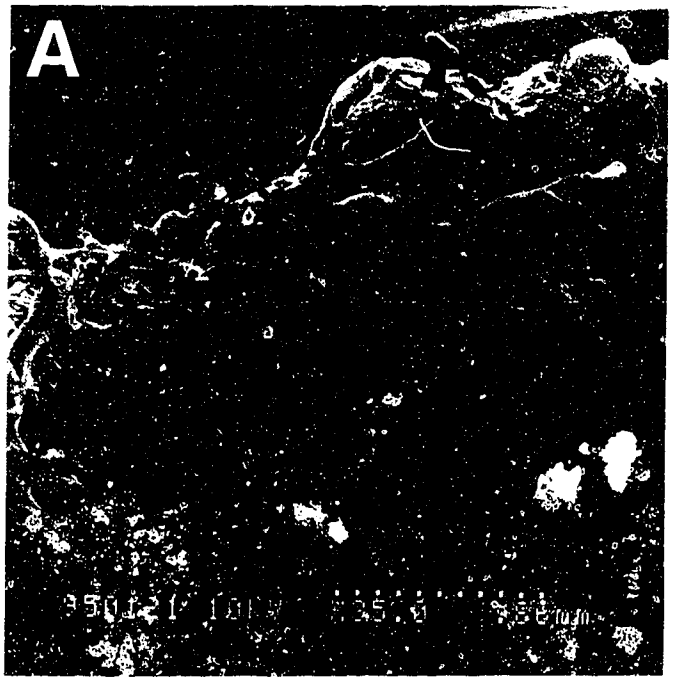
veins attached to the underside of the dura, small feeding channels were also present, extending superficially toward sites of extensive granulations (**Figure 7D**). This occurred on those bridging veins draining to the middle third of the SSS where the granulations were most abundant.

More detailed analysis of these channels was possible with corrosion casting with acrylic or polyester resin viewed with SEM (**Figure 8**). Casts of vessels as small as 0.02 mm diameter were observed using this technique. The terminal branches of channels appeared like fingers wrapping themselves around arachnoid granulations or villi (**Figure 8B**), which could be clearly appreciated under the dissecting microscope during the process of digestion The trunks of this network measure 0.25–2.0 mm diameter, which decreased to as little as 0.02 mm at the finest branches (the apparent limitation of our casting technique).

Intradural Injections

Intradural injection of coloured saline from an epidural approach into the parasagittal region readily established flow into the SSS, which could be seen issuing from the opening made in the sinus roof posteriorly. Saline infusion pressures noted through a single 20 gauge hypodermic needle at rates up to 1.5 ml/minute ranged from 0–20 cm of water in both formalin–fixed and fresh autopsy specimens. Upon removal of the dura, subdural collections of coloured saline were not seen, though in one half of the injections, the relatively viscous vinyl acetate had ruptured through trabeculated areas of dura. This technique readily filled the intradural network of channels (**Figure 9**), and the saline was observed to flow into the SSS through the described ostia, again represented by the small trunks emanating from the superolateral wall of the SSS following corrosion. Results were the same with formalin fixed and fresh post mortem specimens.

Figure 2-8: corrosion casts of the parsagittal dura using acrylic resin and viewed with SEM



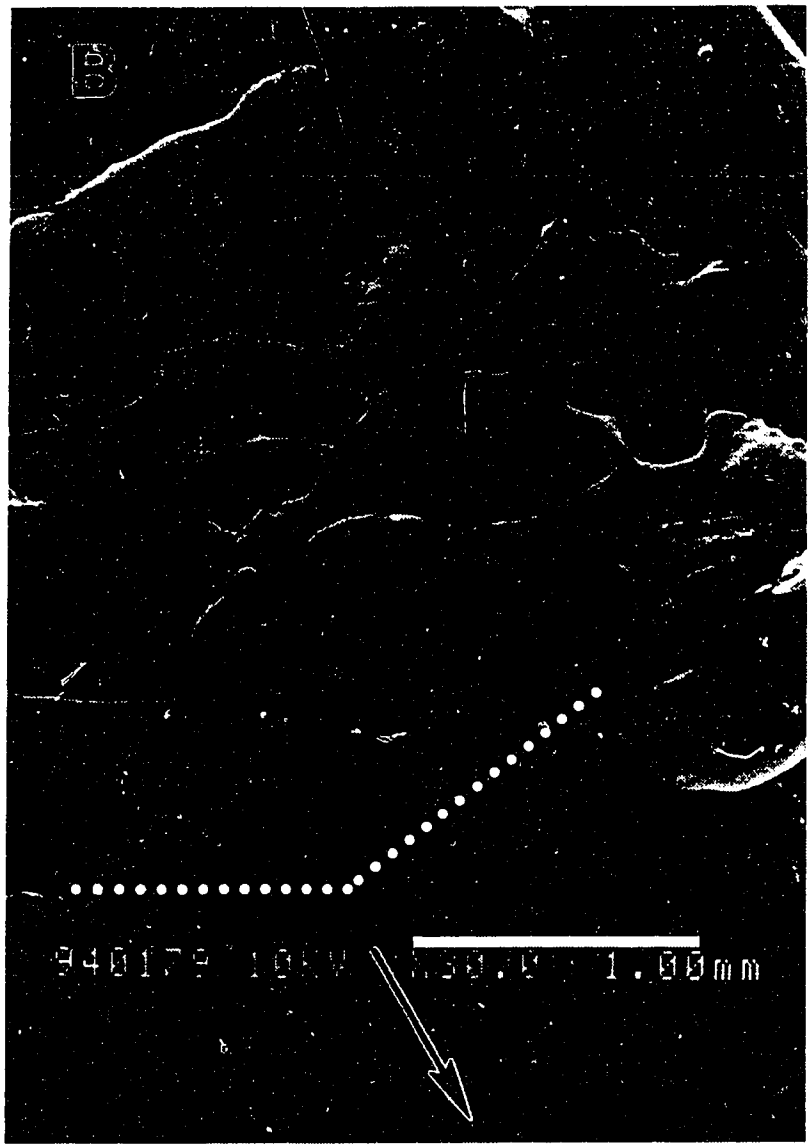
A: Back-filled acrylic resin corrosion cast of intradural channels similar to those in figure 7, viewed with SEM. The acrylic resin, by virture of its lower viscocity, is able to provide higher resolution (though delicate) casts. Seen here are numerous tiny channels branching from a larger one, revealing the extensive intradural parasagittal network of channels which exists in this area.

B: Higher magnification view of specimen similar to A, revealing a hand-like arrangement of channels. During the corrosion process, with the aid of a dissection microscope, arachnoid granulations can be seen nestled into the dura, intimately associated with these structures.

Figure 2-9: corrosion casts of the parasagittal dura and sagittal sinus following intradural injection with vinyl acetate

A:
Ventral view of a corrosion cast of a dural specimen from a 59 year old male following bilateral intradural parasagittal injections with vinyl acetate at the regions indicated(**arrowheads**). The s Intradural channels are filled and collect into trunks entering the middle-third segment of the SSS which is running transversely through the centre of the photograph. Leakage of the relatively viscous vinyl acetate casting medium into the subdural space (s) occurred during the infusion process.

Figure 2-9: corrosion casts of the parasagittal dura and sagittal sinus following intradural injection (continued)



B:

SEM of acrylic resin corrosion cast following parasagittal intradural injection in a region of parasagittal dura similar to A. The detailed morphology of the intradural channels is seen as they collect into the lateral edge of a lacune seen at the bottom of photograph, delineated by dotted line. The midline lies approximately 2 cm in the direction of the **arrow.**

Discussion

This study has demonstrated an extensive plexus of endothelial lined channels stemming from the SSS along nearly its entire length, and particularly along its anterior two-thirds (**Figure 10**). Intermittently, and particularly along the middle third of the SSS, these channels appear to coalesce into the lacunae laterales. The smallest branches of these channels embrace the arachnoid granulations which appear to have herniated toward them from below. The endothelium lining these channels is morphologically the same as that lining the lacunae and SSS, (particularly the endothelium draping the granulations in these sites). This particular cell layer has been the subject of research for many years, and is felt to be the final barrier to CSF absorption into blood. The mechanism by which this takes place remains uncertain. There are two generally accepted theories, not mutually exclusive: transient transcellular channels formed of multiple vacuoles carrying CSF from the arachnoidal core (i.e. the subarachnoid space) into venous blood,[3, 4, 7, 19-21] and trans- or inter- cellular tubules or pores which open in response to raised CSF pressure to drain freely into venous blood.[4, 5, 10, 11, 22, 25] Considering the multitude of sites at which granulations occur along the craniospinal axis, one might view these Pacchionian bodies as parasitic to any potential recipient vessel. Clearly their development continues well into adult life. This finding may well represent the response to an increasing demand for CSF absorption in adulthood compared with infancy and childhood. The plexus of channels we describe also continues to proliferate through life. That the lacunae conduct CSF was perhaps first postulated by O'Connell with the observation that clot was never found in them at post mortem.[15] It is still unclear to us the primary role of these structures. The density of the plexus seems out of keeping with the arterial supply to the dura, which tends to taper off medially. We suspect their main role to be CSF transport.

Figure 2-10: interpretation of the anatomy of the parasagittal dura

Diagram of proposed anatomy of the parasagittal dura. An extensive network of intradural channels are depicted which arborize laterally, and are distinct from, though anastamose with, the meningeal veins. They drain directly into the SSS through trunks located on the sinus wall, generally superior to the termination of cortical bridging veins. The coalescence of these channels forms the lacunae. The intimate relationship of the arachnoid granulations to these channels is emphasized.

Several features of these parasagittal intradural channels are of interest. Firstly, their shear numbers suggest a large fluid-carrying capacity, which in *vivo* may include CSF. Their tendency to proliferate and become lacunae over time suggests that there may be a process to accommodate increased flow. These channels originate from the SSS in a plane distinctly superficial to the termination of cerebral cortical veins, extending far laterally to the SSS. This suggests that the flow of fluid through these channels is quite independent of the cerebral circulation. Finally, our initial attempts at accessing the SSS via these intradural channels from an epidural approach were encouraging. The SSS may yet be a viable destination for the diversion of CSF through an entirely intracranial shunt using this plexus of parasagittal channels.

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Chapter 3

General Characteristics and Responses to Mechanical Injury of Vascular and Lymphatic Endothelium

Introduction

Our research regarding the microanatomy of the parasagittal dura has revealed a network of endothelial-lined channels extending laterally within the substance of the dura from trunks which open directly into the superior sagittal sinus. It is our impression that these channels are involved with the transportation of cerebrospinal fluid into the superior sagittal sinus. This concept is based on the widely held belief that the arachnoid granulations are the portal through which cerebrospinal fluid leaves the subarachnoid space on its way the venous system. Consistent with that notion is the finding in our study that this network of channels occurs in intimate relation to the granulations, and the density of the network increases (sometimes coalescing to form lacunae laterales) in proportion to the extent of the arachnoid granulations. Our hope is that the thick, spongy parasagittal dura which houses these channels will prove to be a useful site for the diversion of cerebrospinal fluid by way of a purely intracranial shunt. Our first and somewhat crude attempts to access this network of channels in cadaveric specimens have been very encouraging. It is not presently clear how this network of channels should best be classified — venous or "lymphatic-like" (obviously, they do not fit the classical definition of true lymphatics as they do not involve a system of lymph nodes and do not ultimately drain into the thoracic duct or other major lymphatic vessels). One issue of concern is the predicted response of these endothelial channels to the introduction of a foreign body—namely a conduit for cerebrospinal fluid.

Endothelial cells are ubiquitous in man, forming a lining for all the cardiovascular and lymphatic systems, from the largest arteries to the smallest capillaries. The functions of endothelium are legion, and vary depending on the site examined. Their roles include balancing the forces of coagulation and fibrinolysis, as well as controlling vascular tone. Endothelium demonstrates a remarkable ability to proliferate and migrate in the process of angiogenesis, or in repair of injury. These characteristics are central to our ability to mechanically manipulate the circulatory and lymphatic systems.

General Characteristics

Endothelial cells are flattened cells of mesodermal origin which form a monolayer lining the vascular and lymphatic systems. Their cytoplasm is extremely attenuated except around the nucleus which bulges into the lumen of the vessel, giving the luminal surface a quilted appearance. Though similar in appearance, significant differences exists between vascular and lymphatic endothelium. Vascular endothelium can be highly metabolically active, as evidenced by the large number of mitochondria found in certain vascular sites such as the CNS.[15] This reflects the necessity for carefully controlled transfer of substances into and out of the vascular space such sites. Lymphatics, like much of the capillary endothelium in the periphery, are much less active metabolically, consistent with the fewer numbers of mitochondria spread through the cytoplasm.[11] Distinguishing between endothelium of lymphatic and vascular capillaries is at times difficult. They have similar growth requirements and characteristics[27]. Immunohistochemical reactivity is similar, with both vascular and lymphatic endothelium reacting to antibodies to factor VIII, and to Ulex Europias. It has been suggested that lymphatics may only weakly express factory VIII related antigen, thus providing an immunohistochemical basis for distinction.[9] Some basic differences are generally accepted.

Lymphatics may be larger and more irregularly shaped than vascular capillaries and still have only an endothelial monolayer separating them from the surrounding connective tissue, whereas vascular endothelium rests upon a continuous basement membrane. [26] In contrast, lymphatics typically have no basement membrane, or one which is highly fragmented.[11] This arrangement provides unobstructed passage of excess tissue fluid to the abluminal aspect of lymphatic endothelium.

The junctions between vascular endothelial cells vary at different body sites. The most common type found in tissues excluding the CNS are a junctional complex including a

zonula or macula adherens, without tight junctions. In the central nervous system, pentalaminar tight junctions exist with high electrical resistance between the endothelial cells of the capillaries in all sites except for the circumventricular organs, which exhibit fenestrated capillaries, similar to those elsewhere in the body.[15] Such fenestrations allow rapid communication between the blood and organ tissue. Examples of this outside the CNS include the small intestine, endocrine glands, and the kidney.[26] The junctions between lymphatic endothelial cells, however, are limited to macula adherens. A network of filaments anchors the endothelial cells to the surrounding connective tissue, such that in the setting of tissue edema, the distention of the surrounding tissue is transmitted to the endothelial cells, resulting in their distraction, which widens the intercellular clefts where they are not held fast by the "spot welds".[11, 12]

Transport Mechanisms

There are three routes for substances to cross the endothelial cell layer of a vessel. In endothelium with tight junctions, there are two potential pathways across the cells. Firstly, molecule-specific channels act as selective conduits, which may be passive or active. A more non-specific mode of transporting fluids and particulate matter is a system of transient transcellular channels formed by vacuoles as they become confluent across the cytoplasm, joining one plasma membrane to another. This has been described in muscle capillaries,[19] in the canal of Schlemm in the eye,[3, 22, 25] and in the endothelium of the lacunae laterales and dural venous sinuses overlying arachnoid granulations.[8, 22-25] Also, paracellular clefts or channels have been described in lymphatics (as mentioned above), and in dural venous sinuses,[8] as well as fenestrated capillaries in the circumventricular organs of the CNS in addition to many tissues in the periphery.

Growth Characteristics

Endothelium, which is normally not dividing in the adult, is capable of angiogenesis in certain settings. This is the focus of much interest in regards to neoplasia which depends on angiogenesis for continued growth. Fibroblast growth factor (FGF) has been shown in vitro to induce angiogenesis.[16] Lymphangiogenesis has been observed *in vitro* when lymphatic endothelium is cultured as a monolayer, andit has been shown that collagen type I is a stimulus for the formation of these capillary-like channels.[13] Rat thoracic duct segments, when cultured on plasma clot or collagen, demonstrate both lymphatic angiogenesis with tubules traceable to the thoracic duct lumen, as well as "hematic-like channels" which develop from the microvessels of the thoracic duct adventitia.[17] The process of growth and response to injury of endothelium involves reproduction and migration of endothelial cells, with migration arrested through contact inhibition when the cells have reached confluence. It has been shown in vascular endothelial monolayer cultures that movement to repair endothelial damage is dependent on functioning centrosomes and microtubules, and that the process is made more efficient with the presence of microfilaments.[5]

Response to Injury

Vascular endothelium embraces a balance of opposing forces of coagulation and thrombolysis,[7,28] as well as modulation of blood flow through vasodilatation and constriction. The triad of coagulation potential, rate of blood flow, and endothelial surface condition are believed to be involved in determining whether thrombosis will occur. However the relative importance of endothelial damage may be less significant than former two factors.[21]

Endothelium is directly involved in the clotting cascade, expressing factor V, VIII, and Von Willebrand Factor, as well as fibronectin which binds fibrin.[2] In addition, high molecular weight kininogen and tissue factor bind to the endothelial cell as part of the coagulation cascade.[7] In opposition to the clotting cascade, endothelium also produces prostacyclin (PGI_2) which inhibits platelet aggregation, thrombomodulin which binds thrombin, preventing it from activating clotting factors and factor C, and heparan sulfate which blocks thrombin by binding with anti thrombin III.[2] In addition, it also produces tissue plasminogen activator, involved in fibrinolysis.[2,20] There may be differences between the relative amounts of pro- and anticoagulant factors produced by the endothelial cell depending upon the size of the vessel it is located in. For instance, Speiser *et al* reported greater amounts of tissue plasminogen activator and less Von Willebrand Factor in microvessels compared to large veins, perhaps explaining why spontaneous microvascular thrombosis is not a more common occurrence.[20]

Vasomotor control, in the normal state as well as in response to injury, is mediated in larger vessels through vascular smooth muscle. This process is affected by autonomic vasomotor control, as well as by the effects of PGI_2 on dilation and thromboxane A_2[2] and endothelin[6] on constriction. PGI_2 relaxes smooth muscle by stimulating production of cAMP and endothelium derived relaxing factor now identified as nitric oxide.[1] Microfilaments are contractile elements found in endothelial cells which may have a role in vasoconstriction even at the capillary level.[2,5]

Endothelial responses to direct, focal injury to the endothelium itself is of primary concern to vascular surgeons. Exposure of collagen underlying vascular endothelium is one of the strongest stimulants for fibrin adherence and subsequent thrombosis. Vascular grafts, angioplasty, and endarterectomy are examples of procedures where the ability of the endothelium to recover from injury is critical. In these settings, large-vessel endothelium will show rapid "sheet migration" of cells to cover defects in its continuous monolayer.[14] In another study, venous endothelial healing following anastomosis was observed within

48 hours of the procedure in dogs.[10] However, an intense inflammatory response occurs locally after autogenous vein grafting causing endothelial sloughing,[18] which was prevented in this study with high doses of methylprednisolone one hour before and four hours following the procedure in dogs.

However, this local-injury response is to be distinguished from injury to surrounding soft tissue, where the release of angiogenic factors such as FGF incites endothelial cells to proliferate and migrate into the injured tissue to form new capillaries, presumably to deliver increased blood flow. Interestingly, following repair of the injured tissue, these microvessels recede.[14] Lymphatic endothelium responds in a similar angiogenic fashion to vascular endothelium following such perturbations as trauma or inflammation to deal with increased tissue fluid from edema[13]. Similarly, reformation of lymphatic pathways following organ reimplantation is also well described.[4]

Vascular and lymphatic endothelium possesses remarkable ability to respond to local and systemic perturbations through alterations in vessel calibre by balancing between vsoconstriction and vasodilation. Similarly, coagulation and fibrinolysis are held in balance, with the latter being more prominent in the microcirculation. The capacity for angiogenesis in the process of repair or response to increased demands of tissue fluid drainage (in the case of lymphatics) provide compliance for structures which vary in their requirements over time. However, from a morphologic standpoint, this distinction seems to blur between vascular and lymphatic capillaries. We thus speculate that the parasagittal dura, rife with endothelial lined channels, may accommodate increased fluid delivered to it artificially, and that these channels will enlarge and proliferate as they appear to do in the living state.

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Chapter 4

Intracranial Shunts

Intracranial Shunts

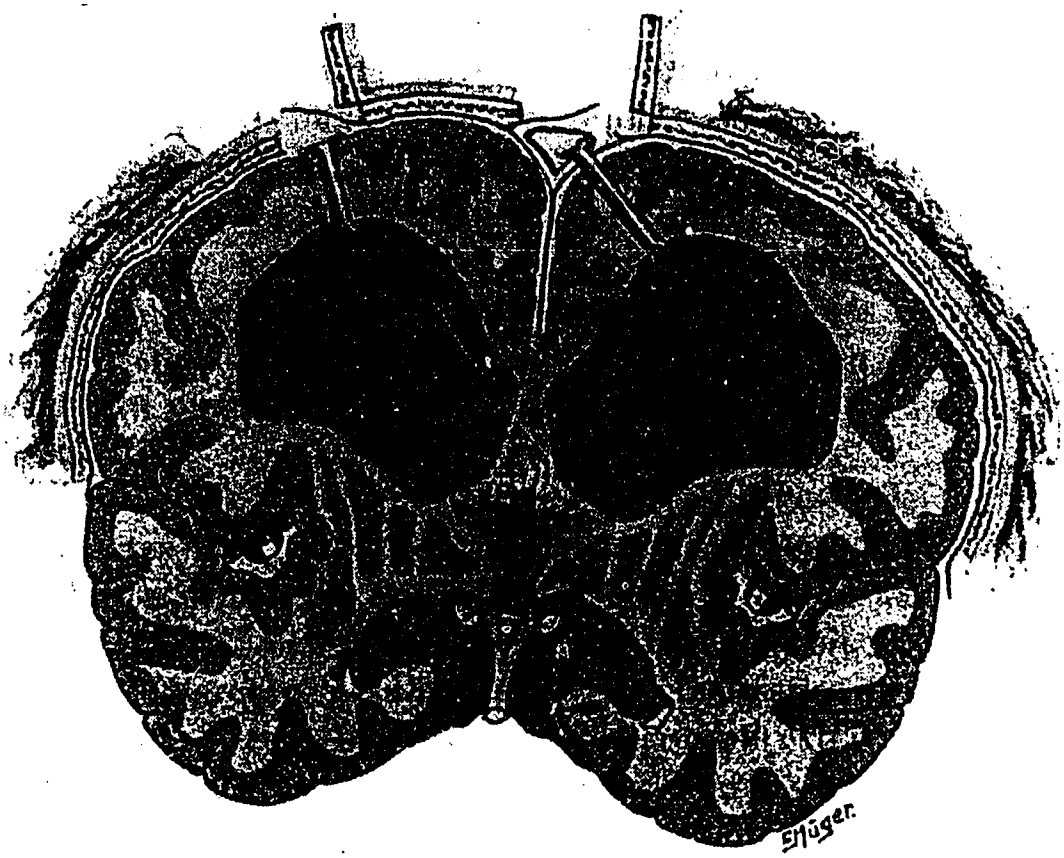
The concept of cerebrospinal fluid (CSF) shunts is not a new one. Since the understanding of hydrocephalus as being an excess of CSF within the brain, the obvious solution to the problem has been to divert the CSF out of the ventricular system. The Greeks may have been the first to establish open external ventricular drainage, but needless to say were hampered by infection.[5] Subsequent attempts to divert the CSF to the subgaleal, epidural, and subdural sites have been tried with various wicks and conduits, but have met with high morbidity and mortality rates, and little success.[5, 13] CSF diversion techniques during this century have included purely intracranial shunts, as well as ones to divert fluid to almost every possible body cavity or viscus below the head. Intracranial diversion procedures include third ventriculostomy through the floor of the third ventricle into the interpeduncular cistern, or puncture of the lamina terminalis. Dandy was perhaps the first to successfully perform these procedures as early as 1922.[5, 13] This was a favourable treatment option for non-communicating hydrocephalus until recent times when superior materials permitted shunting of CSF to other sites in the body with greater success. Scarff's summary of 527 patients from 12 centres spanning nearly 40 years revealed approximately 15% operative mortality and 70% initial success.[13] For the patient with an otherwise normal subarachnoid space and CSF absorptive mechanism, this procedure has long been acknowledged as intuitively the best option from a hydrostatic point of view.[13] However, technical limitations have restricted advancement in this area until recently. Third ventriculostomy has found renewed interest recently with the development of modern ventriculoscopic techniques.[4]

Intracranial shunts have been employed in the setting of non-communicating hydrocephalus to divert CSF with tubes from the lateral ventricles to various basal cisterns. These include the ventriculo-cisternostomy of Torkildsen, wherein a rubber or plastic tube was routed through an occipital approach into the temporal horn of the lateral ventricle, and the

distal tip placed into the cisternal magna. His 1960 report of 35 cases from 1947-48 documented 22% operative deaths, including 30% operative deaths in patients with benign aqueduct stenosis. The long term survival for this latter group was 20%. Similar results were obtained with this procedure performed subsequently by other surgeons.[13] Needless to say, these numbers are not conducive to widespread support for the procedure in the modern day Neurosurgical community. However, in the 1950s, this procedure had "become an accepted and effective method in relieving non-communicating hydrocephalus."[14] Other intracranial shunts, based on the same concept as the Torkildsen procedure, have also been performed during the 1950s. These include shunting from the lateral ventricle to the anterior supracallosal space (Lazorthes, 1953), the ambient cistern (Kluzer and Geuna, 1955), and the chiasmatic cistern (Feld, 1951).[13] The mastoid air cells have also been used.[9] Procedures involving the placing of stents from the third to fourth ventricles through the aqueduct have been performed with limited success[13]. The subdural space has been similarly utilized to decompress the ventricles in the past by Forrest, Laurence and MacNab in 1957. A ventriculosubarachnoid transcerebral fistula has also been described and has met with some success in the laboratory setting in dogs.[6]

Intracranial vascular shunts have been attempted in the past only to a very limited extent. In 1908, Payr was the first to report a ventriculo-superior sagittal sinus shunt using formalin-fixed calf vein as a conduit.[10] **(figure 4-1)** A remarkable 8 out of 15 patients survived.[5] The incidence of shunt malfunction including sinus or shunt thrombosis is not clear. This somewhat crude but pioneering attempt may have represented the most physiologic vascular shunt procedure from a hydrostatic point of view. Attempts to shunt CSF into the sagittal sinus and into superficial cerebral veins using a more conventional ventricular catheter routed via an epidural pathway to the recipient vessel met with the predictable results of thrombosis. (Dr. Peter Allen, personal communication, 1995) A single recent report from Russia suggests potential utility of shunting into the transverse sinus in selected cases.[1a]

Figure 4-1: historical intracranial shunt techniques



Rechts Ventrikeldrainage in den Sinus sagitt. super., links gegen den Subarachnoidealraum.

The German Surgeon Payr, reported on a series of 15 patients who underwent intracranial vascular shunt procedures involving interposing a tube of formalin-fixed calf vein between the lateral ventricle and the superior sagittal sinus. Remarkably, 8 of these 15 patients actually survived the procedure. Pictured above is the venticulo-sinus shunt, as well as another form of intracranial shunt —the ventriculo-subdural shunt. From Payr E: Drainage der Heirnventrikel Mittelst FreiTransplantatirter Blutgefässe; Bemerkungen über Hydrocephalus. **Aus der Königl Chirurgeschen Klinik zu Greifswald; Archiv für Klinik Chirurgie 87:**1908, Figure 5.

Scarff points out that intracranial shunts provide the advantages of a shorter shunt tube and freedom from the effects of growth of the child. He also suggests that having both ends of the tube bathed in CSF is beneficial to patency, though this is not substantiated elsewhere in the literature. Another advantage of such a construct is that no mechanism for controlling pressure or flow is required; there is no hydrostatic effect present with the proximal and distal ends of such a shunt at approximately the same level in all positions. Thus complications related to over-drainage of the ventricles due to large negative hydrostatic forces created by a long distal shunt catheter in the upright position are avoided.

In the situation of intracranial ventriculo-vascular shunts, the success of the system is dependent on the downward pressure gradient from ventricle to recipient venous structure. Although it has been shown that the cortical venous pressure is consistently higher than the ventricular pressure in both normal and hydrocephalic models,[3,8] the SSS remains protected from intracranial pressure. In normal dogs, SSS pressure is one half that of the lateral ventricle (approximately a 5mmHg difference), and in the hydrocephalic canine model the SSS pressure is still 44% less than the ventricular pressure.[3] In extreme intracranial hypertension, the SSS has been shown in dogs consistently to fall slightly, presumably due to relative compression of its tributary cortical veins, while the relatively stiff walls of the dural sinus itself prevent compression enough to maintain adequate drainage from the cranial cavity.[1] Thus, a one way valve mechanism would be important for a device which drains into the cortical venous system, but perhaps not if the receiving structure is dural based such as the SSS or parasagittal intradural structures.

A further advantage of completely intracranial shunts is the decreased risks of shunt infection compared to those involving extracranial sites. This is a theoretical advantage only, as no literature exists to examine the issue to the author's knowledge.

However, a possible complication related to intracranial vascular shunts is thrombosis of the superior sagittal sinus if this structure is chosen as a recipient site. Occlusion of the longitudinal sinus results in venous cortical venous hypertension with increasing likeli-

hood of venous infarction the farther posteriorly the occlusion occurs along the sinus. As well, occlusion of the sinus can result in further worsening of the CSF absorption *via* the established pathways through the arachnoid granulations.[2, 7, 11] The possibility of sagittal sinus thrombosis truly strikes fear into the heart (?brain!) of the Neurosurgeon. However, such an incident is uncommon in the absence of severe dehydration or hypercoagulability (for example protein S or antithrombin III deficiency)[7, 11, 12, 15]. This is of significance to our studies, as we are considering the vascular (venous) structures in the parasagittal dura as possible conduits to conduct CSF toward the sagittal sinus. It seems highly unlikely that introducing CSF to this region of dura through a device of synthetic material would possibly cause thrombosis in the sinus. During the course of all parasagittal approaches to lesions of the brain, the dura is routinely coagulated, sutured, and onlayed with procoagulant material with impunity. Introducing CSF into the substance of the dura would not in and of itself be expected to propagate thrombosis, as this very technique has been employed outside the cranium in other vascular shunts, with thrombosis only a concern when the distal shunt retracts up into a smaller vein. Our concept for CSF diversion would involve mainly CSF coursing through the network of parasagittal intradural channels, and entering the sinus through their undisturbed natural portals. However, even the remotest possibility of sinus thrombosis needs to be ruled out (if possible) prior to embarking on trials of this techniquein humans.

In conclusion, the concept of intracranial shunts is an old one. It is an intuitive treatment for hydrocephalus, but has previously met with difficulties perhaps largely technical in nature. As we see renewed interest in the third ventriculostomy procedure aided by modern technology, and in particular ventriculoscopy, the many possibilities for intracranial CSF diversion should be revisited. The venous anatomy of the parasagittal dura may also be of use in vascular shunts which would avoid direct contact with the sagittal sinus.

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Chapter 5

Conclusions

Conclusions

As our understanding of the cerebrospinal fluid system broadens, so does our need to find better ways of managing hydrocephalus. The CSF is critically involved with the development and functioning of the central nervous system, and disruption of its flow can have devastating effects at any stage of life. Our ability to treat the various forms of hydrocephalus remains less than ideal, and the search continues for the ideal CSF diversion procedure.

Our studies have clearly demonstrated that the parasagittal dura contains an extensive network of channels which project laterally from the superior sagittal sinus, and are intimately related to the arachnoid granulations, which have been shown repeatedly to be involved in transfer of CSF out of the subarachnoid space. Although their presence has been suggested in previous work [1-3], we have provided a detailed description of their location, extent, and microscopic characteristics using multiple modalities. We have also demonstrated that these channels proliferate through life, as do the arachnoid granulations. This study has shown clearly that the lacunae laterales are formed by the coalescence of these channels, as was proposed by earlier authors.[2, 3] This differs from more recent description implicating the middle meningeal vessels as the precursors.[4]

It has been suggested in the past that the lacunae laterales contain CSF mixed with blood.[2, 3] We are unsure at this point exactly what is carried in the parasagittal intradural channels. We suspect that it is largely CSF, and likely mixed with blood. These channels exist in disproportionately high density to the arterial supply of the dura in this region, and, to re-iterate, they occur where arachnoid granulations are most prolific. Although these channels are not lymphatics by definition, they may proliferate in the way lymphatics do—that is, in response to increase tissue fluid pressure.

We have shown that access to the SSS through these parasagittal channels is readily achieved at low pressures. If indeed these structures convey CSF *in vivo* , then doing so by way of a CSF diversion procedure may be a physiologic approach to delivering CSF to the venous blood. Such an approach would avoid the risks of placing foreign bodies such as catheters into the SSS itself. It would also obviate the need for long CSF shunt tubes and complex, expensive valve systems, as in the proposed approach, no swings in hydrostatic pressure would occur with changes in posture.

This anatomic study may provide the groundwork for further efforts to develop alternate intracranial CSF diversion procedures. It addition, it may also may provide us with a better understanding of some of the vascular pathology affecting the dura, such as dura arteriovenous fistulas.

Future work is planned to focus on development of a device to introduce CSF into the parasagittal dura through a convenient epidural approach. Further studies are also required to examine potential risks of thrombosis of the SSS associated with introducing foreign bodies into the parasagittal region. An animal model will hopefully provide us with a means to explore some of these issues.

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