"PHYSIOLOGICAL AND PATHOLOGICAL CHANGES IN CRANIAL CEREBRO-SPINAL FLUID VOLUME IN MAN, AS DEFINED BY MAGNETIC RESONANCE IMAGING"

© Dr. Robert Grant MBChB, MRCP.

Thesis submitted for the degree of

M.D.

in the
Faculty of Medicine
of the
University of Glasgow

Magnetic Resonance Imaging Unit
Institute of Neurological Sciences
Southern General Hospital
Glasgow.

September 1987.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

TABLE OF CONTENTS

TABLES

FIGURES

ACKNOWLEDGEMENTS.

I would like to express my gratitude to the following people:

- All the staff at the Neurological Institute, relatives of staff and friends who acted as normal control subjects for many of the studies.
- The patients who volunteered to take part in the various CSF volume clinical trials, and the consultants who gave me permission to study patients under their care .
- Paticular thanks go to my supervisor, Professor G.M. Teasdale for his advice and encouragement throughout the time I spent in the M.R.I. Unit and for stimulating discussions on developments and applications of this technique in the clinical management of neurological and neurosurgical patients.
- Sincere thanks are owed to Dr. Barrie Condon,(M.R.I. Research Physicist), who devised the CSF volume sequence, and to Dr. J Patterson,(Principal Physicist), who always managed to combine the attributes of objective criticism and practical help with a friendly and patient manner.
- I am indebted to Mrs Audrey Lawrence the statistician in the MRI department for invaluable help in analysing much of the data obtained from these studies.
- I am grateful to Dr. I. Bone, (Consultant Neurologist at the Neurological Institute, Glasgow), for his enthusiam and advice on all clinical neurological matters relating to the work embodied in this thesis.
- This study would not have been possible without the help of Dr. D. Hadley, Senior Radiological Research Fellow in M.R.I., the physics technicians and radiographer staff of the M.R.I. unit
- Finally, I would like to thank my wife, Joy, for her support and understanding during the writing of this thesis.

DECLARATION

This thesis was commenced and completed while I was employed as full-time Clinical Research Fellow in Magnetic Resonance Imaging, at the Institute of Neurological Sciences, Southern General Hospital, Glasgow. The post was funded by a Medical Research Council(MRC) Grant SPG 82Q1316 (ID 81). The Magnetic Resonance Imaging Unit was supported by grants from the Medical Research Council(ID 81), the Greater Glasgow Health Board and the University of Glasgow, the Scottish Hospitals Endowment Research Trust, the Institute of Neurological Sciences Research Trust and the Chief Scientist, Scottish Home and Health Department.

Dr. Barrie Condon devised the CSF Volume Sequence (IRCP 300/400/5000) and the image non uniformity correction used in the calculation of intracranial CSF volumes.

Testing of samples of CSF for pH, pCO2 and pO2 were performed in the Biochemistry Department of the Southern General Hospital under the guidance of Dr. Moyns (Principal Biochemist).

Weighing and sealing of reference phials were performed with the help of Graham Conkey,(Pharmacist) at the Pharmacy Department, Southern General Hospital.

Mrs Audrey Lawrence helped in the computer based statistical analyses of many of the studies.

I have presented work from this thesis at the following meetings:
Surgical Research Society: Neurosurgical Satellite (Surrey-1987).
Picker International Users Group (London-1987).
European Workshop-Magnetic Resonance in Medicine (London-1987).
Association of British Neurologists (Newcastle-1987).
Joint Meeting-Finnish Neurological Assoc and Assoc of British Neurologists (Savonlinna,Finland-1987).
The Physiological Society (Glasgow 1987).
Scottish MRI Users Group (McNetic) (Glasgow-1987).
Society of Magnetic Resonance In Medicine (New York,USA-1987).

Others have presented work from this thesis at the following meetings:
Society of Magnetic Resonance Imaging (San Antonio,USA-1987).
Society of British Neurosurgeons (Coventry-1987),
European Congress of Neurosurgery (Barcelona,Spain-1987)

SUMMARY

SUMMARY

An accurate and reproducible method for measuring the volume of the cranial CSF spaces was developed in the MRI unit in Glasgow by Dr. B. Condon in 1986. Using this MRI method the total cranial, cortical sulcal, ventricular and posterior fossa CSF volumes could be accurately measured, whereas only ventricular CSF volume could be estimated by previous techniques. The aim of this thesis was firstly to examine the technique critically and to reduce factors that might affect the accuracy or reproducibility of CSF volume measurement; secondly, to determine the normal range of CSF volume; thirdly, to study physiological factors that might influence the cranial CSF volume; and lastly to assess the research and clinical potential of these measurements in conditions where the CSF volumes might be altered.

The original technique was modified. The accuracy of the method was improved by using 0.9% sodium chloride as a calibration reference solution, rather than water, as saline was found to produce a signal intensity per unit volume closest to that of anaerobically obtained CSF. The reference phial was sealed, in order to eliminate errors due to phial filling, and placed in an insulated casing that was designed to fit inside the MRI standard head coil. The insulated casing reduced error due to phial cooling during the examination. As the phial was no longer strapped to the head, errors due to phial movement were minimised and the overall examination took leLs time as patient positioning was less critical. The effect of CSF motion on image quality and volume measurement was studied. It was found that CSF motion could result in "background" blurring of the image and errors of approximately 5% could occur. The amount of background blurring was related to the amount of motion within the fluid filled phantom.

Background blurring was seen most frequently in patients with obstructive hydrocephalus and in patients with normal pressure hydrocephalus. It is possible that in future the background signal level may be used as an index of CSF motion "in vivo".

Cranial CSF volumes increased significantly with age and males had more cranial CSF than females, but there was a wide variation of normal. Total cranial and cortical sulcal CSF volumes increased more significantly than ventricular and posterior fossa volumes reflecting age related cortical atrophy. The normal ratio of ventricular CSF

volume to cortical sulcal volume (V:CS ratio) was less than 0.33.

The CSF volume measurements were found to be highly reproducible in the short term, but there was a significant increase in CSF volume premenstrually when compared with the mid-cycle CSF volumes. The premenstrual increase may have a hormonal basis or reflect reciprocal changes in intracranial blood volume. Further work is needed to examine intracranial pressure and blood volume changes related to the menstrual cycle and measure CSF volumes in patients with pre-menstrual syndrome, catamenial epilepsy and premenstrual migraine. Total cranial CSF volume decreased during hypercapnia and increased during hypocapnia. This reflected the reciprocal changes in cerebral blood volume and thus provided confirmation of the modified Monro-Kellie Doctrine. Large amounts of CSF were often lost following lumbar puncture and the reduction in CSF volume was related to the presence of headache 24 hours after LP.

The preliminary clinical studies included patients with dementia, normal pressure hydrocephalus (NPH), obstructive hydrocephalus and benign intracranial hypertension (BIH). Patients under 70 years of age who had dementia had more cortical sulcal and ventricular CSF than healthy elderly controls, but there was no clear separation between patients over 70 years of age with dementia and healthy elderly subjects. The V:CS ratio separated patients with NPH from patients with dementia of other causes and from healthy volunteers. This measurement may be valuable in the diagnosis of NPH. Patients with a V:CS ratio greater than 1.00 had a significant clinical improvement after V-P shunting but further work is necessary to compare the predictive value of this test with the numerous other tests that claim to be able to predict a good post-operative outcome. The degree of reduction in ventricular CSF volume post-operatively was readily measured and these measurements may be important in the management of patients if a shunt blockage is suspected. Although the diagnosis of obstructive hydrocephalus is easily made by CT or MRI scanning, the CSF ventricular volume and V:CS ratio are potentially useful in the diagnosis of this condition and may separate the more acute cases from the more chronic cases. In BIH the ventricular volumes were often smaller than those of normal subjects, but the total cranial and cortical sulcal volumes were commonly normal. The total CSF volume was not increased in patients with BIH and there was no evidence of cerebral oedema. The rise in

intracranial pressure therefore was probably related to an increase in the intracranial blood volume. Total and ventricular CSF volumes increased when the symptoms resolved following treatment with weight reduction and diuretics. The relationship between obesity and CSF volume deserves further investigation as the CSF volumes were frequently observed to be smaller in obese subjects.

This method of CSF volume measurement using MRI has many research and clinical applications. Interpretation is hindered to some extent by the lack of data on physiological changes in intracranial pressure, brain volume and intracranial blood volume. Future clinical studies of CSF volume in neurological disorders should include cerebral blood volume or intracranial pressure measurement.

INTRODUCTION

INTRODUCTION.

Cerebrospinal fluid (CSF) is an ultrafiltrate of plasma that is secreted predominantly by the ventricular choroid plexuses[159,217] and to a lesser extent by the ependymal lining of the ventricles.[175] The formation rate of CSF has been calculated to be approximately 20ml/hr.[49] and CSF formation is in equilibrium with absorption from the subarachnoid space via the arachnoid villi[218] or the through the adventita of small cerebral blood vessels.[228] In contrast to the abundant scientific literature concerning CSF formation and absorption in animals and man, very little is known about the CSF volume. The average volume of the total cranio-spinal CSF space is not known. Bradbury[27] refers to the work of Weston,[219] and quotes the average cranio-spinal volume as approximately 140mls. However, the paper to which Bradbury refers contains no information whatsoever about CSF volume. In their comprehensive book on cerebrospinal fluid, Davson, Welsh and Segal[59] also quote 140mls., referring to the work of Last and Tompsett,[135] but in fact the latter authors only measured the volume of the cerebral ventricles. An average cranio-spinal CSF volume of 135mls. is quoted in the Geigy tables[79] which refer to the book by Lups and Haan,[141] yet these authors give no indication of how they measured the CSF volume. Several other major textbooks and authoritative papers[48,121,152,157] also refer to the average cranio-spinal CSF volume as 130-140mls. but they do not give a reference source for these figures. Post-mortem measurements of cranio-spinal CSF volume are likely to be inaccurate since the volume of the ventricles and cortical sulcal spaces is markedly reduced in the first six hours after death because CSF is absorbed into the tissues.[61,191] It has not previously been possible to measure cranial CSF volume accurately during life and it has been assumed that the volume of cranial CSF generally remains relatively constant, over short periods of time. A reliable method for measuring cranial CSF volume would provide fundamental information on physiological alterations in CSF volume and pathological changes in certain neurological and neurosurgical conditions such as dementia, normal pressure hydrocephalus (NPH) and benign intracranial hypertension (BIH).

Since the development of Magnetic Resonance Imaging as a clinical

investigative technique in the early 1980's[64,101,197] the number of reports of its value as a method of imaging has risen exponentially. Using it simply as an imaging modality underutilises its capabilities and ignores important quantitative information present in the data acquired from each scan. Thus special pulse sequences have been devised that can provide an estimate of blood flow in major vessels or can quantify cardiac wall motion[124] and more recently, a new method to quantify the cranial CSF volume has been developed in the Magnetic Resonance Imaging (MRI) Unit at the Institute of Neurological Sciences, Glasgow.[41] The pulse sequence used(IRCP 300/400/5000) produces images of cranial CSF only and is the only method currently available of accurately measuring the total cranial CSF volume in vivo. As MRI does not involve radiation or radioactive isotopes serial measurements of CSF volume are possible and these studies may provide some insight into physiological or pathological alterations in the volume of cranial CSF and variations with time or as a result of treatment. Total cranial CSF volumes can be further subdivided by this technique into more discrete regions, thus enabling measurement of ventricular, posterior fossa and estimated cortical sulcal CSF volumes.

The purpose of this thesis is firstly to try to improve the technique of measurement of CSF volumes by identifying and quantitatively assessing any possible sources of error and where possible minimising these errors. Secondly, to assess the "normal" range of cranial CSF volumes accounting for age and sex differences and to measure any alterations in CSF volume that occur as a result of physiological changes such as menstruation, carbon dioxide inhalation, hyperventilation or changes in response to lumbar puncture. Finally, the technique was used to investigate pathological alterations in CSF volume associated with neurological disorders where the CSF is suspected to be reduced (BIH), increased (dementia with cerebral atrophy) or altered by obstruction to flow either within the ventricular system (Obstructive Hydrocephalus) or at the level of the arachnoid villi (NPH) and to relate these CSF volume measurements to the clinical state and response to treatment.

A basic introduction to Magnetic Resonance Imaging and a glossary of abbreviations is given in Appendix A. and before describing this method of CSF volume measurement in detail, previous methods used to estimate CSF volume are discussed in Chapter 1.

CHAPTER ONE

THE HISTORY OF CEREBROSPINAL FLUID VOLUME ESTIMATION.

1.1. Post-Mortem CSF Volume Measurements.

1.2. In Vivo CSF Volume Measurements.

a) Pneumo-encephalography & Isotope Ventriculography.

b) X-ray Computed Tomography.

c) Magnetic Resonance Imaging.

1.1. POST-MORTEM CEREBROSPINAL FLUID (CSF) VOLUME MEASUREMENTS.

Recorded interest in the anatomy of the human cerebral ventricular system dates back at least to the early 15th century, when Leonardo da Vinci made wax casts and drew sketches of the cerebral ventricles (Figure 1a). He injected softened wax into the ventricular system, at post-mortem, via the fourth ventricle. Once the wax had hardened, the surrounding brain was removed, leaving the moulded wax cast.

Harvey (1911)[99] made the first ventricular volumetric measurements after he sliced ten fixed brains into four sections and then made casts of each section. The volume of the lateral ventricles was estimated by measuring the volume of water displaced from a waterbath, by the cast (Archimedes method). The lateral ventricular volume measurements ranged from 6.3mls-67.9mls (mean 28.6mls). Unfortunately the ages of the subjects and the causes of death were not recorded. In another study, Locke[139] injected hardener into the ventricles of unfixed brain in order to produce a cast for volumetric measurement but due to problems with tearing of the brain during injection and distortion of the ventricles of unfixed brain, these measurements were not considered accurate. Last and Thompsett[135] instilled Marco resin into the ventricles of brains that had been fixed in formalin for six weeks. This study is regarded by most anatomists and pathologists as the most accurate method for estimating ventricular volume and they reported "normal" lateral ventricular volumes ranging from 7.4-56.6mls. While the individual measurements were most probably reasonably accurate, it is doubtful whether the range of ventricular volumes could be considered "normal", for the material sectioned included 24 adult and 5 foetal brains obtained at random autopsies and these were presumed normal because "the pathologist did not state an interest in examining the brain" and no "unusual" features were noted when the surrounding brain was separated from the cast. The causes of death and past medical histories of their cases were not recorded. Post-mortem ventricular volume decreases due to shift of CSF into the brain after death.[61,191] Last and Thompsett calculated that inaccuracies of approximately 2% resulted from post-fixation brain shrinkage, however, this error was far outweighed by the technical limitations and errors in measurement with unfixed brain.

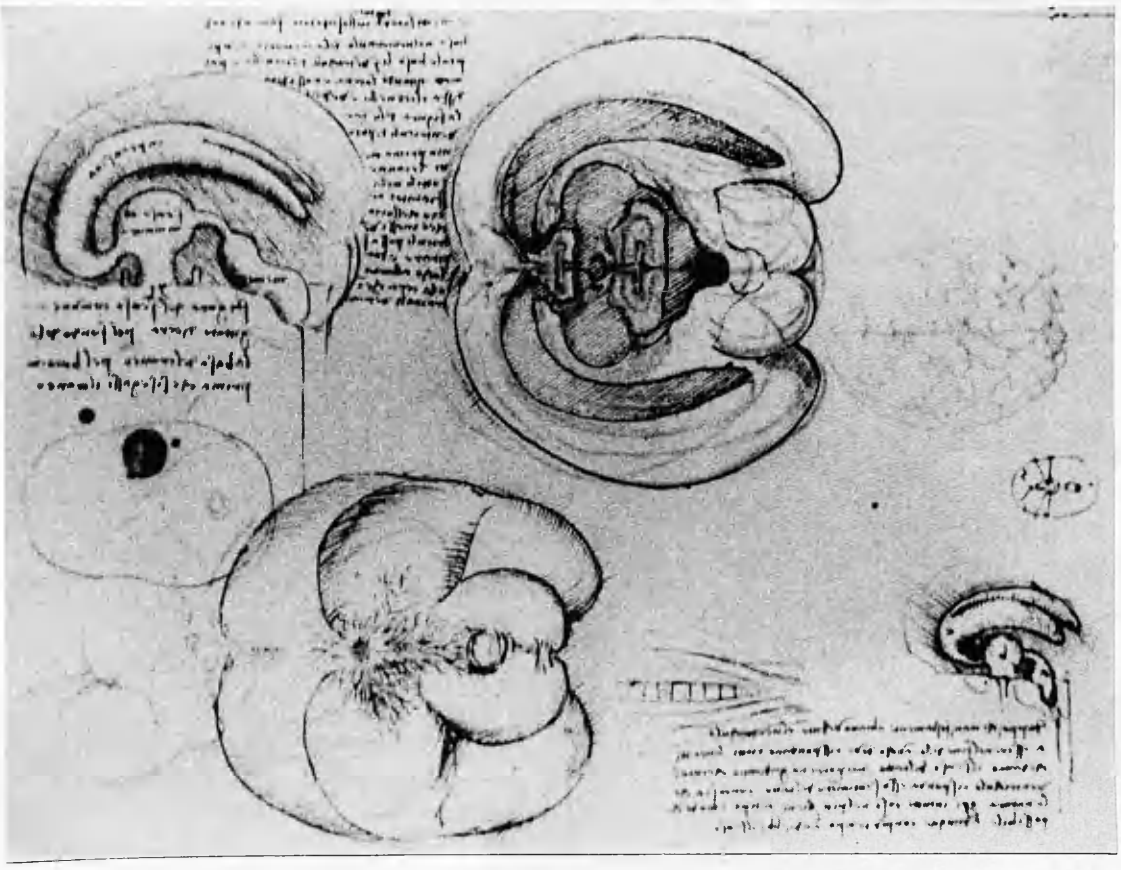

Figure 1a. Sketches of the cerebral ventricles by Leonardo da Vinci.

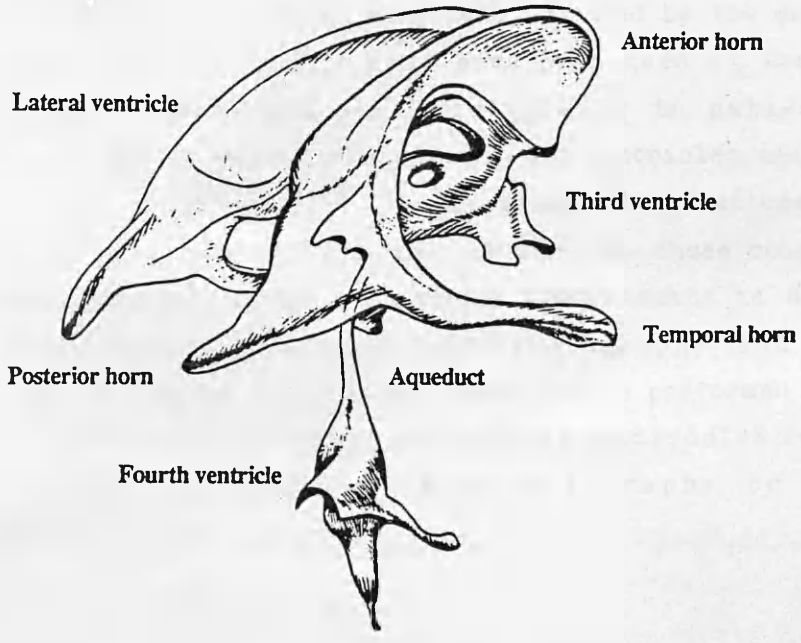

Figure 1b. The human cerebral ventricular system.

In a large autopsy study, Knudsen et al.[125] examined fixed brains of 183 cadavers, where the brains were presumptively normal. The ventricular volume was quantified by an elaborate method of introducing air into the ventricles and then estimating the volume of air displaced when the brain was submerged in water. Knudsen estimated the volume of an average single lateral ventricle was 7mls. There was, however, a very wide range of "normal" (1ml-39mls) and ventricular volume appeared to increase with age.

To date it has not been possible to measure total cranial CSF volume. Extra-ventricular cranial CSF volume at post-mortem could be estimated using a technique similar to that described by Davis[57] and Harvey[98]. Davis measured cranial cavity volume at autopsy by expanding a water filled lubricated balloon until it filled the skull. The balloon was then removed and weighed and the brain volume was measured by Archimedes's displacement method. If the brain volume was subtracted from the total cranial cavity volume, the resultant volume would be an approximate measure of the total cranial CSF volume (minus the ventricular volume).

1.2. IN VIVO CSF VOLUME MEASUREMENTS.

a).Pneumo-encephalography and Isotope Ventriculography.

Linear measurements such as the Evans ratio[70] (the maximum width of the anterior horns of the lateral ventricles divided by the diameter of the skull) and the ventricular span have been used at the time of pneumo-encephalography and ventriculography in patients with hydrocephalus to try to assess the size of the ventricles and estimate the ventricular volume.[34,37,56,78] The wide natural variations in shape of the ventricles severely limit the accuracy of these measurements. The estimated error associated with linear measurements is as high as 30%[225]. Furthermore, isotope ventriculography and pneumo-encephalography are highly invasive and would not be performed on normal subjects. Thus the "normal" range of cerebral ventricular volume has not been studied using pneumo-encephalography or isotope ventriculography.

b).X-ray Computed Tomography (C.T.).

i) Ventricular CSF Volume.

Since the introduction of CT, several approaches have been designed to estimate ventricular size or volume.[60,114,168,179] Some have involved linear measurements such as the maximum width of the anterior horns of the lateral ventricles[81] or the Evans ratio.[70] These are inaccurate because of the complex shape and wide variability of normal cerebral ventricular size (Figure 1b.). Other workers have measured the ratio of the ventricular area to that of the intracranial area, in a 10mm. axial slice through the ventricles (Ventricular-Brain Ratio (VBR)).[14,185,201] These area measurements, often made from photographic paper or by planimeter, have been little better than linear estimates and inter-reporter measurements on the same scan often varied by a factor of two.[117] A semi- automated method of measuring total ventricular CSF volume has also been described by Reveley[182] which involved the summation of ventricular areas and wrongly assumed fixed densities for brain and CSF.[10]

Using water filled balloons as phantoms of the cerebral ventricles, Penn demonstrated that CT measurements of volume were accurate to within 16% of the true volume.[168] More modern ("high resolution") scanners improved this accuracy in phantoms to within 10%. CT assessment of ventricular volume "in vivo" has depended heavily on choosing the correct threshold to represent CSF, and an uncertainty of 2-3 Houndsfield units[108] has resulted in a volume change of up to 30%.[181,225] The Houndsfield numbers of human brain change with aging and thus errors of up to 20% can be produced.[227] Two further sources of error have been the partial volume artifact that occurs at the CSF/ventricular interface,[181] and the inclusion of extra-ventricular CSF such as the ambient cistern and sylvian fissures. The errors produced are greater when the subject has normal or small ventricles Computed Tomography also misses out small regions such as the septum pellucidum and small CSF spaces eg. normal temporal horns. Since the introduction of higher resolution CT scanners, the borders of the ventricles are more easily defined, but it is doubtful whether the multiple axial slices used are truly contiguous.[33] Repeated CT scans on normal subjects to assess the reproducibility of ventricular volume measurements have not been performed.

ii) Total or Cortical Sulcal CSF Volume.

The estimation of total cranial and cortical sulcal CSF volumes by CT is subject to even greater errors than ventricular volume measurement. This is due to variations in chosen Houndsfield numbers to represent CSF, partial volume effect between grey matter and CSF, the convoluted structure of the sulci and gyri, as well as technical inaccuracies in slice profile. Initially, estimates were made by linear measurements of the maximal width of the largest sulcus or the sum of widths of the four largest sulci on sections above the level of the ventricles, in order to give an index of cortical atrophy.[11,80,94,100.111]

A semi-automated computer programme developed by Jernigan[116] and later evaluated by Zatz[227] and Reveley[182] purports to measure total "central" fluid volume, which can be divided into ventricular and cortical sulcal CSF volumes. This method has assumed fixed densities for brain and CSF, but these will vary depending on the type of scanner, the patients age, the cranial size, dehydration and different relationships of grey to white matter.[10,154,221] Total cranial CSF volume was assessed as the number of pixels which could represent CSF summated over 8 axial slices each 10mm. thick. The lowest section capable of being adequately analysed was above the petrous pyramids and orbital roof and did not include the posterior fossa or the vertex. The CSF volume was recorded in pixels and could not be translated into mls. Because of these limitations it has not been possible to measure total cranial CSF volume reliably during life in man.

c) Magnetic Resonance Imaging.

A basic introduction to the theory of MRI and terminology is given in Appendix A. Magnetic Resonance Imaging produces high quality images of the brain or other body structures without using ionising radiation or radioactivity. A Magnetic Resonance RF pulse sequence has been developed in order to produce an image of CSF only by reducing the signal from grey and white matter almost to zero and exploiting the inherent differences between CSF, white matter and grey matter. Accurate measurements of both ventricular and total intracranial CSF volume are now possible using a MRI method designed by Condon et al.[41] This technique was developed in Glasgow using a 0.15T resistive imager (Picker) and forms the foundation of this thesis and as such will be dealt with in more depth.

Theory.

The "null-point" of a given tissue is where the longitudinal magnetization of tissue following a 180° inverting pulse equals zero during an Inverse Recovery(IR) sequence.[226] The null points of grey and white matter, using a Picker 0.15T resistive magnet operating at 6.36MHz., correspond to delay times(T_I) of 300 msec. and 170 msec. respectively.[41] If the pulse sequence is arranged so that the actual delay time (300msec.) lies between that of grey matter and white matter, the residual negative signal from the grey matter will cancel out the positive signal from white matter. In order further to decrease the signal from grey and white matter a greatly extended echo time (400msec.) is used. This results in a 97-99% reduction in signal from grey and white matter due to their short transverse relaxation times (T_2 : grey 118msec. : white 66msec.), yet signal from CSF will only be reduced by less than 16% as it has a much longer T_2 (T_2 : 2269msec.(aerobic)[42] and 3052msec.(anaerobic - Chap 2).

These two methods of reducing signal from grey and white matter are combined with a very long repetition time(5000msec.) in order that CSF has sufficient recovery time to produce a high signal. The net result of this sequence is to provide an image of CSF, with an effective contrast of greater than 200:1 between a unit of CSF and a unit of combined grey and white matter.

Pulse Sequence.

This specially designed sequence is an Inverse Recovery sequence with a 4-echo Carr-Purcell data collect ; the delay time is 300msec., the overall echo time is 400 msec. and the repeat time is 5000 msec.:

(IRCP 300/400/5000)

Using one average and a 64 X 64 matrix, the acquisition time for such a sequence is 5.3 minutes per slice.

Reference (Calibration) Phial.

The T_1 and T_2 values of distilled water at 37°C closely approximate those of CSF (T_1 - CSF 3302+/-170msec. ; water 3499+/-128msec. : T_2 - CSF 2269+/-126msec. ; water 2025+/-101msec.). A phial containing a known volume of water (30mls.), at body temperature, is used as a "reference" phial. This avoids errors due to day to day differences in signal level because of magnetic field instability and variations due to

tuning of the head coil.

Preliminary Findings (Condon[41])

1. Phantom Studies.

Phantom studies were performed by Condon[42] using perspex ventricular casts and capillary tubing of different diameters, containing a known volume of water, to represent the cortical sulci and cisterns. The standard deviation of the differences between true and estimated volumes was 3.9% for the ventricles, 4.6% for the total c.s.f. and 7.9% for the sulci alone. Reproducibility studies demonstrated standard deviations of 0.65% for ventricles, 2.3% for total CSF and 3.5% for sulci alone.

2. Clinical Imaging.

The subject was positioned in the MR imager using the standard head coil and the reference phial was strapped on top of the head(Figure 2). An initial coronal "pilot" scan (SE40/200) of the head was performed to ensure that the subject was central and to gauge the diameter of the lateral ventricles(Figure 3).

A sagittal scan of the head with a slice select gradient (or slice thickness) of 240mm. was performed. The sagittal image obtained, although presented as a two dimensional image contains signal (or information) from all the CSF in the head, i.e. from the 240mm thickness (Figure 4a). A second sagittal head scan was then performed with a slice thickness selected to include the ventricles but exclude the overlying and underlying cortical sulci and sylvian fissures.(Figure 4b).

3. Image Non-Uniformity Correction.

The standard head coil was used for imaging because it had a more uniformly homogenous field, although there was a reduction in signal intensity at the top and bottom of the sagittal CSF volume images. This "image non-uniformity" was corrected by an empirically determined correction coefficient[43] for the phial position in the 240mm. and the thinner section, and by separate corrections for the head in each scan. Therefore once these corrections were made there were 4 images;

a) 240mm scan with head corrected for image non-uniformity.

b) 240mm scan with phial corrected for image non-uniformity.

c) Narrow section with head corrected for image non-uniformity.

d) Narrow section with phial corrected for image non-uniformity.

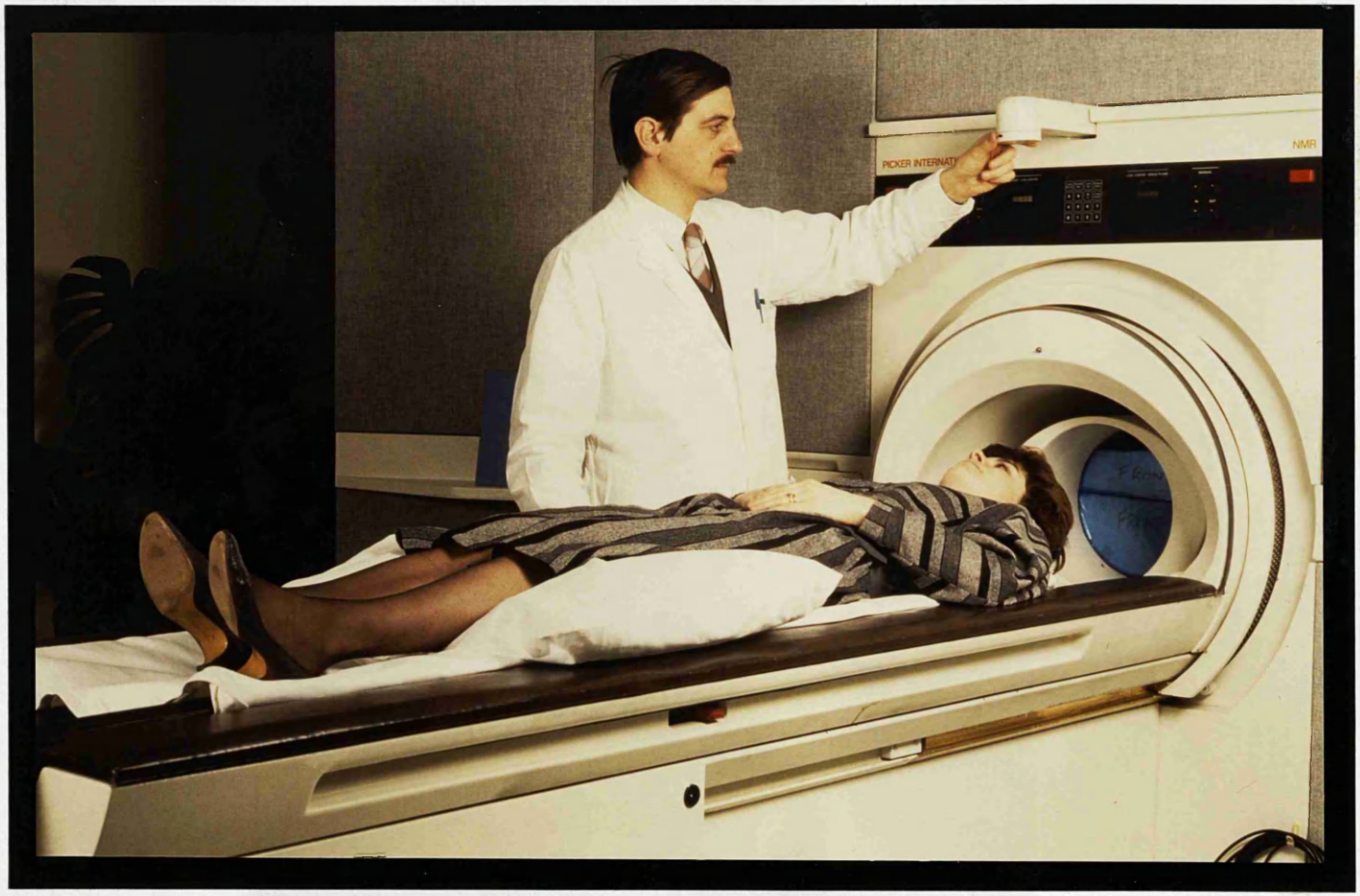

Figure 2. Positioning of subject in the imager.(Reference phial in "blue" moulded insulated casing.)

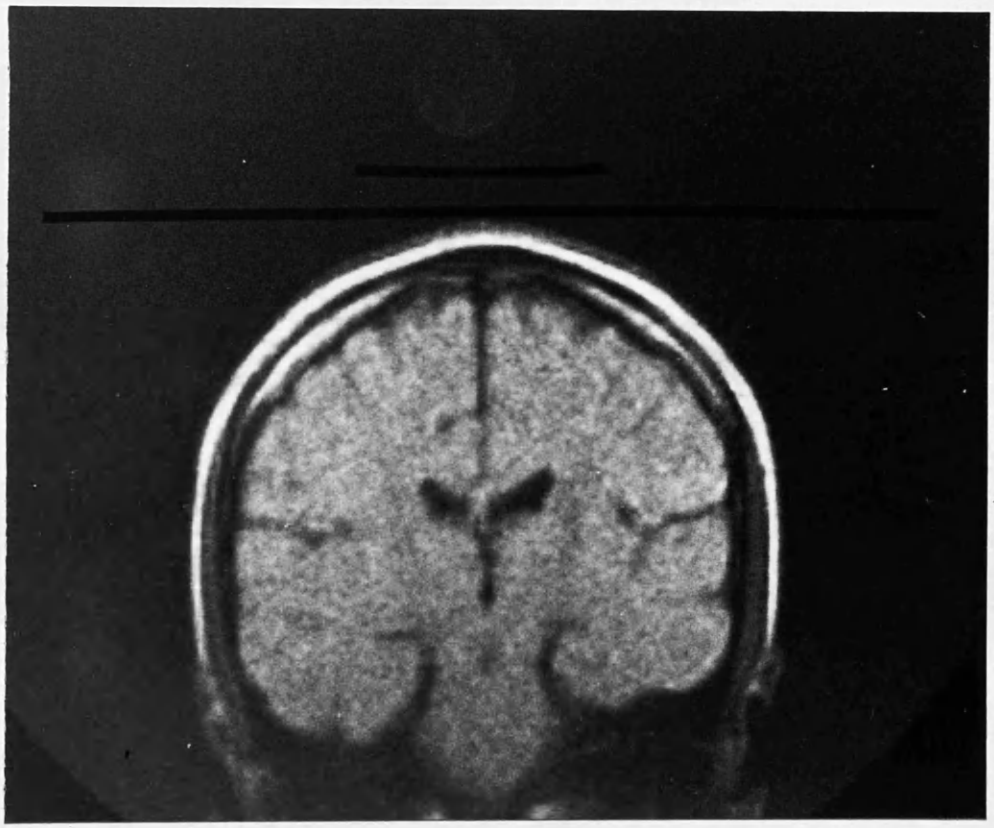

Figure 3. Coronal "pilot " scan of the head and reference phial (72mm and 240mm markers).

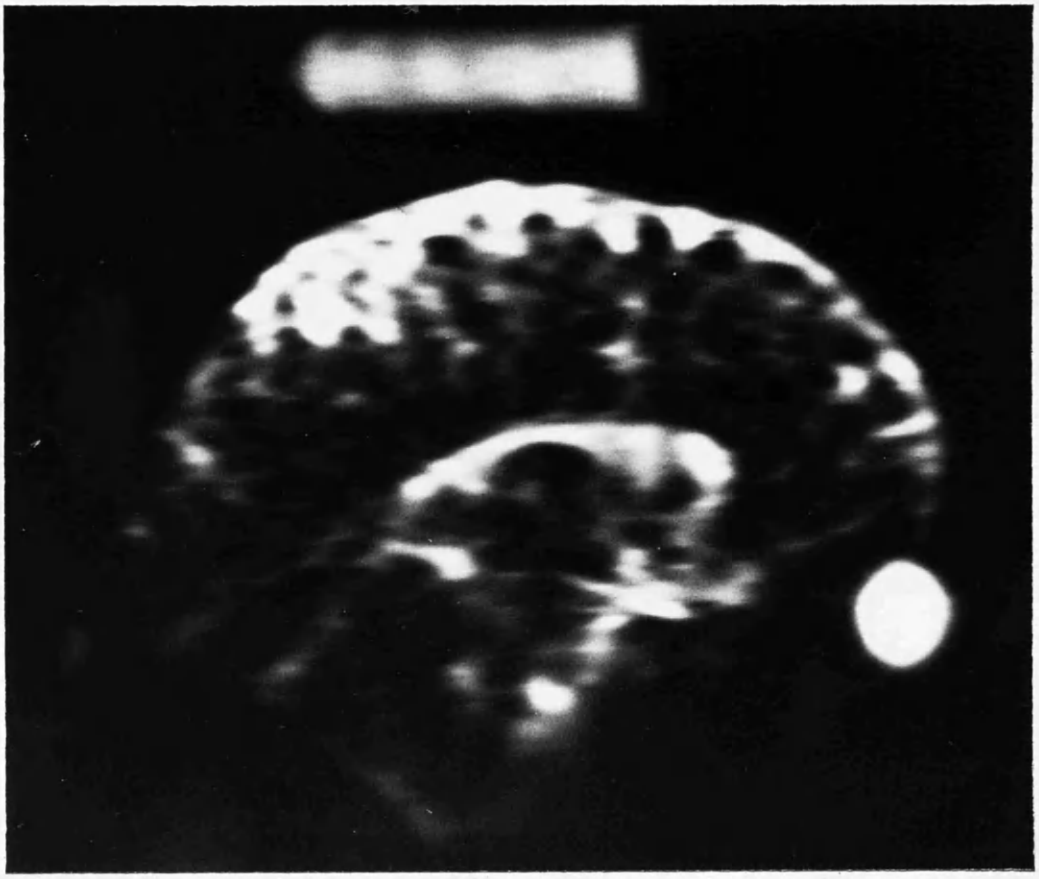

Figure 4a. Sagittal CSF volume image of the head - 240mm thickness.

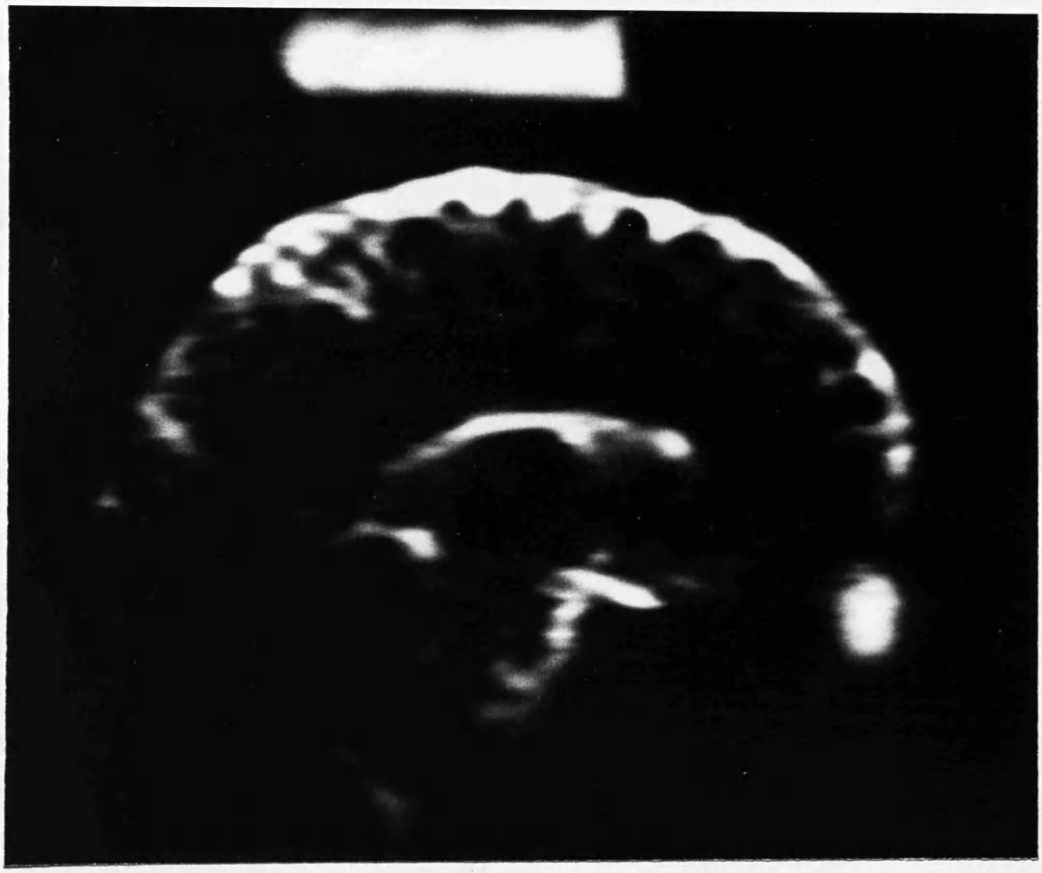

Figure 4b. Sagittal CSF volume image of the head - 72mm thickness.

4. CSF Volume Calculation.

Using the computer assisted electronic cursor, a region of interest(ROI) was drawn, on the corrected scans;

a) around the head(excluding eyes) on the 240mm. sagittal scan.

b) around the phial on the 240mm scan.

c) around the ventricles and post. fossa on the narrow slice.

d) around the phial from the narrow slice.

Measurements of the area and mean signal intensity of the region of interest were displayed automatically. Signal from background "noise" was subtracted from each image. As the volume of the "reference phial" was already known, it was then possible to calculate the volume of the region of interest:

$$\frac{\text{(Mean signal ROI - Mean background signal) X area of ROI. X30ml}}{\text{(Mean signal phial - Mean background signal) X area of phial}}$$

5. Preliminary Clinical Study.

Measurements of total cranial CSF volume and ventricular CSF volume were reported in 10 normal subjects, aged from 18-74 years to establish the approximate range of normality and to test the feasibility of performing these studies in healthy subjects and patients. The CSF volume measurements were repeated three times in one subject.

Total cranial CSF volume ranged from 54.8 - 202.7mls. Ventricular CSF volume ranged from 14.3 - 27mls. Reproducibility expressed as a standard deviation of these measurements was 3.2mls for total CSF volume and 0.5ml. for ventricular CSF volume. From this preliminary study of healthy subjects, it appeared that the CSF volumes correlated with age and sex and that there was a wide range of "normal", just as had been found in autopsy and CT studies.

Conclusion.

The phantom studies demonstrated that the MRI method is more accurate and reproducible than any previous method of measuring ventricular CSF volume, that it has the advantage of virtually eliminating signal from brain tissue, and that it is less subject to partial volume artifacts. However, possible sources of error still required careful evaluation and an assessment of the normal range of intracranial volume and physiological changes in CSF volume would also be necessary before its application to clinical situations could be studied.

CHAPTER TWO

DETERMINATION OF RELAXATION TIMES OF ANAEROBIC CSF AND POTENTIAL SOURCES OF ERROR.

2.1. Introduction

2.2. Relaxation times of CSF.
  a) The effect of contact with air.
  b) The effect of oxygen exclusion.
  c) Adaptation to use with NMR Spectrometer.

2.3. Relaxation times of reference phial contents.

2.4. Filling and placement of phial.

2.5. The effect of phial cooling.

2.6. The effect of CSF motion.

2.7. CSF contamination.

2.8. Summary.

2.1. INTRODUCTION.

The aim of this chapter is to assess factors that may contribute to inaccuracies in CSF volume measurements. The MRI measurement of cranial CSF volume is dependent on the signal from the reference (calibration) phial being very similar to the signal from CSF "in vivo". The signal obtained from both the CSF and reference phial is affected by the biochemical composition of these fluids and by physical factors such as the temperature of both fluids and motion of CSF. It is therefore vitally important to study firstly the relaxation parameters of CSF in as physiological a state as possible, secondly to identify which reference solution gives a signal closest to that of CSF, thirdly to improve the technique of CSF volume measurement if possible, and lastly to assess quantitatively how changes in temperature, motion and CSF contamination affect signal obtained from CSF.

The following observations are relevant:-

1).Chemical composition of CSF.

Cerebro-spinal fluid has a well defined chemical composition. The predominant constituents are sodium (145mmol/l) and chloride (125mmol/l). Very small concentrations of protein(0.1-0.4g/l) and dissolved oxygen (0.015mmol/l) are also present and iron is present in insignificant concentrations(0.8umol/l). The pH of CSF is approximately 7.3 +/- 0.1 and is poorly buffered because CSF has such a low protein content and is free from blood .

T_1 and T_2 relaxation times of CSF may be altered by changes in paramagnetic ions content, pH, temperature, CSF motion and by contamination of CSF either by cells or markedly elevated CSF protein levels. There are potential sources of error in CSF volume measurement, which can be quantified and possibly corrected:

2).The relaxation times of anaerobic CSF have not been studied.

The T_1 and T_2 relaxation time measurements of CSF performed by Condon et al.[40] were made on CSF that had not been withdrawn under anaerobic conditions. Changes in the CSF composition occur as it equilibrates with air if the CSF is not collected anaerobically and analysed quickly.

3).Better reference standards for CSF may be available.

If the relaxation times of the reference phial were different from that of anaerobically obtained CSF a consistent error in measurement would be introduced. This would affect the accuracy but would not affect reproducibility studies. The relaxation times of fluids other than water should be tested to assess their potential as a reference standard for CSF.

4).Errors in reference phial filling and placement may occur.

Despite careful technique inconsistent errors may arise from incomplete reference phial filling, variations in C_2 content, temperature and positioning of the reference phial and patient in the imager. These would influence intra and inter-individual reproducibility studies.

5).Phial cooling may affect signal intensity of the reference solution.

The temperature of the reference phial should be 37°C and maintained as near to this as possible or errors may be introduced as the T_1 and T_2 of the reference solution will decrease as the temperature falls. The effect of this on the signal intensity should be estimated.

6).CSF motion may affect the signal intensity of the image.

The effect of systolic vascular pulsations and movement of CSF due to respiratory motion are difficult to assess because of the complexity of intracranial CSF movement. Movement of CSF may cause a reduction in CSF signal in these sequences and this should be estimated.

7).CSF contamination may affect signal intensity of the image.

CSF does not normally contain blood or significantly elevated levels of cells or protein. This can occur however in certain conditions, most notably in subarachnoid haemorrhage and meningitis. If CSF volumes are measured in these cases there may be an error due to the effect of cells and protein on the relaxation times of CSF. The effect of subarachnoid blood on T_1, T_2 and CSF signal intensity change was estimated.

EXPERIMENTAL PROCEDURES.

In order to quantify the magnitude of these potential sources of errors the following experiments were performed:

2.2. DETERMINATION OF THE RELAXATION TIMES OF CSF.

Reported relaxation time measurements of body fluids vary considerably.[38,65,123,198] One fundamental cause for this, which has not yet been fully studied is the biochemical change that occur when a fluid is removed from its physiological milieu. Thus so far no account has been taken of the possibility that the results of "in vitro" measurements of T_1 and T_2 of CSF might be influenced by contact with air and hence differ from the true "in vivo" values.

It has been suggested that it may be possible to extrapolate from "in vitro" results to interpret data obtained from clinical imaging and for example to estimate or monitor protein or oxygen content of CSF "in vivo".[107] CSF with various concentrations of albumin artificially added has been used as a simple model of cerebral oedema[5,107] and extrapolation from such experiments to intracranial pathology need a basis in valid measurements of CSF relaxation times. Lastly, the signal intensity of CSF, in the CSF volume sequences, will be dependent on the relaxation times which in turn may be affected by the changes in the chemical composition of CSF. It is therefore important to determine the T_1 and T_2 of CSF as accurately as possible. The reported relaxation times of CSF "in vivo" and "in vitro" vary widely; T_1 ranging from 1000 - 5500msec. and T_2 from 166 - 2640msec..[38,65,123,198] The possible clinical diagnostic implications of these vast differences were reviewed by Condon et al..[40] Imager estimates become inaccurate at long repetition times due to field inhomogeneities and slight errors in the 180° pulses, while spectroscopic determination of CSF T_1 and T_2 values are inaccurate because the pH, pCO_2 and pO_2 of CSF alter when CSF comes in contact with air. A satisfactory technique for removing CSF and measuring relaxation times anaerobically has not yet been developed.

The biochemical changes occurring in CSF collected with and without contact with air were studied and a method was developed to provide a small enough sample of anaerobically obtained CSF that could be used to measure T_1 and T_2 relaxation times "in vitro" using a Bruker NMR spectroscope(Appendix B) (Figure 5). The Bruker (Minispec) NMR spectroscope (6MHz.) works at a similar frequency to the MR imager (6.4MHz.)

Figure 5. Nuclear Magnetic Resonance spectrometer (Bruker Minispec PC 20) (from left to right) Oscilloscope, Control Module, Magnet Module, water bath (Grant) and pump.

Experiment 2.2a. The effect of contact with air.

In order to study the changes in CSF composition due to contact with air CSF was removed anaerobically, analysed biochemically and then allowed to equilibrate with air and resampled at intervals.

Methods.

A patient who had lumbar myelography performed for a suspected herniated intervertebral disc had CSF removed allowing minimal contact between CSF and air. The lumbar puncture needle was inserted into the sub-arachnoid space and the stylette removed. A length of plastic tubing was then attached to the lumbar puncture needle and the distal end of the tubing was connected to a three way tap. CSF was then withdrawn, via the 3-way connector into a glass syringe. The air present in the "dead space" of the nozzle was expressed through the side limb of the 3-way tap. When there was no evidence of air in the glass syringe, 2 mls. of CSF were removed and the syringe nozzle was capped with a rubber bung. When collection of CSF was complete the time was designated "zero" minutes.

The CSF was analysed using a calibrated blood gas analyser (Corning Blood Gas Analyser). pH, pCO_2 and pO_2 were measured at 5.6 minutes. The remainder of the sample was placed in an MRI spectrometer sampling tube which was left open to equilibrate with air and further analyses were performed at 9.4, 20, 36, 51, 71, 104, 137, 174, and 247 minutes. The glass syringe was kept at 37°C in a water bath between analyses.

Results.

The results of CSF analysis are recorded in Table 1. and shown graphically in Figure 6a. On initial recording, CSF pH was 7.35 (pCO_2 40.7mmHg., and pO_2 82.3mmHg.). The most significant changes in pH, pCO_2 and pO_2 occurred within the first 30 minutes. By 104 minutes the pH had increased to greater than 7.7 (above which it was not possible to accurately measure) and the pCO_2 had decreased to 15 mmHg. and at 174 minutes pCO_2 was recorded as 0.8 mmHg. The pO_2 started at 82.3 mmHg. and closely followed the curve for pH, reaching a plateau at 171 minutes when the pO_2 reached 178 mmHg.

TIME (min)	pH	pCO2 (mmHg.)	pO2 (mmHg.)
5.6	7.35	40.7	82.3
9.4	7.38	37.0	86.0
20	7.50	26.4	107.9
36	7.59	19.2	126.6
51	7.59	20.1	126.5
71	7.63	16.4	132.0
104	7.71	15.0	149.0
137	7.74	5.9	168.9
174	unrecordable	0.8	178.5
247	unrecordable	0.4	173.4

Table 1. Changes in " Aerobic " CSF with time.

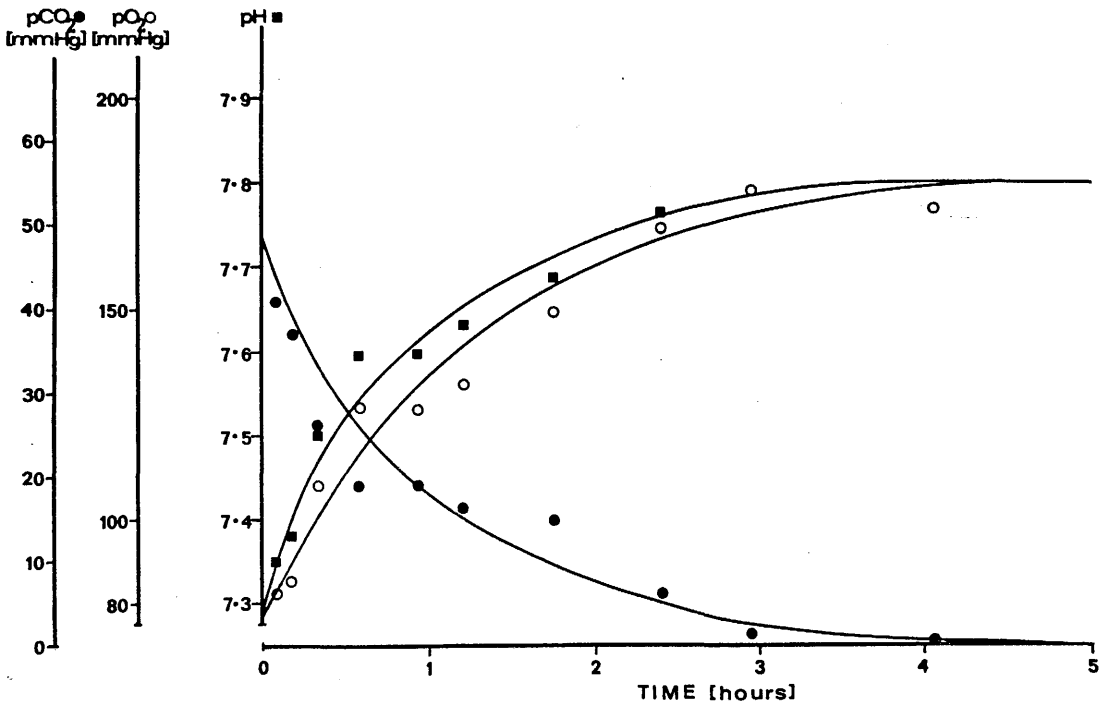

Figure 6a. Changes in pH, pO2 and pCO2 of CSF as it equilibrates with air.

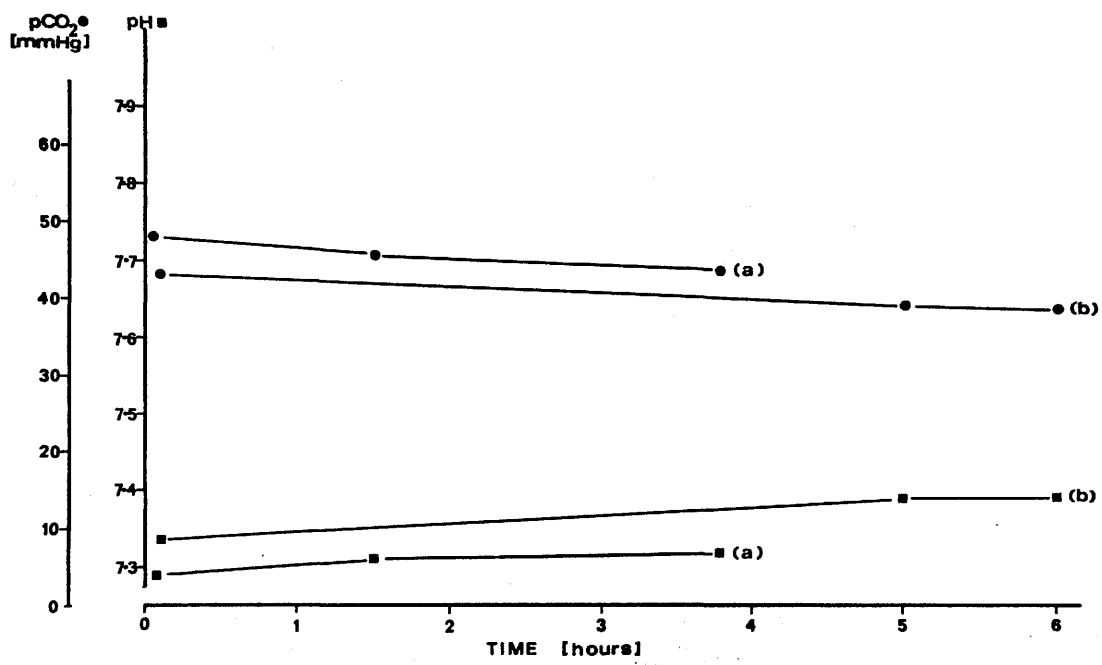

Figure 6b. Changes in pH and pCO2 of CSF with oxygen exclusion.

Conclusion.

The initial pH, pO_2 and pCO_2 are in close agreement with results of other authors who have measured "anaerobic" CSF.[20,28] After removal of CSF from the body, the O_2 quickly becomes equilibrated with air and CO_2 is released. This results in a increase in pH. These changes occur quickly within the first 30 minutes and are probably complete by 3 hours.

Relaxation times have not previously been measured on samples of freshly obtained anaerobic CSF and as repeated measurements of T_1 and T_2 by NMR spectrometry may take some hours, previous measurements of CSF T_1 and T_2 by other authors are not likely to accurately reflect the true relaxation times of CSF.

If CSF relaxation times are to be accurately measured a technique must be developed to enable anaerobic CSF to be collected and measured either using the MR imager or by the NMR spectrometer. To measure T_1 and T_2 of CSF accurately using the MR imager one has to be certain that white or grey matter is not included in the image slice to be analysed. Because of this thin slices (approx. 10 mm) are usually necessary. Relaxation times of CSF in thin slices are profoundly affected by motion as "excited" hydrogen ions will quickly move out of the slice and "unexcited" hydrogen ions will move in during each MR sampling time. Imager estimates will therefore produce highly significant underestimates of T_1 and T_2 due to the effect of CSF flow. A technique must therefore be developed whereby anaerobic CSF can be collected and the relaxation times measured by NMR spectrometry.

Experiment 2.2b. Anaerobically obtained CSF.

The efficacy of the method of collecting and sealing CSF under anaerobic conditions was studied by examining changes in pH, pCO_2, and pO_2 of CSF with time.

Methods.

CSF was removed from two patients undergoing myelography for lumbar disc disease as described in section 2.2a. In the first case (a) CSF pH., pCO_2 and pO_2 were measured at 3min., 90min. and finally sampled at 220min. In the second case (b) pH, pO_2 and pCO_2 were sampled at 4min., 5hrs. and at 6hrs. On each occasion the glass syringe was resealed by replacing the rubber bung

immediately after sampling the CSF. The syringes were kept at 37°C and CSF protein, glucose and cell counts were within the normal range in each patient.

Results.

The results of the biochemical analyses are recorded in table 2a When the CSF samples were capped the changes in pH, pCO_2, and pO_2 occurred much more slowly than when there was direct contact with air (Figure 6b). Initial pH was very similar to the starting pH in section 2.2a and only rose by 0.05 over 6 hour. The pCO_2 fell by only 5mmHg. and pO_2 increased by 5mmHg. over a similar period.

Conclusions.

In contrast to the abrupt changes in pH., pCO_2 and pO_2 in section 2.2a, the slight variation with time in these measurements when the sample was capped suggests that glass is an efficient medium for storing anaerobicaly obtained CSF and the rubber stopper was effective in minimising changes in pH., pCO_2 and pO_2.

Experiment 2.2c. Adaptation to use with a NMR Spectrometer.

To measure the relaxation times of CSF using the NMR spectroscope, a very small sealed sample of CSF is required. The sample to be tested must fit inside the spectroscope sample tube and only be in the sensitive region of the magnetic coil of the spectroscope ($7mm^3$). Oxygen must also be effectively excluded from this sample. Glass is suitable for use with the spectrometer because the small signal from glass is completely relaxed before the first pulse of the T_1 and T_2 sequences, thus it does not contribute to the signal from CSF.

Methods.

Phials were made from soda glass with an internal diameter of 5mm. and extenal diameter of 6.5mm. These phials were 10mm. in length and were sealed at one end (Figure 7). A plastic stopper provided an airtight seal. The signal from the stopper fully relaxed within 1msec. therefore did not contribute to the T_1 or T_2 of CSF. These small phials could be inserted into the 7mm diameter spectrometer sample tubes.

A 3mls. sample of CSF was removed at the time of cervical spinal

	TIME (min)	pH	pCO2 (mmHg.)	pO2 (mmHg.)
Sample 1.				
	3.1	7.29	48.2	48.6
	92	7.31	45.4	69.0
	224	7.32	43.8	91.2
Sample 2.				
	6.0	7.34	43.3	96.4
	300	7.39	39.3	101.7
	360	7.39	38.6	97.7

Table 2a. Changes in " Anaerobic " CSF with time.
Samples 1 & 2 - Capped glass syringes.

	TIME (min)	pH	pCO2 (mmHg.)	pO2 (mmHg.)
Phial B.	7.3	7.23	45.2	86.6
Phial C.	329	7.25	42.4	84.7

Table 2b. Changes in " Anaerobic " CSF with time.
Phials B & C - Capped spectrometer phials.

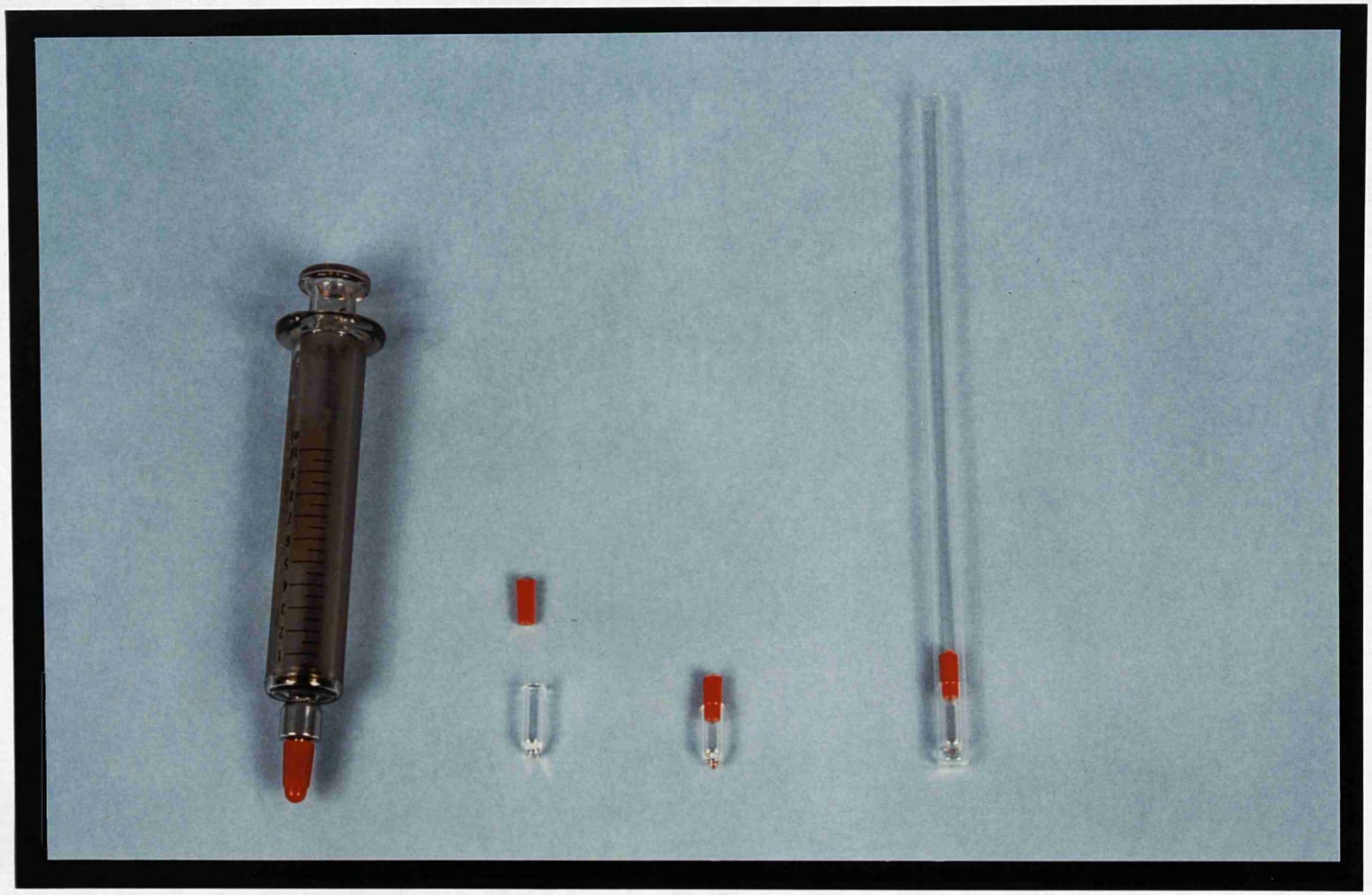

Figure 7. Sealed glass syringe and phials designed to fit NMR sample tubes.

puncture from a patient suspected of having a nerve root pressure due to a herniated cervical disc. CSF was collected in a glass syringe as outlined in section 2.2a and immediately transferred to 4 phials (A,B,C and D), 3 of which were sealed immediately with the plastic stoppers with the minimum contact with air and without inclusion of an air bubble.

Phial A was immediately placed in the Bruker spectroscope sample tube and T_1 and T_2 calculations were made. Phial B was analysed within 8 minutes of removal of CSF for pH., pCO_2 and pO_2. Phial C was analysed for pH., pCO_2 and pO_2 at 8hrs.. Phial D was left unsealed, and hence equilibrated with air, and T_1 and T_2 estimations performed after 6-8hrs. All estimations were performed at 37°C.

Results.

T_1 relaxation time was repeated on Phial A seven times and the mean T_1 was 4098msec.(+/-379msec.). T_2 was repeated nine times and mean T_2 was 3052msec.(+/-255msec.) . When analysed, CSF in phial B had a pH of 7.23, pO_2 of 86.6mmHg. and pCO_2 of 45.2mmHg. Phial C, opened after 8hrs., had a pH of 7.25, pO_2 of 84.7mmHg. and pCO_2 of 42.4mmHg.(Table 2b.) T_1 and T_2 estimation of CSF in Phial D were 3525msec.(+/-138.2msec.) and 2576msec. (+/-192msec.), respectively.

Discussion.

This method proved to be an effective way of collecting and storing CSF and allowed the relaxation times of true "anaerobic" CSF to be measured, as demonstrated by the very small changes in CSF pH and gases with time between Phial B and Phial C. The inital pH, pCO_2 and pO_2 levels in this study were in close agreement with the results of other authors who have measured biochemical parameters of "anaerobic" CSF.[20,28,79] If precautions were not taken to exclude oxygen, the poor buffering capacity of CSF resulted in the pO_2 and pCO_2 equilibrating with air and this led to an increase in CSF pH. The estimates for T_1 and T_2 of anaerobic CSF in this study were greater than those of CSF previously reported by ourselves[42], Go[82] and Castro[38], where CSF was not collected under anaerobic conditions. The discrepancy was most likely because the increase in dissolved O2 and the fall in pH, that result from CSF coming in contact with air, cause a decrease in T_1 and T_2 of

approximately 12%.

When "in vitro" relaxation times of body fluids are being measured, care must be taken to maintain similar biochemical characteristics to those occurring "in vivo". This is particularly important for CSF volume studies where the true relaxation times of anaerobic CSF must be known. The reference phial used in calculating CSF volume must give a similar signal to that of CSF "in vivo" or an error will be introduced.

2.3. RELAXATION TIMES OF REFERENCE PHIAL CONTENTS.

The T_1 and T_2 relaxation times of three substances were measured, using the Bruker NMR spectroscope, and compared with the relaxation times of anaerobically obtained CSF to determine if distilled water was indeed the best reference substance.

Method.

T_1 was determined by the IR sequence with an interval at least 5 times as long as the T_1 between the readings. The T_2 was measured using a Carr-Purcell-Meiboom-Gill(CPMG) pulse sequence (see Appendix A). Sterilised, particle free, samples were analysed at 18°C., 21°C., 25°C., 30°C., 34°C., 37°C. and 40°C. The sample being analysed was kept at the desired temperature (+/- 0.5°C.) by a waterbath. T_1 relaxation times were repeated at least 4 times and T_2 at least 6 times at each at each temperature interval.

Reference Substances:

(a) distilled water.
(b) 0.9% sodium chloride solution.
(c) deoxygenated,double distilled, de-ionised water.

Sample (c) was de-oxygenated by bubbling under nitrogen and de-ionised.

Results.

The mean and standard deviations of T_1 and T_2 values are recorded in Table 3. De-oxygenated water had the longest T_1 and T_2 relaxation times. However, when the T_1 and T_2 values were substituted in the equation for signal intensity (Table 3), using

$$S_{IRSE} = kp(e^{-TE/T2})\,[1 - 2e^{-TE/T1} + 2e^{-(TR-TE/2)/T1} - e^{-(TR/T1)}]$$

S gives the signal intensity from a unit of tissue with relaxation times T1 and T2, using an IRSE sequence.

k = constant ; p = proton density (1.0 for pure fluids)
TR = repetition time (msec) ; TE = echo time (msec)
TI = delay time(msec)

Therefore,

$$S_{IRCP300/400/5000} = e^{-400/T2}[1-2e^{300/T1}+2e^{-(4800)/T1}-e^{-(5000/T1)}]$$

Test Solution	Relaxation Times (msec +/- s.d.) T1	T2	Signal Intensity (relative to anaerobic CSF)
1. Anaerobic CSF (cervical)	4098(+/-379)	3052(+/-255)	1.00000
2. Aerobic CSF (cervical)	3525(+/-138)	2576(+/-193)	1.03525
3. Aerobic CSF (lumbar)*	3302(+/-170)	2269(+/-128)	1.03589
4. Tap water	3376(+/-527)	2766(+/-435)	1.06171
5. 0.9% Saline	3689(+/-607)	2746(+/-347)	1.02817
6. De-oxygenated water	3715(+/-374)	3382(+/-132)	1.05393

Table 3. Signal Intensity equation and signal intensities of solutions relative to anaerobic CSF.

* Condon et al. (Ref. 42).

"anaerobic" CSF as unity, sodium chloride solution (0.9%) produced the smallest error (2.8% - Table 3).

Conclusions.

The calculated signal intensity from 0.9% sodium chloride solution was very similar to that of anaerobic CSF and would be the best reference solution for CSF "in vivo" using the CSF volume imaging sequences. The concentrations of sodium and chloride (sodium 150mmol/l: chloride 150mmol/l) are closely similar to those found in the CSF "in vivo" (sodium 145 mmol/l: chloride 125 mmol/l).

2.4. FILLING AND PLACEMENT OF THE PHIAL.

In the method used by Condon[40], the reference phial was initially filled before imaging each patient and contained approximately 30mls of water. However it was often difficult to fill this completely and if only 29mls was introduced then CSF volume was overestimated by 3.3%. This inconsistent error due to inaccurate phial filling was eliminated by sealing a glass reference phial containing 0.9% sodium chloride. The reference phial was sealed under sterile conditions and accurately weighed. It contained 30.7mls of 0.9% sodium chloride solution.

Placement and strapping of the phial to the subjects head as suggested by Condon was time consuming and if the phial moved during the scan or if the phial was tilted then blurring occurred on the image and made accurate measurement of the phial mean signal intensity and area difficult and variable. If the patient were placed too far into the head coil the phial would appear high in the image where image non uniformity was greatest. To overcome this problem, the reference phial was placed in a polystyrene casing that not only insulated the phial but also fitted the internal diameter of the head coil and ensured that the phial was in a central position, in a more uniform area of the field. The phial and phial casing was placed in the head coil just prior to imaging therefore no strapping or phial positioning was neccessary.

2.5. THE EFFECT OF PHIAL COOLING.

Excited protons take longer to relax at high temperatures as they are more "mobile". If phial insulation is not satisfactory, the phial will cool and this will effect the T_1 and T_2 relaxation times of the

reference solution and may influence the signal intensity thus introducing a possible error into CSF volume calculations. In order to assess the effect of phial temperature on the relaxation times, the T_1 and T_2 of 0.9% sodium chloride solution were recorded at various temperatures using the Bruker Minispec. A waterbath kept the magnet temperature stable (+/- 1°C) at the desired temperature.

Results.

The T_1 and T_2 of saline reduced as the temperature fell, as was expected. The reductions in T_1 and T_2 were not linear. When the relaxation times were substituted in the equation for signal, the 2.8% error at 37°C increased steeply to 9.5% at 20°C (Figure 8). The polystyrene casing proved to be a very effective and after 1 hour in the magnet the temperature in the casing had only decreased by 1-2°C.

Conclusions.

In view of the temperature related changes in signal intensity it is important to start imaging patients with the phial at body temperature and to maintain this temperature throughout the duration of the scan. The reference phial is therefore kept in a waterbath at 37°C and placed in an insulated casing immediately before scanning. The polystyrene insulating casing keeps the saline at this temperature for the duration of the scans. (Two CSF volume sequences (IRCP 300/400/5000) take10.6 minutes.)

2.6. THE EFFECT OF CSF MOTION.

Natural movements in intracranial CSF, due to vascular and respiratory changes, are impossible to measure accurately or to correct for at present but may introduce errors in measurement of CSF volumes. The mean CSF volume change through the foramen magnum during cardiac systole is thought to be 1.67mls (s.d. 0.96).[8] Movement of CSF may cause loss of signal and an underestimate of CSF volume. The CSF volume sequence should theoretically not be seriously affected by motion, because the slice select thickness used is so wide (72-240mm.), the majority of "excited spins" within the stimulated slice will not be lost from the slice. The effect of motion and of changes in volume, on the CSF volume image were assessed "in vitro" using a phantom. The aim was to quantify

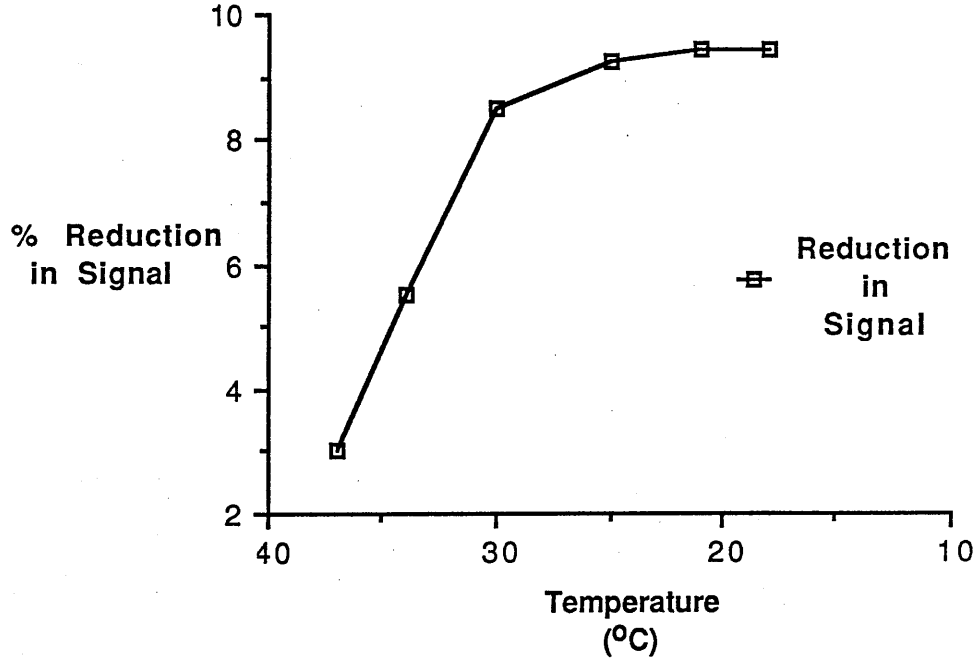

Figure 8. Estimated error in CSF signal caused by phial cooling.

the possible errors occurring due to movement of fluid as a result of physiological volume and pressure changes in a system that was designed to reflect a range of total CSF volumes.

Method.

Plastic bags containing known volumes(100-205mls) of saline were used as phantoms, to represent the total cranial CSF volume. A Swan Ganz right heart catheter with a balloon volume of 1.5mls was inserted into the phantom. A pressure monitor (Gould Statham P50) was connected to the distal infusion port. The apparatus and method of studying the effect of motion on CSF volume are shown in Figure 9. The pressure in the phantom was measured continuously and the volume and pressure was raised by injecting aliquots of saline , through the proximal port of the Swan Ganz catheter. Once the desired initial volume and pressure was reached movement was induced by inflating and deflating the balloon at the distal end of the Swan Ganz cather. The balloon contained 1.5mls of air and was inflated and deflated manually 30-60 times every minute to represent the CSF pulse pressure wave and to produce motion within the phantom. The volume of saline in the bag therefore remained constant but the overall volume of the bag changed due to inflation of the balloon with 1.5mls of air. The amount of motion depended on the rate of inflation and deflation of the balloon and the pressure change varied from 1-2mmHg. depending on the initial volume in the bag.

The CSF volume was calculated as in chapter 1.2c. by subtracting the background signal of the region of interest (ROI) from the mean signal of the ROI and multiplying the result by the area of the ROI. This was then divided by the product of the reference phial mean signal (minus the phial background signal) and the area of the reference phial. The result was then multiplied by the known volume of the reference phial (30.7mls).

Experiment 1.

Initially, 3 sets of volume sequences were performed, alternating between "resting" CSF volume and "pulsating" volume. Following the completion of these sequences, the contents of the bag were measured (107mls). The estimated volume of saline was then

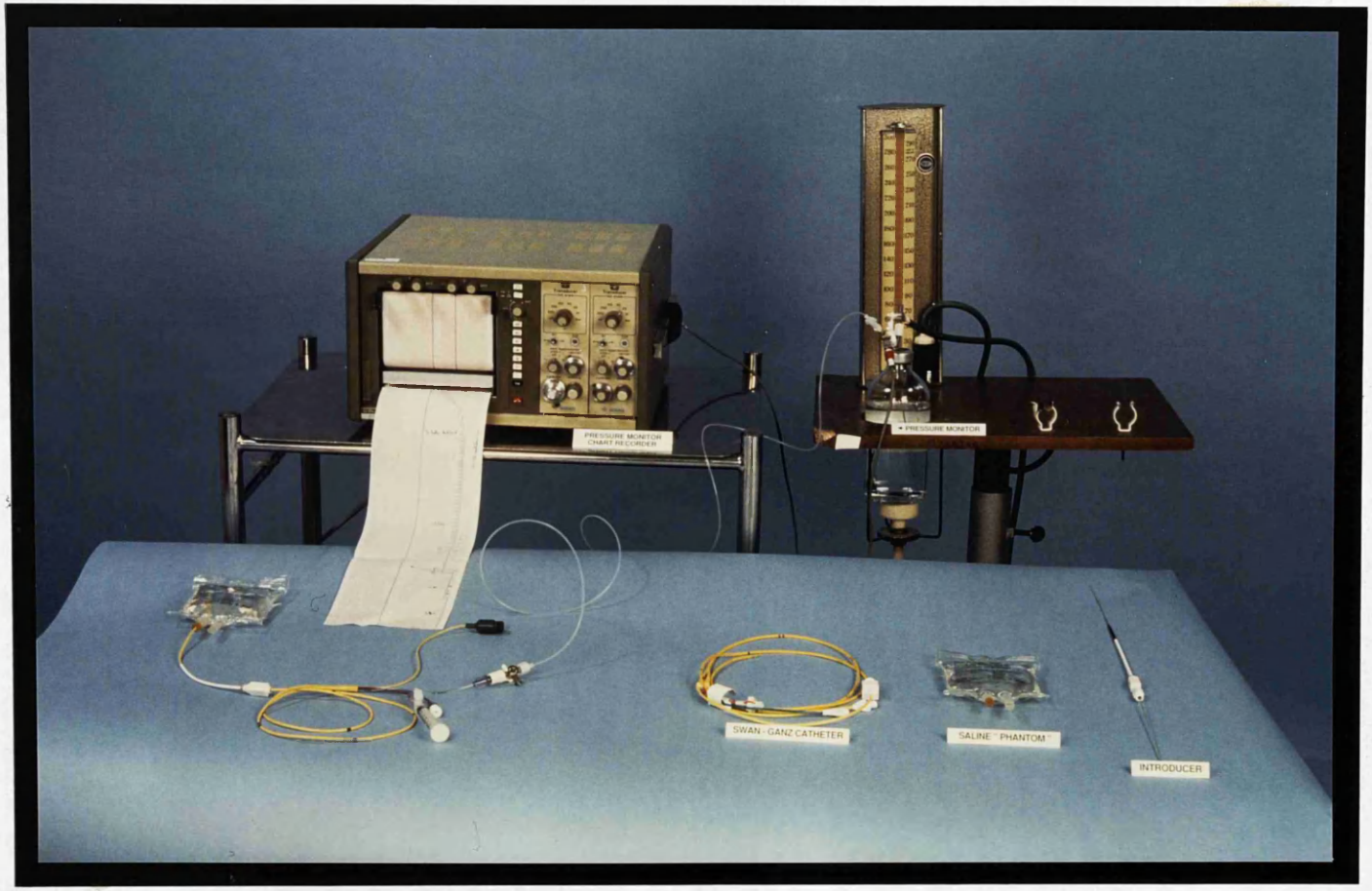

Figure 9. Apparatus and method of studying the effect of motion on the CSF volume sequences in a phantom.

. Pressure monitor chart recorder -Gould 2202.
. Pressure transducer - Gould Statham P50.
. Swan-Ganz catheter
. Saline phantom (0.9% Sodium Chloride).
. Introducer.

calculated as described above comparing the phantom signal at rest and "pulsating" with the reference phial containing 30.7mls of saline. The estimated results were compared with the true phantom volume to assess the accuracy and study the effect of motion.

Experiment 2.

CSF volume images were obtained from phantoms containing different volumes of saline (147mls, 185mls, 185mls, 185mls, 208mls.). The resting pressure within the bag of saline was directly related to the initial volume. This study was to establish if the effect of motion was directly related to the initial volume or to the change in pressure.

Results.

The effect of pulsatile motion (1.5mls/sec.) on the images was clearly seen when compared with the resting phantom images (Figure 10). The "background" of the phantom appeared "smeared" with signal in the horizontal plane (lateral to to phantom. i.e. in the phase encode direction). Interestingly, the phial background also very occassionally appeared "smeared" to some extent although this was not in contact with the phantom and therefore not likely to be directly affected by movement of the bag. The reason for this is not readily apparent. The signal from the moving phantom was greater than the signal from the resting phantom, but after subtraction of phantom background signal in each case, the signal was greater in the resting phantoms. Where there was signifcant "smearing" of the phial and the mean signal from the phial background was high, this resulted in an apparent and uncharacteristically large reduction in phantom saline volume.

Experiment 1.

Estimated "resting" phantom volume ranged from 112.5 - 114.7mls. (mean 113.9mls.) and "pulsatile" phantom volume ranged from 95.8-106.1mls. (mean 101.6mls.) when the true phantom volume was 107mls. i.e. movement resulted in a reduction of 5.0% from the true volume.

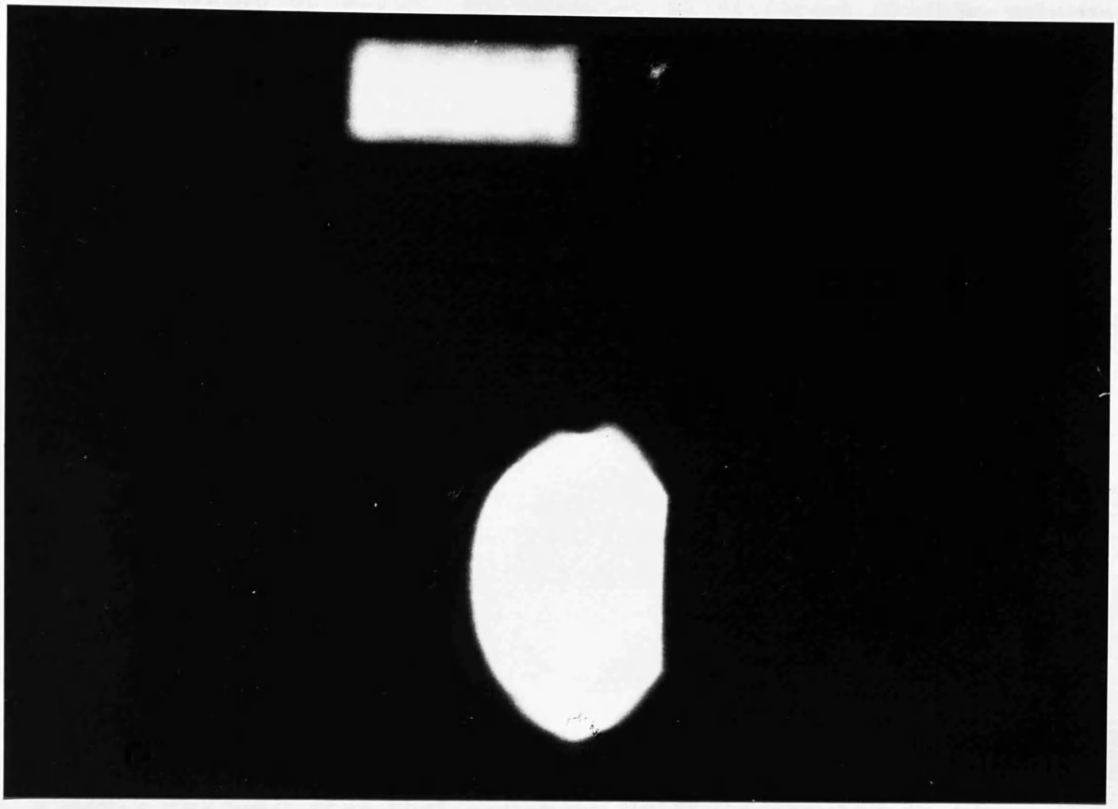

Figure 10a. Phantom at "rest".

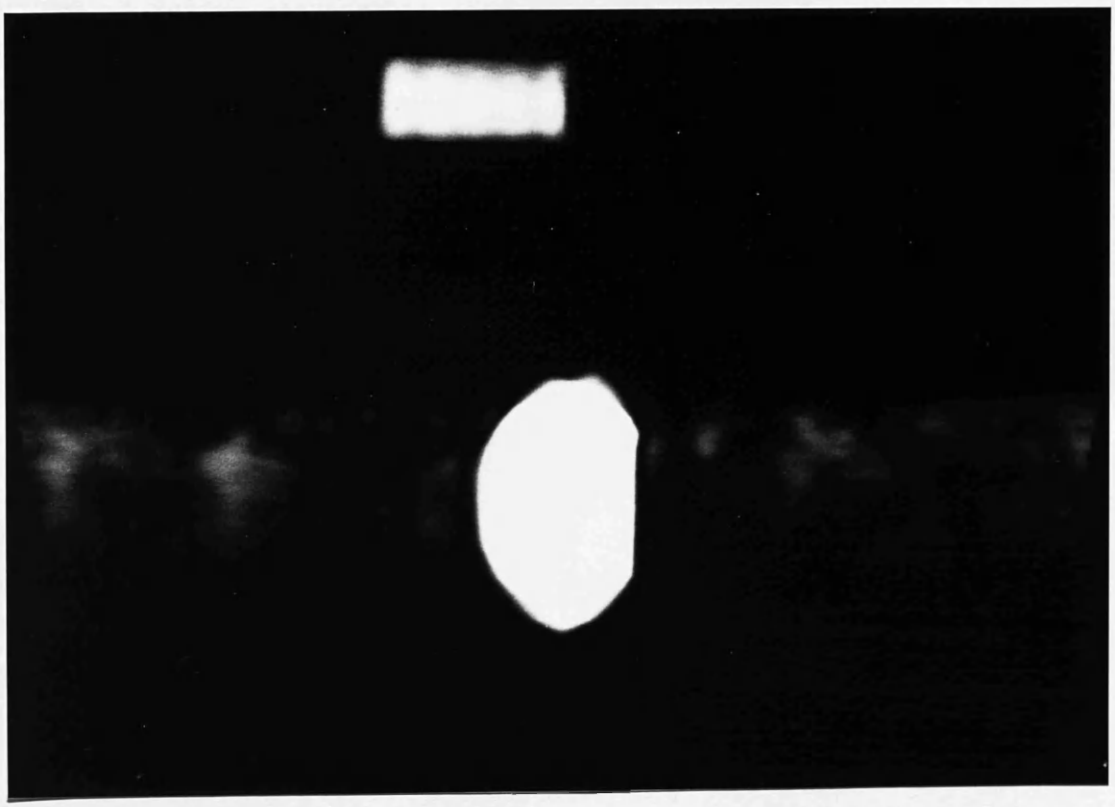

Figure 10b. The effect of pulsatile motion (1.5ml / sec.).

Experiment 2.

The effect of motion was repeated at different phantom volumes (147mls., 185mls. and 205mls.). Movement caused blurring and an apparent reduction in phantom volume in all cases. The error between the true and estimated volumes ranged from 4.3 - 21.8mls. (mean 9.8mls.). This represented a mean reduction in phantom signal of 5.25%. Blurring was not obviously related to the initial resting phantom volume or to the pressure change within the bag on inflation of the balloon but did appear to be greater when the balloon was inflated and deflated at rates greater than 50 times per minute.

Conclusions.

It is likely that movement of the CSF "in vivo" is variable at different sites and bulk flow is maximum at the foramen magnum. This phantom model probably overestimates the error due to CSF motion because blurring of the degree found in this study is not generally seen in subjects with comparable volumes of total cranial CSF. Nevertheless, it clearly demonstrates that movement of fluid results in increased signal in the phantom but more importantly increased background signal. This will introduce an error into the measurement depending on the amount of motion occuring at different sites in the CSF pathways. While this will lead to a small error in CSF volume measurement, it may actually be of use as an index of CSF motion.

A second important point is that occasionally "smearing" or "blurring" of the phial background can occur, despite it being uncoupled from the phantom. It is most likely that this is due to magnetic field instability or a problem with image reconstruction during the Fourrier transform and when this occurs it results in a greater error in measurement. Should this be obvious on "in vivo" CSF imaging, the sequences should be repeated.

These "CSF" motion studies are of practical importance when considering what corrections should be made for "background noise" or blurring. As can be seen from these "in vitro" studies, blurring or smearing can occur from motion. In clinical practice this can have two sources "extracranial" (eye movement and patient head movement) and "intracranial" (CSF motion). Motion of any kind will cause blurring in the horizontal plane. This takes the form of "generalised" smearing if

there is significant head movement and "discrete" smearing or "ghosts" of the eyes at one or two points on the image in the horizontal plane if there is continuous eye movement. When blurring is from an extracranial source such as the eyes, they should not be included in the background region of interest as signal to be subtracted unless one of the ghosts also lies inside the region of intracranial CSF. Eye movement artefact is not usually a significant problem and can be easily remedied. However, as demonstrated in the "in vitro" CSF motion experiment, excessive head movement or excessive CSF motion will lead to an increase in background signal. If this blurring is included in the background region of interest when the CSF volume is being calculated an underestimate of the true cranial CSF volume will occur. If blurring is due to head movement, the CSF volumes should be repeated after asking the subject to keep as still as possible or with the patient's head more firmly restrained. If blurring is excessive due to CSF motion, as is occasionally the case when the ventricles are dilated, one may see a discrete ghost of the ventricular system outside the head. If this is included in the background region of interest the resulting volume should be considered to be an underestimate of the true volume by approximately 5%.

2.7. CSF CONTAMINATION.

Ventricular CSF protein is approximately 0.2g/l which is less than 0.25% that of plasma. At this concentration protein content is unlikely to have a significant effect on T_1 or T_2.[107] If however, CSF is contaminated by blood following a sub-arachnoid haemorrhage, the T_1 and T_2 of the CSF is reduced significantly and inaccurate measurements of CSF volume are obtained. T_1 and T_2 relaxation times of CSF contaminated with blood have already been reported from this department.[93] At the approximate concentrations of bloodstained CSF found over the convexities of the brain, (0.04ml.blood/10ml.CSF) T_1 is 2940msec and T_2 is 1943msec and at concentrations of 0.08ml.blood/10ml.CSF, T_1 is 2583msec. and T_2 is 1633msec. Using the signal equation, CSF volume will be overestimated by 3.8% or 2.4% respectively. At a concentration of blood in CSF comparable to that found in the basal cisterns following subarachnoid haemorrhage (0.16ml/10mls), T_1 is 1590msec and T_2 is 928msec. If these figures are substituted in the equation for signal intensity, cranial CSF volume is

underestimated by 16.6% . Similar errors may occur in severe meningitis where the cell count could be several thousands per cubic mm. and protein may be greatly elevated.

2.8. SUMMARY.

The aim of this chapter was to investigate factors that might lead to inaccuracies in CSF volume measurement. These inaccuracies can be considered as being "consistent" errors that would affect the accuracy of measurement and "inconsistent" errors that would affect the reproducibility of CSF volume calculations in the same patient and also would lead to variability between patients. The main contributing factor in producing "consistent" errors was differences between the signal of CSF "in vivo" and the signal of the fluid in the reference phial used for calibration. Previously, water was used as a reference solution as this appeared to give the closest signal to that of CSF. However, the signal from water was compared with CSF that had been in contact with air. This study demonstrated that significant biochemical changes occurred when "anaerobic" CSF, as it was "in vivo", came in contact with air. The pH and pO_2 increased and pCO_2 decreased when CSF equilibrated with air. This equilibration occurred rapidly over the first 2 hours and was complete by 4 hours. The biochemical changes that took place altered T_1 and T_2 values of CSF and thus affected the signal intensity of CSF. The relaxation times of "anaerobic" CSF were measured using a NMR spectrometer that worked at a similar frequency as the MR imager and the results were compared with various possible reference solutions. Sodium chloride 0.9% gave the closest signal to that of "anaerobic" CSF and therefore this was used as the reference solution for clinical studies. A "consistent" error still existed and this was estimated at 2.8%. In effect this would result in an underestimation of CSF volume "in vivo" by 2.8%.

"Inconsistent" errors would result from incomplete reference phial filling and poor positioning of the phial on top of the head. Errors would also occur as a result of variable reduction in phial temperature during scanning, variable CSF motion and contamination or pathological changes in the biochemical constituents of CSF such as in subarachnoid haemorrhage and meningitis. To overcome these problems a sealed reference phial was made that contained a known volume of saline and this was placed in an insulated casing that fitted inside the standard

head coil. The insulated phial maintained its initial starting temperature (37°C) for the duration of the CSF volume scans. The time required to position the reference phial and the patient was also reduced. The reference phial was in the same position in the head coil each time and the phial signal was not affected by patient head movement during the scan. It was demonstrated that motion in a saline filled phantom increased the signal from both the phantom and from the phantom background. The net result was an underestimate of true phantom volume by approximately 5% when there was gross pulsatile movement. The degree of blurring and therefore the error between the true volume and the estimated volume was greatest when the frequency of pulsation was increased. The degree of blurring did not appear to be directly related to the initial phantom volume or the pressure within the phantom. The blurring of the background in this experiment was much greater than that found in practice in patients and therefore 5% is probably an overestimate of the error due to motion. In future it may be possible to use the degree of background blurring as an index of CSF motion. Lastly, the signal obtained from the CSF contaminated with blood was decreased and therefore the CSF volumes from patients with subarachnoid haemorrhage or severe meningitis will be underestimated. The degree of underestimation will depend on the quantity of blood in the CSF in subarachnoid haemorrhage or the quantity of protein or white blood cells in the CSF in meningitis. While the CSF volumes will not be accurate they may be helpful in following the resolution of these conditions without resorting to repeated lumbar puncture or if there is clinical doubt about either rebleeding or resolution of meningitis.

Factors that cause a variability of CSF measurement have been assessed and where possible the sources of error have been reduced. This should improve the accuracy and reproducibility in the clinical studies that follow.

CHAPTER THREE

NORMAL RANGE FOR CRANIAL CSF VOLUMES.

NORMAL RANGE OF CRANIAL CSF VOLUMES.

Introduction.

Human total intracranial CSF volume has hitherto been impossible to measure during life and methods used to estimate the volume of the cerebral ventricles have been highly invasive or subject to errors of 20 - 30%.[225] Attempts have been made to relate ventricular volume to specific neurological disorders such as cerebral atrophy, normal pressure hydrocephalus[114,184] and benign intracranial hypertension.[60,179] These studies however, have been hindered by the inaccuracies of CSF volume estimation or by using patients as controls. As a result there has been considerable controversy concerning changes in ventricular volume and brain volume with age in normal subjects.

The MRI pulse sequence (IRCP 300/400/5000) described by Condon[41] was used to assess the normal variations in total cranial volume, cortical sulcal volume, ventricular volume and posterior fossa volume, but the technique was modified as outlined in Chapter 2. . An index of the proportion of intraventricular CSF compared with the supratentorial subarachnoid CSF was also calculated (ventricular:cortical sulcal ratio (V:CS ratio)). These measurements were then correlated with age, sex difference and skull circumference and the reproducibility of this technique was assessed. The purpose was to determine if changes in CSF volume occurred and if so to quantify such changes.

Subjects and Methods.

Sixty four healthy volunteers were studied. There were 25 males and 39 females. Ages ranged from 18 to 64 years, and were similarly distributed in both sexes with a mean age of 38.4 years for males and 37.1 years for females. The subjects were alert and orientated and were not taking any medication, except for oral contraceptives in the case of some young women. All gave written informed consent. They did not complain of neurological symptoms at the time of MRI and did not have any previous history of neurological or cardiovascular disorder. Ophthalmoscopic examination of fundi was performed, and papilloedema was excluded in each subject. Age, sex, and skull circumference were recorded.

Cranial CSF volumes were measured using the IRCP 300/400/5000 pulse sequence with a standard head coil in a 0.15T resistive magnet (Picker International). A sealed reference phial containing 30.7mls of saline at body temperature was placed in an insulated moulded casing which fitted into the standard head coil. The two CSF volume scans were immediately repeated in 25 subjects after the reference phial was removed and replaced. The aim was to test the short term reproducibility of the technique. The CSF volume studies were repeated where the CSF image background appeared badly blurred due to movement.

After the image non uniformity correction was applied, a manually controlled computer generated region of interest was drawn around the ventricles on the thinner CSF volume image. This included the frontal horns, body, trigone and occipital and temporal horns. A second region of interest was placed around the posterior fossa to include the basal cisterns, prepontine cistern, aqueduct and fourth ventricle, but excluding the quadrigeminal cistern as this could overlap with the third ventricle. A third region of interest was drawn around the whole head, but excluding the eyes, on the 240mm. sagittal slice. The signal intensity of a region of interest was directly proportional to the volume in that region.

Results.

The individual results for total cranial, ventricular, posterior fossa and cortical sulcal CSF volumes and the ventricular:cortical sulcal ratios are given in Table 4. Total cranial CSF volume ranged from 57.1-286.5mls. The mean total CSF volume for males (146 mls.) was significantly greater than that of females (114.5 mls.) and for this reason the results in males and females were considered separately. Head circumference was significantly larger in males ($p<0.001$), but neither in males nor in females was there a significant relationship between an individual's head circumference and total cranial CSF volume. Linear regression analysis showed that total cranial CSF volume increased significantly with age in both sexes ($p<0.001$)(Figures 11 & 12). The slopes of the lines were not significantly different and the mean change per year in males was 1.9% and in females 1.6%.

Ventricular CSF volumes ranged from 6.8-30mls.(Figures 11 & 12).

No	Age (Yrs)	Sex	Skull Circ. (cms)	Total Cranial CSF Volume (mls)	Ventric CSF Volume (mls)	Post Fossa CSF Volume (mls)	C.Sulcal CSF Volume (mls)	V:CS Ratio
1.	18	F	57.0	83.2	10.2	10.3	62.7	0.16
2.	18	M	57.5	107.1	15.3	14.3	77.5	0.20
3.	19	M	58.0	90.2	11.6	11.5	67.1	0.17
4.	20	F	56.8	81.6	11.0	7.5	63.1	0.17
5.	22	M	57.0	130.7	22.9	12.6	95.2	0.24
6.	22	F	57.0	101.2	9.5	10.5	81.2	0.12
7.	23	F	53.5	79.3	14.0	9.0	56.3	0.25
8.	23	F	57.0	64.2	9.5	6.6	48.1	0.20
9.	23	M	57.2	123.0	11.6	10.5	100.9	0.11
10.	23	F	55.8	142.4	27.0	9.9	105.5	0.26
11.	24	F	55.0	114.4	16.8	10.6	87.0	0.19
12.	24	F	56.0	131.3	17.9	10.1	103.3	0.17
13.	25	F	55.6	123.1	12.3	12.0	98.8	0.12
14.	25	F	55.8	135.8	10.7	8.5	116.6	0.09
15.	25	F	54.5	57.1	6.8	5.3	45.0	0.15
16.	26	M	57.5	113.0	10.7	9.0	93.3	0.11
17.	26	F	56.0	101.6	8.1	4.8	88.7	0.09
18.	26	F	55.5	123.2	15.9	8.0	99.3	0.16
19.	27	F	54.0	81.7	9.3	8.3	64.1	0.15
20.	27	M	57.8	127.8	17.3	16.1	94.4	0.18
21.	28	F	55.0	99.1	12.7	9.1	77.3	0.16
22.	28	M	57.5	141.6	20.6	14.6	106.4	0.19
23.	28	F	56.5	122.9	11.1	11.2	100.6	0.11
24.	28	M	56.0	114.0	16.7	14.6	82.7	0.20
25.	29	F	55.0	105.0	13.1	12.3	79.6	0.16
26.	30	M	60.0	110.9	11.1	7.9	91.9	0.12
27.	30	F	56.0	77.5	7.7	7.8	62.0	0.12
28.	30	M	60.0	126.5	11.9	9.4	105.2	0.11
29.	32	F	56.7	95.0	7.4	9.1	78.5	0.09
30.	32	M	58.5	115.5	22.2	14.8	78.5	0.28
31.	33	F	55.9	208.8	27.0	11.5	170.3	0.16
32.	33	F	55.2	133.7	20.2	12.7	100.8	0.20

Table 4. Results of CSF volume studies in normal subjects.

No	Age (Yrs)	Sex	Skull Circ. (cms)	Total Cranial CSF Volume (mls)	Ventric CSF Volume (mls)	Post Fossa CSF Volume (mls)	C.Sulcal CSF Volume (mls)	V:CS Ratio
33.	33	F	53.0	95.9	30.0	5.9	60.0	0.50
34.	34	M	57.3	123.8	10.6	9.2	104.0	0.10
35.	35	M	58.5	156.6	16.8	13.1	126.7	0.13
36.	36	F	56.5	90.8	7.8	8.0	75.0	0.10
37.	37	M	59.1	166.9	13.9	21.8	131.2	0.11
38.	38	M	58.0	157.1	22.1	8.6	126.4	0.17
39.	38	M	56.7	128.2	11.9	9.1	107.2	0.11
40.	40	M	57.4	202.7	16.8	20.6	165.3	0.10
41.	41	F	54.0	102.5	9.2	8.9	84.4	0.11
42.	43	F	57.2	91.2	12.9	9.8	68.5	0.19
43.	45	F	58.5	91.1	16.4	11.0	63.7	0.26
44.	46	F	53.0	158.7	16.1	14.5	128.1	0.13
45.	47	M	58.2	147.5	10.8	12.8	123.9	0.09
46.	48	F	53.8	108.7	12.0	7.8	88.9	0.13
47.	48	F	54.6	160.8	25.4	18.2	117.2	0.22
48.	49	M	59.2	182.1	20.0	16.7	145.4	0.14
49.	50	F	56.0	134.6	13.4	13.8	107.4	0.12
50.	51	F	56.7	136.8	20.3	9.6	106.9	0.19
51.	52	F	56.5	164.6	19.4	13.5	131.7	0.15
52.	53	M	59.0	157.8	19.7	12.5	125.6	0.16
53.	55	F	53.5	141.1	22.0	9.6	109.8	0.20
54.	56	F	55.2	107.1	10.8	12.7	83.6	0.13
55.	57	F	55.5	116.5	11.3	13.2	92.0	0.12
56.	57	F	54.0	142.7	14.8	10.0	117.9	0.13
57.	60	F	53.0	127.6	9.7	10.0	107.9	0.09
58.	60	M	60.0	183.3	17.0	8.6	157.7	0.11
59.	60	M	57.6	194.3	23.4	25.6	145.3	0.16
60.	61	M	58.7	255.9	26.1	26.9	202.9	0.13
61.	61	M	59.7	148.0	12.3	13.5	122.2	0.10
62.	62	F	55.5	118.9	11.2	12.3	95.4	0.12
63.	63	F	56.0	286.5	16.3	13.7	256.5	0.06
64.	64	M	57.5	214.8	26.9	16.8	171.1	0.16

Table 4. Results of CSF volume studies in normal subjects (cont.).

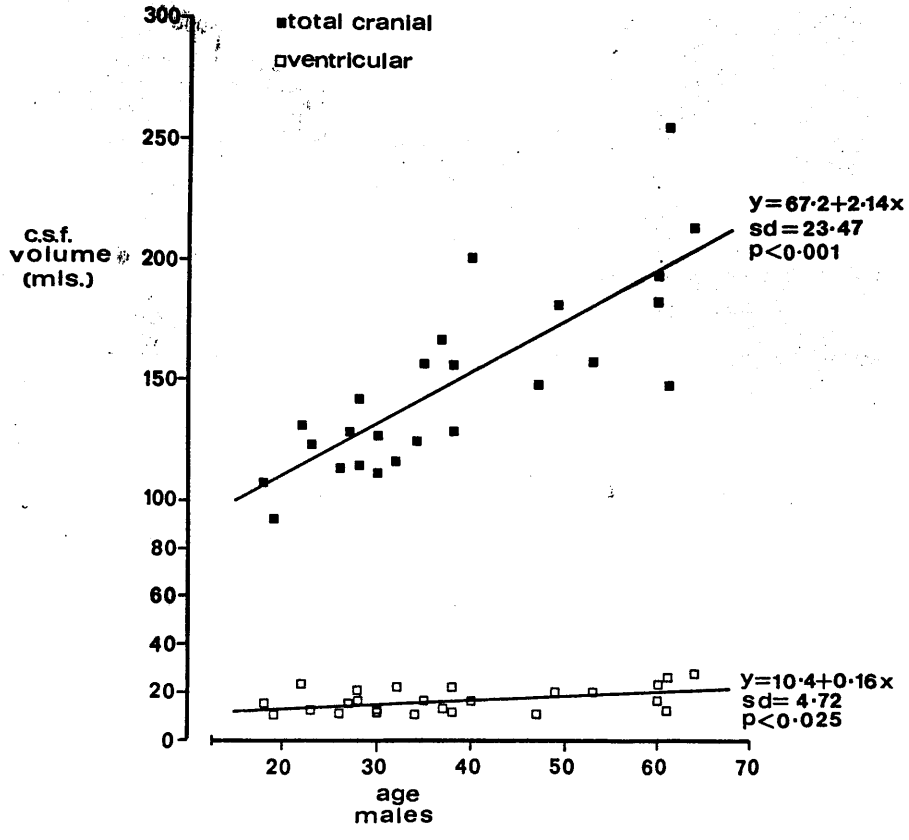

Figure 11. Relationship between age and total cranial and ventricular CSF volumes in males.

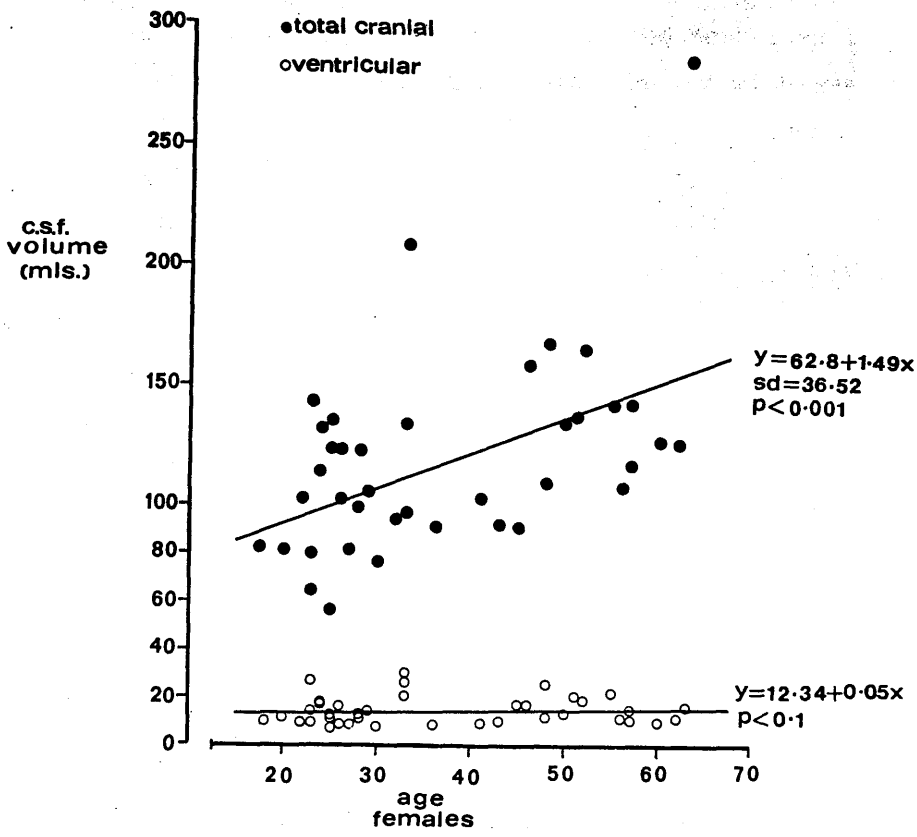

Figure 12. Relationship between age and total cranial and ventricular CSF volumes in females.

There was a positive correlation between total cranial CSF volume and ventricular volume in both males and females($p<0.001$). A difference in ventricular volume between males and females was not demonstrated. There was a small but significant increase in ventricular volume with age in males. In females between the ages of 18 to 64 there was no significant increase in ventricular CSF volume with age; this may have been influenced by large ventricular volumes in two young females who will be described later.

Cortical sulcal volume increased steeply with age in both males and females(figures 13 & 14). This increase also was more marked in males, but there was a wide range of cortical sulcal CSF volumes in both sexes, within each decade examined. The standard deviation about the mean values increased with each decade in both males and females.

Posterior fossa CSF volume ranged from 4.8-26.9mls and was greater in males than in females and increased significantly with age(Figures 13 & 14). This increase was greater in males than in females, with regression slopes of 0.16 and 0.09 respectively .

The ventricular:cortical sulcal ratio (V:CS ratio) was less than 0.30 in 63 of the 64 subjects (Figure 15) and decreased with age , with no-one over the age of 50 having a ratio greater than 0.2. However, in one 33 year old female ventricular CSF volume was 30 mls.(the highest recorded ventricular volume) and cerebral sulcal volume was only 60 mls., giving a ventricular:cortical sulcal ratio of 0.50 . The CSF volumes were repeated on this subject, and the second ratio was greater than 0.48. Further scans on this woman (SE80/2000 and IR400/500/40) demonstrated a stenosis of the aqueduct . She was asymptomatic, and there were no signs of raised intracranial pressure on neurological examination.

In two females (aged 33 and 64 years) total cranial CSF, cortical sulcal CSF and possibly also ventricular CSF volumes were larger than would be expected when compared with their peers. The 33 year old female had 2 years previously lost a significant amount of weight and had been amenorrhoeic since that time. After endocrine studies a possible diagnosis of anorexia nervosa or amenorrhoea secondary to cachexia was made. The 64 year old woman had been thyrotoxic 3 years previously and was subsequently treated with radioactive iodine and was now euthyroid. These were the only two

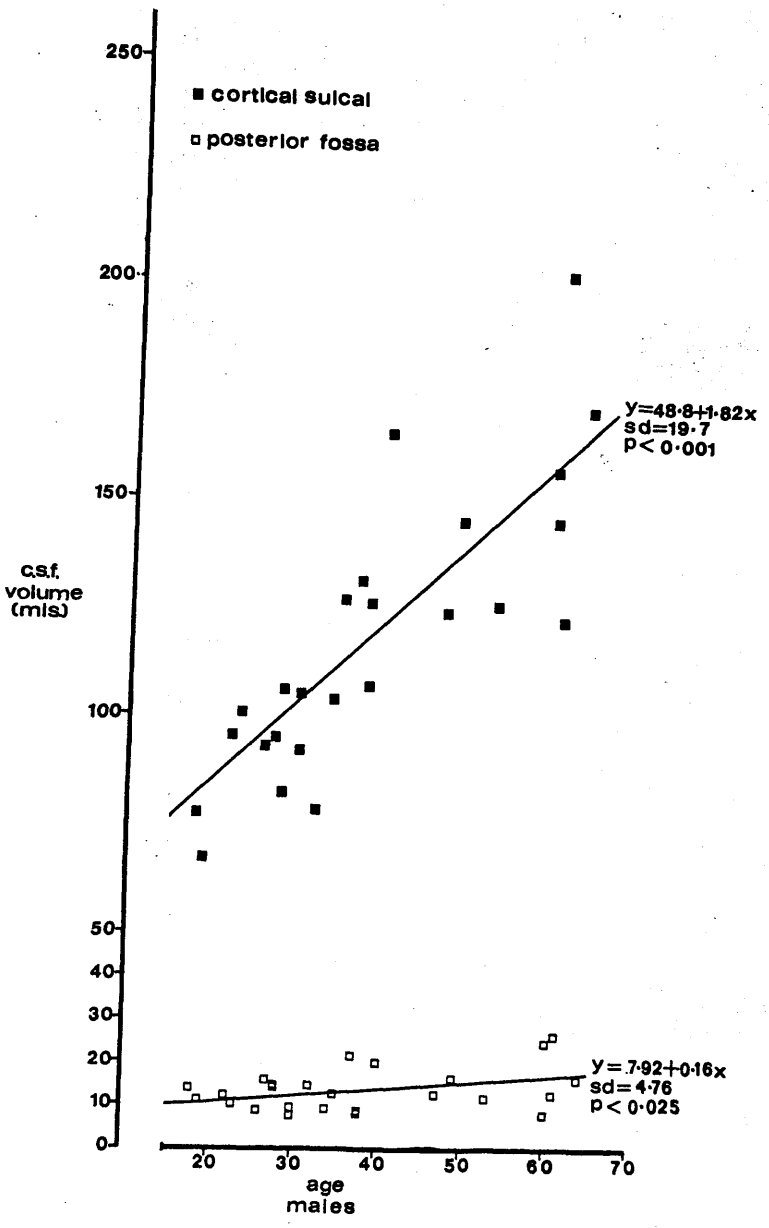

Figure 13. Relationship between age and cortical sulcal and posterior fossa CSF volumes in males.

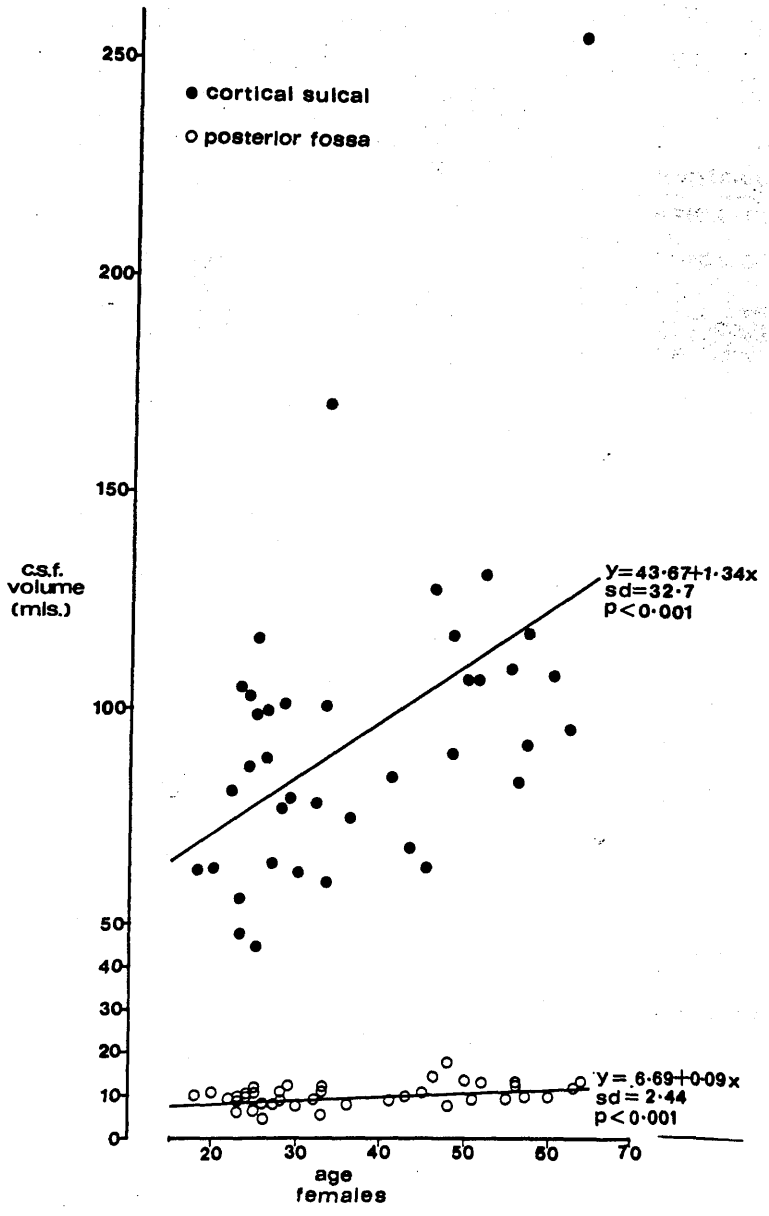

Figure 14. Relationship between age and cortical sulcal and posterior fossa CSF volumes in females.

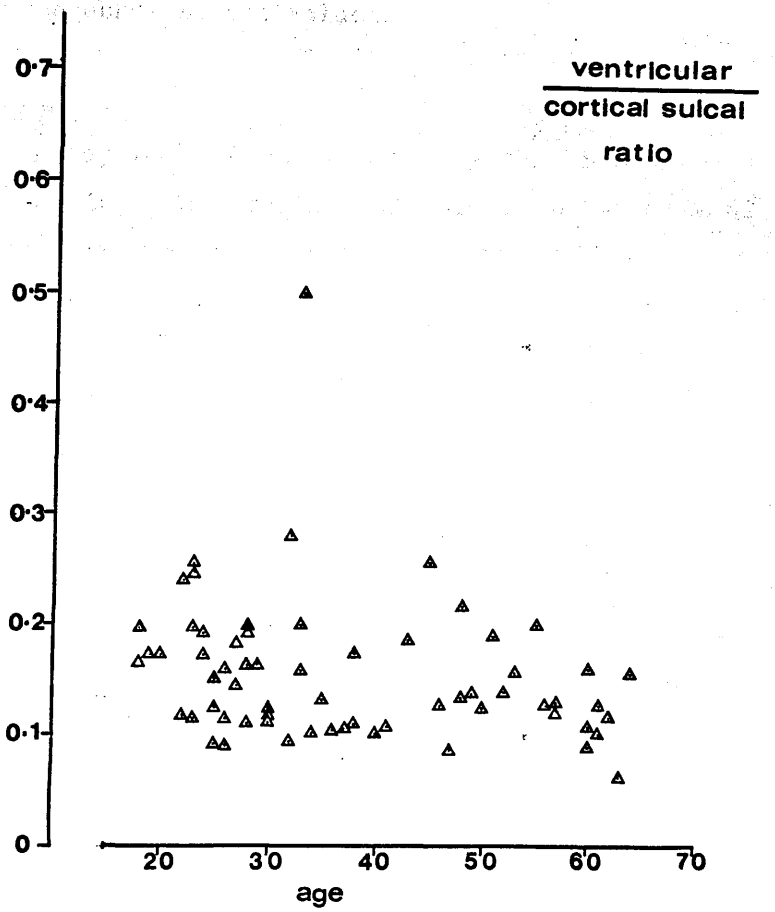

Figure 15. Relationship between age and ventricular:cortical sulcal ratios.

patients with a past history of endocrine disease.

The individual results of CSF volumes measurements of subjects who had CSF studies immediately repeated are given in Table 5. These demonstrated a median difference between the initial and immediately repeated result for ventricular and cortical sulcal CSF volumes of -0.2mls. [interquartile range-1.1,0.3.] and -2.8mls.[interquartile range -6.8,1.8], respectively. These represent a mean change of 1.3% in ventricular volume and of 2.5% in cerebral sulcal volume.

Discussion.

This study of CSF volumes using MRI demonstrates a significant difference in total cranial CSF volume between males and females and that there is a marked increase in total CSF volume and cortical sulcal CSF with increasing age from 18-64 years, in both sexes. The "in vivo" reproducibility studies support the "in vitro" phantom studies and confirm that its reproducibility is far superior to that of other techniques.

Total cranial and cortical sulcal CSF volumes do increase significantly with age, in males and females, and this undoubtedly reflects predominant loss of supra-tentorial cerebral structure in particular, cortical atrophy , rather than ventricular dilatation. These findings are supported by autopsy studies of Pearl,[167] Blinkoff,[21] and Burger,[35] who noted a gradual reduction in brain weight from the early 20's or 30's onwards but particularly over the age of sixty and by Brody,[31] who found a reduction in brain weight of 90-100grams by the age of seventy, due to generalised atrophy with predominant loss of the outer pyramidal layer of the cortex being affected earlier than other areas.

The range of values for ventricular CSF volume are similar to estimates of other authors who used post-mortem ventricular casts or CT methods.[135,227]

There is also a significant increase in posterior fossa volume with age which probably reflects cerebellar atrophy as this is known to occur with aging, even in asymptomatic individuals.[67,96,127]

Reports of previous radiological studies indicated an increase in the incidence of cortical atrophy and ventricular dilatation with increasing age,[66,80,122] but many of the subjects were patients and the assessments

No.	Age (Yrs.)	Sex	Total Cranial CSF Volume (mls.)		Ventricular CSF Volume (mls.)		Cortical Sulcal CSF Volume (mls.)	
			Scan 1.	Scan 2.	Scan 1.	Scan 2.	Scan 1.	Scan 2.
1.	20	F	85.7	78.7	11.5	11.8	66.7	59.4
2.	22	M	130.7	133.1	22.9	20.4	98.2	100.9
3.	23	F	64.2	68.3	9.5	9.7	48.1	52.0
4.	26	M	113.0	107.6	10.7	10.4	93.3	88.2
5.	26	F	123.2	120.3	15.9	14.8	99.3	97.5
6.	28	M	114.0	104.2	16.7	14.8	99.3	97.5
7.	29	F	105.0	103.8	13.1	12.6	79.6	78.9
8.	30	M	126.5	124.2	11.9	12.4	105.2	102.4
9.	33	F	208.8	206.8	27.0	26.6	170.3	168.7
10.	33	F	133.7	135.0	20.2	18.3	100.8	104.0
11.	33	F	95.9	90.5	30.0	27.5	60.0	57.1
12.	34	M	123.8	120.6	10.6	10.4	104.0	101.0
13.	37	M	166.9	163.7	13.9	13.9	131.2	128.0
14.	41	F	102.5	96.0	9.2	9.5	84.4	77.6
15.	46	F	158.7	148.6	16.1	14.0	128.1	120.1
16.	47	M	147.5	145.5	10.8	10.9	123.9	121.8
17.	48	F	108.7	112.8	12.0	12.3	88.9	92.7
18.	49	M	182.1	173.0	20.0	20.3	145.4	136.0
19.	50	F	134.6	136.2	13.4	13.2	107.4	109.2
20.	51	F	136.8	143.4	20.3	20.2	106.9	113.6
21.	57	F	116.5	113.4	11.3	10.6	92.0	91.5
22.	57	F	142.7	133.1	14.8	13.7	117.9	109.4
23.	60	M	194.3	192.7	23.4	23.3	145.3	143.8
24.	61	M	148.0	173.7	12.3	14.0	122.2	146.2
25.	62	F	118.9	110.6	11.2	10.4	95.4	87.9

Table 5. Results of CSF volume immediate reproducibility study.

were indirect and not quantitative. In contrast, Zatz et al.[227] suggest that ventricular and cortical sulcal volumes did not change significantly below the age of 60 and others[111,131] reported that 86% of normal elderly individuals showed little or no cortical atrophy.

There have been several published reports that ventricular dilatation or cortical atrophy occur in patients with anorexia nervosa. These findings have been considered to be due to increased catabolic activity.[54,68,126,164] The subject in the present study with possible anorexia nervosa supports the CT studies of decreased brain volume. This decrease in brain volume is apparently reversible when the condition is effectively treated.[229] As neurons cannot regenerate, presumably the reduction in brain volume is due to changes in supporting glial tissue, interstitial fluid volume changes or changes in intracerebral blood volume. The increased CSF volumes in the subject who was previously thyrotoxic may reflect irreversible changes from increased metabolic activity in the past, similar to the changes found in anorexia nervosa. Cerebral atrophy has been documented in other endocrine disorders such as Cushings disease,[160] although the cause of cerebral atrophy is not clearly understood.

MRI can be used to measure CSF volumes serially and evaluate temporal changes in cranial CSF volumes. The natural history of certain disorders where there are abnormalities of CSF volume can be followed and the effect of medical or surgical treatments can be objectively assessed. This may have diagnostic or management implications in conditions such as normal pressure hydrocephalus, obstructive hydrocephalus and benign intracranial hypertension and may be of research interest in dementia and endocrine disorders.

CHAPTER FOUR

PHYSIOLOGICAL CHANGES IN CSF VOLUME.

4.1. Introduction.

4.2. Diurnal changes.

4.3. The effect of the menstrual cycle.

4.4. The effect of hypercapnia and hypocapnia.

4.5. The effect of lumbar punture.

4.6. Summary.

PHYSIOLOGICAL CHANGES IN CSF VOLUME

4.1. INTRODUCTION.

Factors affecting CSF formation and absorption rates have been extensively studied, but the factors that influence cranial CSF volume remain obscure. Intracranial volume is essentially fixed and any change in total volume will result in an exponential increase in intracranial pressure.[158] It is assumed that dynamic or short term changes in cerebral blood volume are compensated by changes in the CSF volume but the magnitude of these changes has not been quantified. The purpose of this chapter is: firstly to assess whether there are any diurnal or menstrual changes in cranial CSF volume; secondly to quantify the volume of cranial CSF that changes in response to alterations in intracranial blood volume; and finally to measure the changes in cranial CSF volume that occur following lumbar puncture and establish whether there is a relationship between the volume of CSF lost and the presence of post-lumbar puncture headache.

4.2. DIURNAL CHANGES

Introduction.

Circadian rhythms exist for many human physiological functions. The most well known examples are the diurnal rhythm in ACTH and cortisol secretion, and the diurnal changes in temperature. The "biological clock" responsible for the regulation of such rhythms is thought to be located in the supra-chiasmatic nuclei of the hypothalamus. The hypothalamus also controls autonomic function and may influence secretion of CSF either directly or by secretion of corticosteroids and vasopressin both of which are known to reduce CSF secretion.[59,216] Alternatively, cranial CSF volume may be indirectly affected by changes in intracranial cerebral blood volume.

In order to establish if the time of day that subjects were imaged had any significant effect on cranial CSF volume, CSF volume sequences were performed in the morning and repeated in the late afternoon/early evening.

Subjects and Methods.

CSF volume sequences were performed on 18 normal volunteers at approximately 9.00-10.00am and again between 4.00-6.00pm the same day. There were 9 males and 9 females. Ages ranged from 20-49 years with a mean age of 32.6 years(SD 8.2) for males and 31.4 years(SD 9.1) for females.

The 240mm and "thin" CSF volume sequences were obtained as described previously using the sealed reference phial containing 30.7 mls. of 0.9% sodium chloride solution at body temperature. Total cranial, ventricular, posterior fossa and cortical sulcal CSF volumes were calculated after the images were corrected for image signal non uniformity.(See Chapter 1).

Results.

The individual results for total cranial, ventricular, posterior fossa and cortical sulcal CSF volumes are given in Table 6. There was no significant difference between males and females for any of the morning cranial CSF volume measurements(Mann-Whitney test:

Subj	Age (yrs)	Sex	Total CSF (mls)	Ventric CSF (mls)	Post Fossa CSF (mls)	C.Sulcal CSF (mls)	Total CSF (mls)	Ventric CSF (mls)	Post Fossa CSF (mls)	C.Sulcal CSF (mls)
			I----------a.m.----------I				I----------p.m.----------I			
1.	20	m	132.8	11.4	13.2	108.2	143.1	12.0	16.4	114.7
2.	22	f	151.0	13.6	22.4	115.0	141.7	11.2	14.9	115.6
3.	23	f	161.1	5.3	18.5	137.3	154.0	5.5	16.3	132.2
4.	26	f	92.3	16.6	8.5	67.2	108.5	15.5	9.6	83.4
5.	27	m	167.1	11.6	12.4	143.1	153.7	9.8	10.6	133.3
6.	29	f	118.1	5.5	10.5	102.1	122.4	5.6	10.1	106.7
7.	29	f	180.6	10.9	14.3	155.4	170.4	11.0	15.3	148.1
8.	29	m	163.5	15.9	18.9	128.7	185.6	15.7	18.6	151.3
9.	29	m	184.3	17.2	18.1	149.0	181.7	16.9	16.3	148.5
10.	30	f	141.8	12.1	11.5	118.2	127.9	9.7	10.0	108.2
11.	30	m	146.1	9.8	9.6	126.7	125.6	10.4	9.7	105.5
12.	31	f	173.3	9.6	17.1	146.6	140.9	7.4	13.3	120.2
13.	35	m	153.4	11.9	11.2	130.3	142.4	7.7	14.7	120.0
14.	36	m	117.5	9.3	12.5	95.7	114.3	8.4	9.3	96.6
15.	38	m	246.8	26.0	20.1	200.7	210.4	21.2	18.8	170.4
16.	45	f	156.0	16.5	25.0	114.5	143.6	15.9	19.8	107.9
17.	48	f	144.6	12.2	13.1	119.3	140.4	13.5	12.2	114.7
18.	49	m	243.2	24.2	27.3	190.7	246.6	25.6	27.6	193.3.
Mean	**32**		**159.6**	**13.4**	**15.8**	**130.5**	**153.0**	**12.4**	**14.7**	**126.0**

Table 6. Results of a.m. and p.m. CSF volume measurements.

Total vol p=0.29, Ventric. vol p=0.36, Post Fossa vol p=0.93, C.Sulcal vol p=0.25). There was a decrease in total cranial CSF volume between the a.m. and the p.m. measurements in 13 of the 18 subjects. This just failed to reach significance at the 5% level (applying Sign test on differences would require 14 or more for $p<0.05$.). Ventricular and cortical sulcal volumes were less in the afternoon in 11 subjects and posterior fossa volumes were less in 12 subjects when compared with the early morning values. The median reduction in total cranial CSF volume from morning to afternoon was 8.2mls (inter-quartile range[-13.4,3.4]) and for cortical sulcal volume was 4.85mls (interquartile range[-10.0,2.6]). Although, a significant change ($p<0.05$) could not be identified using either a sign test on the differences between morning and afternoon volumes (two-sided t test, significance $p=0.025$) or a paired t test, the results do favour a generalised decrease in CSF volume from morning to late afternoon.

Discussion.

It has been estimated that CSF is produced by the choroid plexus at a rate of approximately 20mls/hour, therefore about 160mls of CSF would have been produced between the a.m. and p.m. scans. CSF absorption is dependent on the intracranial pressure. The mean CSF pressure is essentially a reflection of the central venous pressure and thus will vary depending on posture and on respiratory factors such as sneezing and coughing. The mean intracranial pressure and thus the cranial CSF volume may vary significantly over an 8 hour period and CSF volume changes of the magnitude found in this study are possible and do not necessarily reflect errors in measurement.

There was a trend for CSF volume to decrease in the evening although this did not reach a 5% level of significance. What other factors could influence the CSF volume over the day? Plasma ACTH and cortisol levels reduce CSF secretion and increase CSF absorption.[119] Levels of these hormones are higher in the morning, hence one might therefore expect lower CSF volumes in the morning, the opposite of what has been found in this study. There is also a circadian rhythm of temperature regulation, with a regular fluctuation of 0.5-0.7°C., with lower temperatures occurring in the morning. This might be expected to lead to an underestimate of the cranial CSF volume in the morning; again this

could not account for the changes encountered in this study. Could the tendency for cranial CSF volume to become less in the evening reflect gravitational redistribution of CSF as a result of length of time spent upright? This is unlikely since the CSF volume sequences are performed in recumbency and redistribution should occur quickly over the space of a few seconds. However, absorption of CSF is also a function of the relative pressure difference between the sagittal sinus and the subarachnoid space. Upright posture results in a decrease in resistance to outflow of CSF, hence more CSF is absorbed and intracranial pressure falls. All the subjects in this study were ambulant and presumably upright between the first and second scans. It is possible that this may account for the tendency for total cranial CSF volume to decrease over the space of the day. To examine this theory in more depth it would be neccessary to repeat the CSF volume measurements in a bed bound group of subjects. Finally, the findings may reflect the experimental error of repeated measurements separated by several hours, the possible causes of which have been studied in detail in chapter 2.

In view of the possible decrease in CSF volume after several hours in the upright position it would seem advisable that, if CSF volume studies are to be repeated on consecutive days or even after prolonged periods, the scans should be repeated if possible at the same time each day.

4.3. THE EFFECT OF THE MENSTRUAL CYCLE

Introduction.

Among the changes occuring before menstruation, are alterations in the electrical activity of the brain. These include an increase in unstable electrical rhythms in both epileptic and non-epileptic females[133] and an increase in seizure frequency at this time.[132] It has been postulated that such cerebral changes are due to premenstrual hormonal imbalance[51,140] or cerebral oedema, occurring as part of premenstrual fluid retention,[7,153] but evidence to indicate the occurrence of brain swelling is lacking. Changes in CSF volume provide an indirect index of alterations in brain volume and therefore this technique was used to determine if there were changes in intracranial CSF volume in relation to the menstrual cycle. The CSF volume findings in women with a normal menstrual cycle, mid-cycle and premenstrually, were compared to those in post-menopausal women, and in males, both groups re-imaged after an interval of 2 weeks.

Subjects and Methods.

Thirty females, aged from 18-75 yrs. and 10 males aged from 19-61 yrs. were studied. Ten of the females had a normal menstrual cycle and were not taking oral contraceptives (mean age 29.8 yrs.), 10 had a normal menstrual cycle and were taking combined low oestrogen dosage oral contraceptive (mean age 26.2 yrs.) and 10 women were postmenopausal (mean age 55.3 yrs.). The males were aged from 19-61 with a mean age of 37.4yrs. Other than the 10 women taking oral contraceptives, subjects were not taking oral medication. Females with a regular menstrual cycle were imaged on day 14 (+/- 1 day) and within the 48 hours prior to menstruation. Post-menopausal females and males had M.R.I. studies repeated after 2 weeks. Repeat scans were performed at the same time of day as the first examination.

All subjects were alert and orientated and did not have neurological or cardiovascular past medical history of note. All were asymptomatic at the time of MRI and examination of the optic fundi did not reveal any papilloedema.

A coronal pilot scan (SE40/200) was performed to ensure that the phial was placed centrally and to measure the diameter of the ventricular system. Two single slice sagittal CSF volume scans (IRCP 300/400/5000) of the brain were then acquired. The first had a slice thickness that included all CSF spaces in the head (slice select 240mm.). The second slice enclosed the subjects' lateral ventricles (generally < 80mm.).

After performing an image non uniformity correction for the phial and the images, computer assisted regions of interest were then drawn around the head and phial on the 240mm. image and around the ventricles, posterior fossa and phial on the thinner image, as in the study on normal volunteers (Chapter 3).

Results.

Total cranial CSF volume in women with normal menstrual cycle ranged from 57.1 mls to 150.9 mls.(mean 107mls.) (Table 7a). Post-menopausal women and males had total cranial CSF volumes ranging from 81.3-147.3 mls(mean 120.3 mls.) and 90.2-181.4mls(mean 134.9mls.), respectively (Table 7b). The total cranial CSF volume increased from mid-cycle to premenstrually in all but one subject (Figure 16). The changes in total cranial CSF volume from mid-cycle to premenstrually were not influenced by the order of the scans (i.e. mid-cycle then premenstrual or premenstrual then mid-cycle). The mean increase premenstrually was by 11.5 mls.(s.d. 10.2)(Paired t test: $p < 0.0001$). In women taking the oral contraceptive pill the change in CSF volume (9.6mls [s.d. 10.4]) was less than that of women not taking oral contraceptives (13.4mls [s.d. 10.1]), but the difference was not significant. Ventricular CSF volume increased premenstrually to an extent similar to the increase in total CSF volume (ventricular CSF volume:- mean 13.4%, total CSF volume:- mean 11.3%.) Total cranial CSF volumes did not change significantly in post-menopausal females or males when measured two weeks apart; The mean change was +5.5 mls. (s.d. 22.9 mls.) and -2.2 mls. (s.d. 9.35 mls.) for post-menopausal females and males, respectively (Paired t test).

	Females : Not Taking OCP					Females : Taking OCP					
Subj	Age (Yrs)	Total CSF (mls)	Ventric CSF (mls)	Total CSF (mls)	Ventric CSF (mls)	Subj	Age (Yrs)	Total CSF (mls)	Ventric CSF (mls)	Total CSF (mls)	Ventric CSF (mls)
		I--Mid-cycle---I		I-Pre-menstrual-I				I--Mid-Cycle--I		I-Pre-Menstrual-I	
1.	18	83.2	10.2	101.1	13.4	1.	22	97.6	6.7	101.2	9.5
2.	20	85.7	11.5	101.7	14.5	2.	23	73.4	11.2	79.3	14.0
3.	24	98.3	14.0	131.3	17.9	3.	23	105.2	13.9	115.6	13.2
4.	26	123.2	15.9	126.3	13.2	4.	24	130.1	18.0	130.5	15.1
5.	26	91.8	16.3	95.9	16.8	5.	25	60.8	7.2	57.1	6.8
6.	28	97.8	10.6	122.9	11.1	6.	25	133.2	10.4	135.8	10.7
7.	33	95.9	30.0	104.0	33.9	7.	26	101.6	8.1	110.4	10.9
8.	36	81.6	4.0	90.8	7.8	8.	29	105.0	13.1	136.1	17.5
9.	41	102.5	9.2	117.8	9.7	9.	32	95.0	7.4	113.0	9.3
10.	46	148.6	14.0	150.9	13.5	10.	33	115.4	13.8	133.7	20.2
Mean	**29.8**	**100.9**	**13.6**	**114.3**	**15.2**	**Mean**	**26.2**	**101.7**	**11.0**	**111.3**	**12.7**

Table 7a. Results of Midcycle and Pre-menstrual CSF volume measurements.

	Post-Menopausal Females					Males					
Subj	Age (yrs)	Total CSF (mls)	Ventric CSF (mls)	Total CSF (mls)	Ventric CSF (mls)	Subj	Age (yrs)	Total CSF (mls)	Ventric CSF (mls)	Total CSF (mls)	Ventric CSF (mls)
		I-----Initial-----I		I----Repeat----I				I----Initial------I		I----Repeat-----I	
1.	48	108.7	12.0	102.4	10.5	1.	19	91.2	10.4	90.2	11.9
2.	50	97.8	9.7	147.1	11.0	2.	23	123.0	11.6	107.6	10.9
3.	51	135.8	8.0	104.9	6.9	3.	26	107.6	10.4	111.6	11.9
4.	51	136.8	20.3	144.6	21.2	4.	28	114.0	16.7	113.5	17.1
5.	53	144.2	11.9	170.5	104.9	5.	30	126.5	11.9	122.3	11.5
6.	55	117.2	21.3	141.4	22.0	6.	38	124.5	9.7	128.2	11.9
7.	56	107.1	10.8	95.1	9.8	7.	47	147.5	10.8	151.4	10.2
8.	57	116.5	11.3	114.1	11.5	8.	49	173.0	20.3	181.4	20.5
9.	57	142.7	14.8	136.7	14.5	9.	53	179.4	21.7	157.8	19.7
10.	57	135.7	17.7	135.0	16.7	10.	61	173.7	14.0	173.9	16.9
Mean	**55.3**	**124.3**	**13.8**	**129.2**	**13.3**	**Mean**	**37.4**	**136.0**	**13.8**	**133.8**	**14.3**

Table 7b. Results of initial and 2 week repeat CSF volume measurements in post-menopausal females and males.

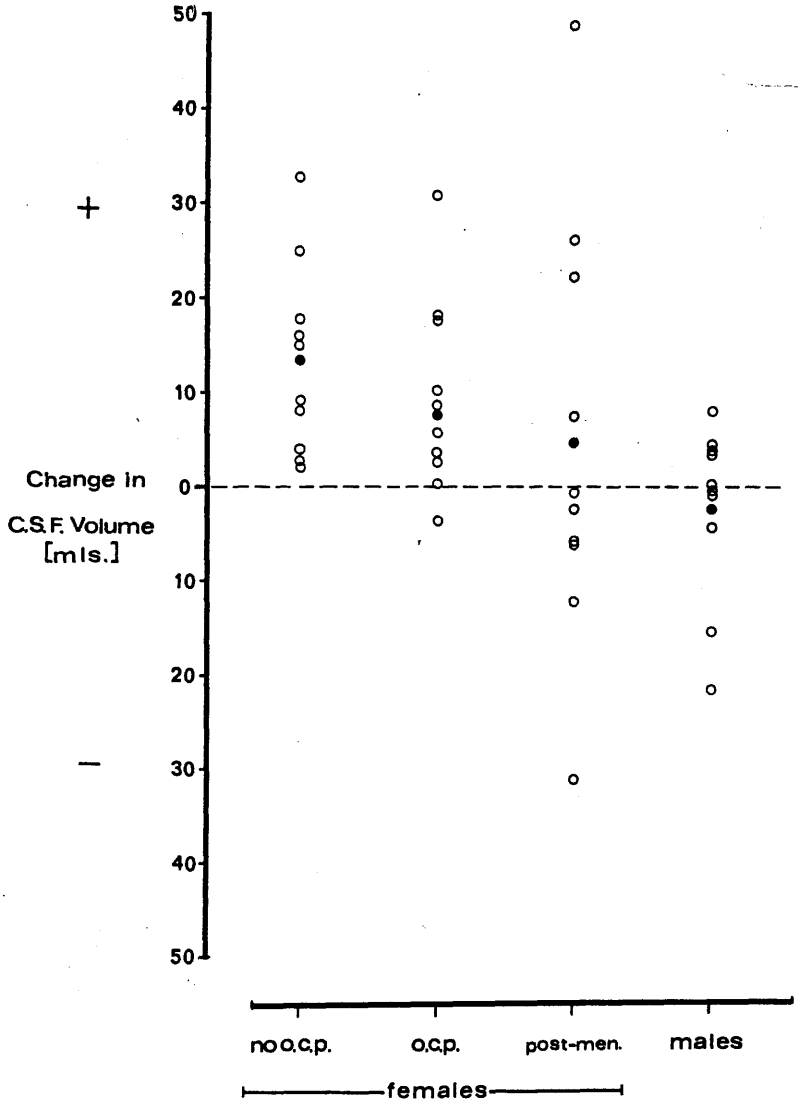

Figure 16. Changes in total cranial CSF volume measurements from midcycle to premenstrual and changes after 2 weeks in males and post-menopausal females.

Discussion.

That total cranial CSF volume increases premenstrually is in conflict with the concept of cerebral oedema occurring at this time. The modified fundamental Monro-Kellie doctrine[36] states that any increase in one of the three intracranial volume compartments (brain, blood, CSF.) must be associated with a compensatory decrease in one or both of the remaining compartments. The findings of this study therefore indicate that, rather than being swollen premenstrually, brain volume is probably reduced. An increased cranial CSF volume is consistent with other premenstrual changes related to the sodium and water retention that have been observed premenstrually. These are thought to result from changes in serum progesterone level stimulating the renin-angiotensin-aldosterone mechanism.[134] Clinical manifestations include premenstrual subcutaneous oedema, engorgement of mucous membranes, vertigo due to increased secretion in the labyrinth of the inner ear, and even raised intra-ocular pressure due to increase in the volume of aqueous humour.[50] Production and absorption of ocular fluid exhibit strong analogies with CSF,[208] and Miller et al.[158] demonstrated that increases in volume of CSF result in an exponential increase in intracranial pressure. Relationships between the menstrual cycle and intracranial pressure have not been reported.

The mechanism causing the increase in CSF volume can only be speculated upon and could involve either increased rate of secretion or decreased absorption. Secretion of the CSF by the choroid plexus is predominantly under the control of the autonomic nervous system.[152] It has been suggested that increased CSF production due to oestrone stimulus is responsible for Benign Intracranial Hypertension[63] and oestrogen administration has been shown to increase brain water content in some animals.[230] Conversely vasopressin and corticosteroids decrease the rate of production of CSF.[59] Absorption of CSF into the arachnoid villi is by transcellular bulk flow[207] and likewise is increased by corticosteroids.[119]

A reduction in cerebral blood volume would also be reflected in increased cranial CSF volumes. Premenstrual "lightheadedness" and syncope could be the result of cerebral underperfusion. CSF and arterial pCO_2 are significantly lower (mean 3.7 mmHg) during the luteal phase of the menstrual cycle, with an inverse relation to plasma progesterone level.[142] It is unlikely, however, that hypocapnic

vasoconstriction could account for the observed changes in CSF volume premenstrually, as the cerebral circulation adapts to changes in $PaCO_2$ if these are sustained for several hours. To cause an increase in CSF volume of 11.5mls. even transiently, the $PaCO_2$ would need to decrease by more than 13 mm.Hg.(Chapter 4.4). Further studies of intracranial dynamics in relation to the menstrual cycle, including the degree of change in CSF volume in patients with marked premenstrual symptoms, would be necessary to evaluate this further.

4.4. THE EFFECT OF HYPERCAPNIA AND HYPOCAPNIA CRANIAL CSF VOLUME

Introduction.

The original Monro-Kellie doctrine[161] concerning intracranial volume, held that intracranial blood volume remained constant in all circumstances. This was corrected by George Burrows in 1846[36] who for the first time incorporated the CSF into the components of the intracranial volume and suggested that the blood and CSF volumes were reciprocally inter-related. Since then cerebral blood volume has been estimated by various techniques, and changes described both in response to physiological stimuli and pathological conditions.[129,196] The volume of the brain in normal adults ranges from 1000mls. to 1500mls.. Intracranial blood volume constitutes 2-4% of the total intracranial volume and would account for 40ml to 75 ml. of the total intracranial volume. Intracranial CSF volume ranges from about 50-300mls.(Chapter 3) Any increase in one of these components must be accomodated by a decrease in one or both of the others.

In this study MRI has been used to observe the effects of vasodilation and vasoconstriction on CSF volume in normal subjects. To induce vasodilation the subjects inhaled 7% CO_2. As well as increasing cerebral blood flow (CBF) this increases cerebral blood volume by approximately 0.05 ml/100g brain/torr $PaCO_2$.[88] Changes in CBF, mean arterial blood pressure (MABP) and arterial pCO_2 may influence the cerebral blood volume and therefore the effect of 7% CO_2 inhalation on CBF, MABP and arterial pCO_2 was also studied. To provoke cerebral vasoconstriction, high flow, high concentration O_2 was inhaled. The aims of this were to discover if indeed there were reciprocal changes in CSF volume, and if so to determine their magnitude.

Subjects.

(a) Control Studies.

In order to ensure that changes in total CSF volume were not related to length of time spent in the recumbent position, the results were compared with the 25 normal volunteers, described in chapter 3, that had CSF volumes immediately repeated after 15-20 minutes.

(b) CSF volume and Carbon Dioxide Inhalation.

Twelve normal volunteers were studied ; 9 males (age range 19-34, mean 26.6 years) and 3 females (age range 20-41, mean 29.3 years). All subjects gave written informed consent and there were no contraindications to MRI or CBF estimation.

(c) CSF volume and Hyperventilation during High Flow Oxygen.

Twelve healthy subjects were studied before and during hyperventilation with high flow O_2(>60%O_2) . There were 8 males and 4 females aged from 20-38years (mean 29.1 years).

Methods.

1) CSF Volume Measurement by MRI.

Total intracranial CSF volume was measured using the IRCP 300/400/5000 pulse sequence with the 240mm thick slice select and imaging in the sagittal plane, as described in the methods section(Chapter 3.).

2) CO_2 Inhalation During MRI.

The method used to deliver and monitor 7% CO_2 in the MRI is shown in Figure 17. The subject was positioned on the MRI couch and a sphygmomanometer cuff was placed around the left upper arm. Pulse rate, systolic, diastolic and mean arterial blood pressure (MABP) were recorded automatically, using a Critikon Dinamap 1846F Version 028, before entering the imager and then at minute intervals. A rubber mouthpiece was placed in the subject's mouth and then connected to a two way valve. A three metre length of tubing extended from the inspiratory limb of the two way valve to outside the MRI radiofrequency shield. The expiratory limb from the valve was connected to a 1 metre length of tubing which was open to the air.

During the assessment of "resting" CSF volume, the inspiratory limb of the tubing was left open so that the subject was able to breathe fresh air. A repeat scan was taken after a cylinder containing 7% CO_2 was attached to a Douglas bag and the outlet from the Douglas bag attached to the inspiratory limb of tubing to the subject, without disturbing the subject's position in the centre of the magnet.

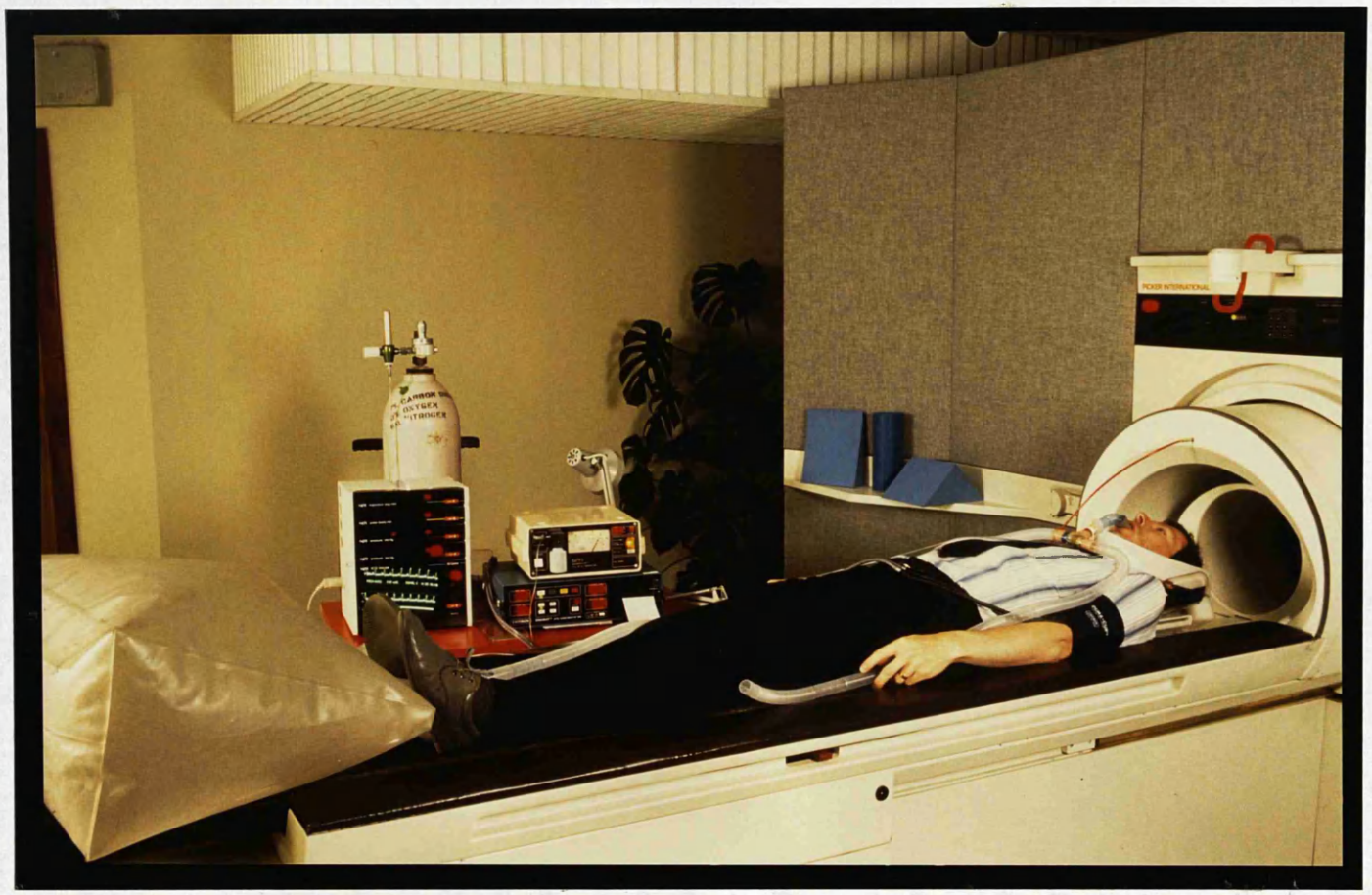

Figure 17. Method of delivering and monitoring the effect of 7% CO2 inhalation in the MRI.

3) Cerebral Blood Flow Measurement.

Cerebral blood flow (CBF) was measured by the Xenon-133 inhalation technique.[223] Bilateral collimated 50mm. diameter sodium iodide detectors were positioned over the parieto-temporal regions, providing a non-invasive simultaneous measurement of CBF in each hemisphere. Corrections were applied to minimise "crosstalk". A spirometer with open and closed systems was employed, into which a mixture of Xenon-133 and air was introduced, to give a specific activity of approximately 40MBq/litre. A CO_2 absorber was incorporated in the closed circuit in order to maintain a stable CO_2 level during the resting flow run. End tidal CO_2 and Xenon-133 concentrations were continuously measured, using a capnograph (Godart Statham 17070) and scintillation counter. The resting CBF was measured. The subject was then switched to the closed circuit and a Xenon-133/air mixture breathed for two minutes after which time the spirometer was returned to the open circuit, thus allowing the subject to breathe fresh air again. After a 30 second lag phase the total counts were recorded in each detector for two consecutive minutes and the clearance rate, and hence CBF, calculated using a stored nomogram. After a period of 10-20 minutes, to allow the Xenon level in the head to fall to a low level, the process was repeated with the CO_2 absorber removed from the system and with the subject breathing a mixture containing 7% CO_2 during the washout phase. The resting flow (CBFr), hypercapnic flow (CBFh) and percentage increase in flow were recorded in each hemisphere. End expiratory CO_2 was measured at 3.5minutes while breathing 7%CO_2.

4) Hyperventilation/O_2 Inhalation During MRI.

The method used was similar to that of CO_2 inhalation but high flow O_2 was delivered at a flow rate of 10 litres/min via the inspiratory limb directly, without the use of a Douglas bag. A capnograph sensor was inserted between the two-way valve and Duo-mask (Lifecare). During the first "resting" scan the inspiratory limb of the system was open to air and at the start of the second scan the high flow O_2 was connected to the inspiratory limb and the subject asked to hyperventilate at a rate of approximately 30

breaths/min. The average O_2 concentration delivered at the mask was 60-65%.

It was not possible to obtain reliable measurements of end-expiratory CO_2 during hyperventilation because the high flow rate of the O2 and fast respiratory rate did not allow sufficient time for the true expiratory CO_2 to register on the capnograph. In order to gain an indication of the degree of reduction in $PaCO_2$ "arterialised" venous blood samples were taken from volunteers before and during hyperventilation and inhalation of O_2 at 10 l/min.. The subject's arm was enclosed in an insulated bag and heated until a thermoelectrode, closely applied to the skin over the dorsum of the hand, gave a constant recording of skin temperature of 43°C. Samples of "arterialised" venous blood were taken via a venous cannula which had been inserted into a vein on the dorsum of the hand close to the thermoelectrode.

While breathing air and after breathing oxygen for 5 minutes, "arterialised" venous blood gases were measured using a Corning 178 pH/blood gas analyser.

Results.

Total intracranial CSF volume was not significantly different after 15-20 minutes recumbency in the 25 healthy volunteers (median difference -2.8 mls(interquartile range 1.8, -6.8) (Table 5). Resting total intracranial CSF volumes ranged from 52.1mls to 160.8 mls. (mean 104.2 mls). A reduction in total CSF volume was recorded in all subjects following inhalation of 7% CO2 (Figure 18). The degree of change ranged from -0.7 ml to -23.7 mls. (mean 9.36 mls,SD 7.67). This represented a percentage reduction in total intracranial CSF volume of 0.9-19.4% (mean 8.6%). The individual recordings of total cranial CSF volume and CEF results are shown in Table 8.

Subjects with large "resting" CSF volumes tended to have a greater reduction in CSF volume after CO_2; However this just failed to reach significance at the 5% level (correlation coefficient 0.528 - minimum significant value of r would be 0.576).

Mean arterial blood pressure (MABP), measured automatically by the Dinamap while in the imager, increased during hypercapnia in 11 of the 12 subjects and did not alter in one case (Table 8;No.11).

As a group the mean rise in MABP was 9.25mmHg. There was no relationship between the degree of reduction in total cranial CSF volume and the MABP in individual cases.

An increase in CBF was recorded in all cases after 7% CO_2 inhalation. The degree of response however was varied (Table 8). The percentage increase in CBF ranged from 10-69% (mean 40.8%, SD 17.2) of the resting flow. The end expiratory CO_2 increased by a mean of 13.25mmHg (+/- 4.16) after 7% CO_2 inhalation. There was no correlation between individual subject's change in CBF or end expiratory CO_2 and the reduction in CSF volume.

Before hyperventilation with 60% O_2, total CSF volumes ranged from 99.5 to 253.3mls(mean 168.1 mls). During hyperventilation there was an increased total CSF volume in all subjects(Table 9)(Figure 19). The change in CSF volume ranged from +0.7 ml to +26.7 mls (mean 12.7 mls). As a percentage of the total CSF volume this was +0.3 to +13.6% (mean +7.6%). Subjects with a large initial CSF volume tended to show the greatest response, but this was not significant (correlation coefficient 0.539).

The effect of hyperventilation on mean "arterialised" venous pCO_2 was to produce a decrease in pCO_2 from a mean of 40.05mmHg(SD 0.95 n=5) before hyperventilation to 29.85mmHg (SD 1.15 n=5) after.

Discussion.

The validity of the original Monro-Kellie concept and of its late modifications provoked considerable controversy.[213] Burrows view that blood volume and CSF volume were variable, with the latter reducing in response to increased blood volume, was supported by Bergmann[15] and by Roy and Sherrington.[167] By contrast, the assumption that cerebral blood volume remained constant was continued by Adamkiewicz,[1] Leonard Hill[104] and even by Weed[212] as recently as 1929. The findings of a consistent reduction in CSF volume with hypercapnia and of increases in CSF volume during hyperventilation provide direct confirmation of the modified Monro-Kellie doctrine and also provide a measure of the extent of the reciprocal interactions between CSF volume and cerebral blood volume in human subjects.

The reduction in CSF volume was not simply a reflection of gravitational changes between CSF in the head and spine, related to time spent in the imager. The redistribution of CSF on recumbency is very

Subject	Age (yrs.)	Mean CBF (mls./100mls/min) Pre CO2	Post CO2	% Increase in CBF	Mean Arterial BP (m m Hg.) Pre CO2	Post CO2	End expir CO2 (mmHg.) Pre CO2	End expir CO2 (mmHg.) Post CO2	Total CSF Volume (mls.) Pre CO2	Post CO2	% Change in CSF Volume
1	19	55.5	72.5	30.5	75	81	27	50	97.7	90.6	7.3
2	20	48.0	62.0	29.5	82	89	30	42	80.5	78.3	2.7
3	23	47.5	64.5	37.0	79	83	32	45	82.5	81.8	0.9
4	23	48.0	73.0	52.5	79	96	30	48	123.3	99.6	19.2
5	27	47.5	59.5	25.5	85	98	33	44	63.4	51.1	19.4
6	28	42.0	60.5	45.5	87	97	33	45	52.1	47.3	9.2
7	29	43.0	59.0	36.5	85	97	40	49	136.6	118.7	13.1
8	33	33.5	55.5	64.0	89	95	40	48	87.0	84.4	2.8
9	33	52.0	57.0	10.0	79	88	38	50	160.8	140.5	12.6
10	34	41.0	60.5	51.0	76	99	35	46	102.5	91.7	10.5
11	35	45.0	62.0	37.5	88	88	35	48	159.5	154.1	3.4
12	41	32.0	54.0	69.0	94	100	26	43	104.8	100.1	4.5
Mean	**28.7**	**44.6**	**61.8**	**40.8**	**83.2**	**92.7**	**33.3**	**46.5**	**104.2**	**94.9**	**8.8**

Table 8. **Results of 7% CO2 Inhalation on CBF, MABP, End Expiratory CO2 and Total Cranial CSF Volume.**

As a group the mean rise in MABP was 9.25mmHg. There was no relationship between the degree of reduction in total cranial CSF volume and the MABP in individual cases.

An increase in CBF was recorded in all cases after 7% CO_2 inhalation. The degree of response however was varied (Table 8). The percentage increase in CBF ranged from 10-69% (mean 40.8%, SD 17.2) of the resting flow. The end expiratory CO_2 increased by a mean of 13.25mmHg (+/- 4.16) after 7% CO_2 inhalation. There was no correlation between individual subject's change in CBF or end expiratory CO_2 and the reduction in CSF volume.

Before hyperventilation with 60% O_2, total CSF volumes ranged from 99.5 to 253.3mls(mean 168.1 mls). During hyperventilation there was an increased total CSF volume in all subjects(Table 9)(Figure 19). The change in CSF volume ranged from +0.7 ml to +26.7 mls (mean 12.7 mls). As a percentage of the total CSF volume this was +0.3 to +13.6% (mean +7.6%). Subjects with a large initial CSF volume tended to show the greatest response, but this was not significant (correlation coefficient 0.539).

The effect of hyperventilation on mean "arterialised" venous pCO_2 was to produce a decrease in pCO_2 from a mean of 40.05mmHg(SD 0.95 n=5) before hyperventilation to 29.85mmHg (SD 1.15 n=5) after.

Discussion.

The validity of the original Monro-Kellie concept and of its late modifications provoked considerable controversy.[213] Burrows view that blood volume and CSF volume were variable, with the latter reducing in response to increased blood volume, was supported by Bergmann[15] and by Roy and Sherrington.[167] By contrast, the assumption that cerebral blood volume remained constant was continued by Adamkiewicz,[1] Leonard Hill[104] and even by Weed[212] as recently as 1929. The findings of a consistent reduction in CSF volume with hypercapnia and of increases in CSF volume during hyperventilation provide direct confirmation of the modified Monro-Kellie doctrine and also provide a measure of the extent of the reciprocal interactions between CSF volume and cerebral blood volume in human subjects.

The reduction in CSF volume was not simply a reflection of gravitational changes between CSF in the head and spine, related to time spent in the imager. The redistribution of CSF on recumbency is very

Subject	Age (Yrs)	Total Cranial CSF Volume (mls)		% Change in CSF.Volume
		Resting	O_2 / Hyperventilation	
1.	20	99.5	111.9	12.5
2.	24	172.7	183.7	6.4
3.	26	100.6	111.3	10.6
4.	26	196.3	223.0	13.6
5.	28	177.1	187.0	5.1
6.	29	119.7	126.4	5.6
7.	29	143.2	143.9	0.3
8.	30	253.3	274.3	8.3
9.	31	224.4	236.4	5.3
10.	32	166.1	174.4	5.0
11.	36	183.4	201.7	10.0
12.	38	180.6	195.1	8.0
Mean	**29.1**	**168.1**	**180.8**	**7.6**

Table 9. Results of total cranial CSF volume measurements before and after hyperventilation with high flow O2.

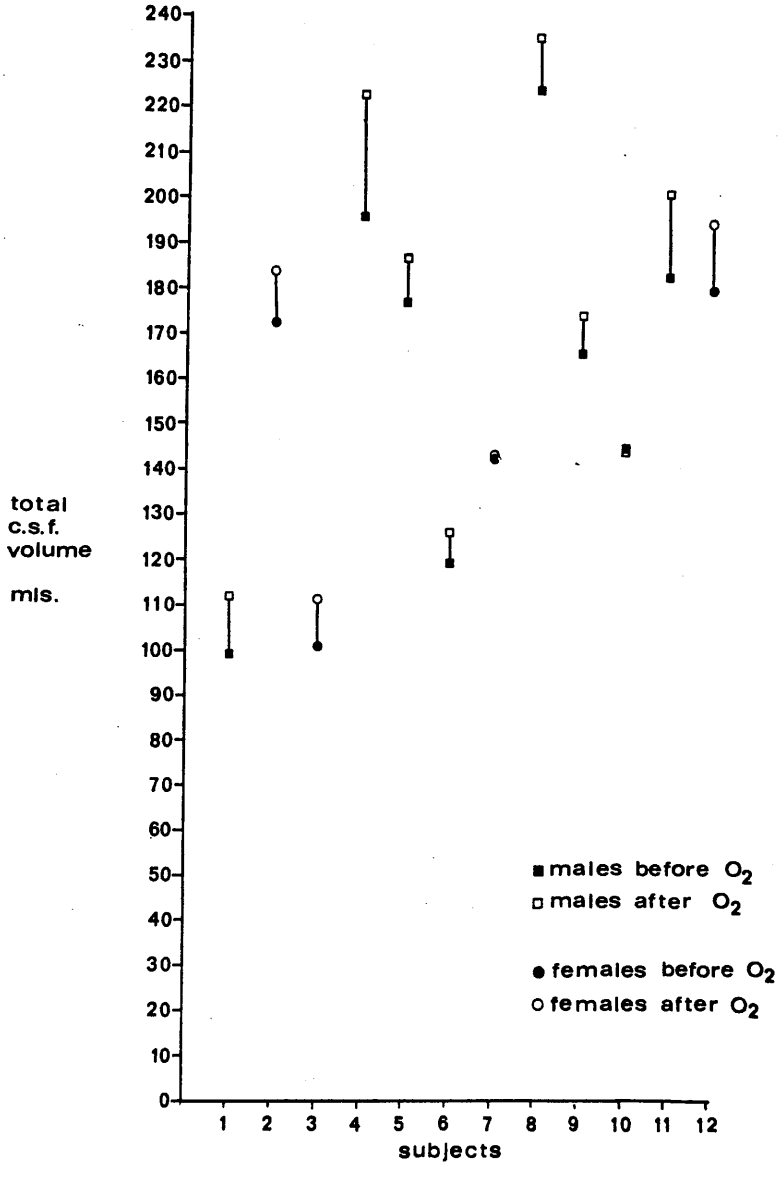

Figure 19. The effect of hyperventilation with high flow O2 on total cranial CSF volume.

small, occurs quickly, stabilises in under one second and is directed cranially.[143] This would have resulted in a slight increase in cranial CSF volume.

End tidal CO_2 correlates closely with arterial CO_2 tension,[195] although it may be 2-3mmHg. lower than arterial pCO_2. The increase in end expiratory CO_2, CBF and MABP during CO_2 is consistent with the results of other studies.[53] Cerebral blood volume (CBV) measurement, in man, is technically difficult to perform and reported values range from approximately 4.2ml/100g brain to 7.0ml/100g brain.[149,162] Hypercapnia induces an increase in cerebral blood volume[90] and an increase in intracranial pressure. Greenberg et al.,[88] using emission tomography and ^{99m}Tc-labelled red blood cells, measured local CBV simultaneously in multiple regions of the brain and studied the effect of alterations in pCO_2 on CBV in ten male volunteers. They found that CO_2 inhalation resulted in an increase in CBV in all subjects, while moderate hyperventilation produced a decrease in CBV from normal levels. An increase in blood volume of 0.0495ml/100g brain/torr $paCO_2$, was demonstrated. Therefore for a brain weighing 1400g, the change in CBV resulting from an increase in pCO_2 of 13.25 mmHg., would be estimated to be 9.2mls. This estimate of the likely average increase in CBV in the subjects studied is remarkably close to the observed decrease in CSF volume (9.36 mls).

The degree of alteration in CBV in individuals depends on differences in brain size, vascular compliance, intracranial pressure and vascular responsiveness to changes in arterial CO_2 tension. These factors may account for the observed variability of the CSF volume changes during hypercapnia or hyperventilation with hypocapnia. In addition, the 2 minute slope technique for measuring mean CBF response to 7% CO_2 inhalation[224] is calculated following 2 minutes rebreathing from a Douglas bag, 2 minute breathing 7% CO_2 and a lag phase of 30 seconds (4.5 minutes) and during MR imaging, information from the CSF is acquired over the duration of the scan (5.3 minutes). The stimulus used to provoke cerebral vasodilatation and the time course of stimulation are similar but not exactly the same. These factors and the inherent errors in the Xe^{133} inhalation method may also account for the wide variability and lack of correlation between CBF changes and changes in CSF volume.

The reduction in CSF volume in response to increase in CBV may mainly reflect its being displaced into the spinal subarachnoid space ; this is distensible and plays an important role in intracranial spatial compensation.[147] On the other hand hypercarbia or raised intracranial pressure might also affect the production or absorption of CSF. Hypercarbia is reported to cause a reduction in CSF production[58,105,147,165] but because CSF formation rate is only approximately 20mls/hr.,[49] this mechanism is unlikely to contribute significantly to the reduction in intracranial CSF volume noted in this study. CSF absorption is dependent on intracranial pressure;[49] the reduction in cranial CSF volume during CO_2 inhalation also might have resulted from increased absorption via the arachnoid villi as well as from displacement of cranial CSF into the spinal subarachnoid space.

Hyperventilation and hypocapnia reduce CBV and intracranial pressure. As intracranial pressure is reduced, CSF may be displaced from the spinal subarachnoid space into the skull. Also, absorption by the arachnoid villi, which is pressure dependent, may be reduced and produce an increase in intracranial CSF volume. Short term changes in total cranial CSF volume can now be identified accurately using MRI, and as the CSF volume is an important factor when studying physiological and pathological conditions, CSF volume measurements may provide fundamental information about neurological and neurosurgical conditions.

4.5. THE EFFECT OF LUMBAR PUNCTURE

Introduction.

Since its introduction as a diagnostic technique, by Quincke, in 1891,[177] lumbar puncture and CSF analysis have been crucial in the diagnosis of several important neurological conditions.[73,102] When performed carefully, serious complications are unusual but sequelae as a result of lumbar puncture and CSF withdrawal are not infrequent.[148] The most common complication, occurring in approximately 10%-36% of patients is headache.[30,222] This has been attributed to persistent CSF leakage into the subdural or epidural spaces at the site of puncture, resulting in intracranial hypotension.[166,173] Kunkle et al.[130] demonstrated that after rapid removal of around 20mls, (approximately 15% of estimated CSF volume), headache was produced in normal volunteers. It has been postulated by Wolff[222] that a reduction in CSF pressure when erect, produces "sagging" of the brain and traction on pain sensitive structures (blood vessels and meninges) in the posterior fossa, with resultant headache. This theory has never been proven.[4]

The CSF volume sequences were used to measure the range of change in cranial CSF volume, and to assess the relationship between headache and CSF volume change. The position of the cerebellar tonsils with respect to the foramen magnum was also studied in some patients to determine if tonsillar descent through the foramen magnum was responsible for occipital headache or neckache which follows lumbar puncture in some cases.

Subjects and Methods.

Twenty patients who underwent lumbar puncture for diagnostic purposes had cranial CSF volumes measured before and 24 hours after lumbar puncture. All patients gave written informed consent for MRI and were excluded if there was any history of headache at the time of admission or if they were taking analgesics. Patients who were to have myelography were excluded.

There were 8 males aged from 25-71 years (mean 41.5 years) and 12 females aged from 14-64 years (mean 38.5 years). The presence and severity of headache was noted at the time of the second scan. The presence, time of onset, severity and duration of post-LP headache

and of associated symptoms were also recorded after contacting the patient 3-4 weeks after lumbar puncture.

Lumbar Puncture.

Lumbar puncture was performed with the patient in the curled lateral recumbent position with the spine parallel to the floor and the vertical plane of the back at right angles to the bed. All spinal punctures were performed with an 18 gauge lumbar puncture needle after infiltrating the skin and interspace with 2% Lignocaine. On penetration of the sub-arachnoid space the stylet was removed and a three way tap and clinical manometer was attached to the hub of the needle. The CSF "opening" pressure was measured after allowing some time for the patient and pressure level to settle. Ten mls. of CSF were then allowed to drain and the CSF "closing" pressure was then measured. The stylet was then replaced and the lumbar puncture needle removed. The patient remained recumbent in bed for 24 hours and CSF was sent for biochemical, neuro-immunological and bacteriological analysis.

Magnetic Resonance Imaging.

Cranial CSF volume measurements were performed as described in chapter 3. Two images were obtained in the sagittal plane. The first had a slice thickness of 240mm and therefore included all CSF in the head. The second was centred on the falx, with a slice thickness set to include the lateral ventricles but exclude the overlying and underlying cortical sulci.

The CSF volumes were calculated in all subjects. A midline SE500/40 scan, to show the anatomical relationship between the cerebellar tonsils and the foramen magnum was performed in 5 subjects prior to lumbar puncture and 24 hours after lumbar puncture.

Results.

Lumbar puncture.

CSF bacteriological and biochemical tests, in particular CSF cell counts and protein levels were within normal limits in all patients. Oligoclonal band were however found in some patients.

The majority of the patients were being investigated for possible or probable multiple sclerosis.

CSF Volumes.

The ages of the subjects were not normally distributed therefore non parametric statistical analyses were performed. Pre-lumbar puncture total cranial CSF volumes were significantly greater in males(median 224.8mls) when compared with females(median 137.8mls) and were significantly correlated with age in males(r=0.77 [p<0.025, one sided]) and in females (r=0.74 [p<0.005, one sided]) (Table 10).

Nineteen of the patients had a reduction in total CSF volume 24 hours after lumbar puncture (Figure 20). One patient (Table 10 [15]) had an increase of 6.6mls.. The post lumbar puncture changes in CSF volume ranged from +8.8mls to -158.6mls. Three patients (Table 10 [11],[15],[20]) were advised to lie prone for 24 hours after lumbar puncture. In these patients cranial CSF volume changed by -15.2mls., +8.8mls and -17.2mls. respectively.

Total cranial, ventricular and cortical sulcal volume fell significantly after LP (all p<0.01, Wilcoxon signed ranks test) while posterior fossa CSF volume did not. The medians and interquartile ranges for the differences are given below:

	Lower Quartile	Median	Upper Quartile
Total Cranial CSF Volume	-33.7	-16.5	-11.1
Ventricular CSF Volume	-2.20	-0.95	-0.30
Posterior Fossa CSF Volume	-4.10	-1.20	-1.90
Cortical Sulcal CSF Volume	-30.6	-15.6	-7.90

The reduction in CSF volume was not significantly correlated with the age or sex of the patient, or with the initial total CSF volume (TV males r=0.216, females r=0.201). The CSF in the posterior fossa and the ventricular CSF volume of males did not change significantly following LP. Since the volume of CSF lost after LP was not significantly different for males when compared with females the results were combined for statistical purposes. The reductions in total, cortical sulcal and ventricular CSF volumes were significantly different from zero(p<0.01) and most CSF was

Subj	Age (yrs)	Sex	Total CSF (mls)	Ventric CSF (mls)	Post Fossa CSF (mls)	C.Sulcal CSF (mls)	Total CSF (mls)	Ventric CSF (mls)	Post Fossa CSF (mls)	C.Sulcal CSF (mls)
			I----------Pre-LP----------I				I----------Post-LP----------I			
1.	14	f	62.9	3.8	10.9	48.2	61.1	3.5	11.5	46.1
2.	19	f	111.2	10.9	12.1	88.2	91.6	10.3	11.6	69.7
3.	21	f	79.5	4.3	8.7	66.5	66.0	2.8	12.8	50.4
4.	25	m	158.5	14.8	14.3	129.4	147.4	16.4	16.8	114.2
5.	33	f	95.2	9.1	7.0	79.1	80.4	6.2	2.9	71.3
6.	34	m	194.5	13.3	12.4	168.8	170.7	13.4	19.1	138.2
7.	35	f	136.4	7.0	9.7	119.7	90.1	5.1	8.2	81.6
8.	35	f	240.8	43.1	22.9	174.8	207.1	42.4	16.4	148.3
9.	37	f	135.7	10.6	9.8	115.3	128.8	9.3	9.6	110.0
10.	38	m	255.0	12.9	22.7	219.4	96.4	9.4	17.1	69.9
11.	39	m	133.9	15.6	9.3	109.0	118.7	14.7	8.4	95.6
12.	39	m	265.7	15.3	13.7	236.7	241.1	15.0	16.9	209.2
13.	41	m	270.4	33.7	23.1	213.6	228.5	28.5	18.3	181.7
14.	45	m	183.3	17.2	11.3	154.8	178.2	17.6	13.7	146.9
15.	46	f	152.9	11.7	14.7	126.5	161.7	17.0	16.6	128.1
16.	50	f	169.4	10.6	10.1	148.7	124.9	7.4	7.3	110.2
17.	51	f	139.2	17.7	12.1	109.4	126.3	15.5	10.0	100.8
18.	57	f	169.5	29.0	25.4	115.1	91.8	21.9	16.3	53.6
19.	64	f	270.9	32.7	23.1	215.1	265.6	31.9	19.0	214.7
20.	71	m	371.8	27.2	30.6	314.0	354.6	26.9	27.2	300.5

Table 10. Results from pre-LP and 24 hours post-LP CSF volume measurements.

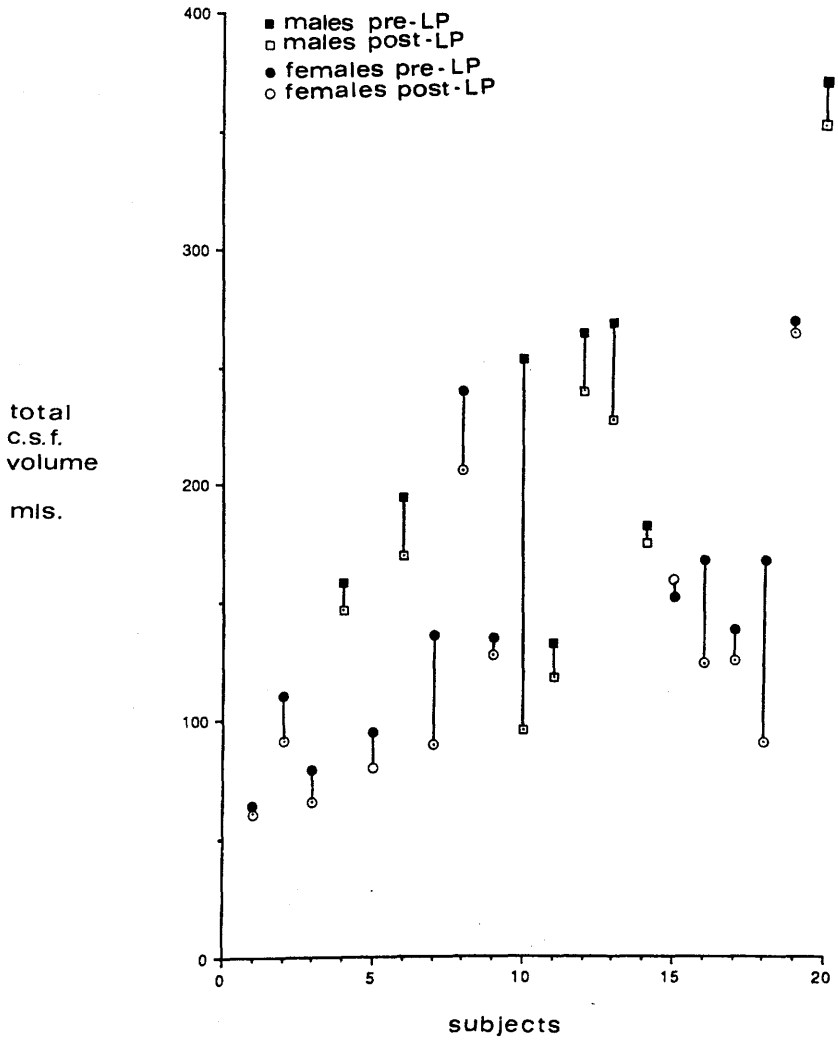

Figure 20. The effect of lumbar puncture on total cranial CSF volume.

lost from the cortical sulci. On visual assessment the CSF lost from the cortical sulci seemed to be predominantly from lateral to the cerebral hemispheres and from the sylvian fissures, rather than from the interhemispheric fissure.

There was no measurable change in position of the cerebellar tonsils in five patients who had 10mm thick midline sagittal structural MRI (SE40/500) scans before and after lumbar puncture to accurately define the posterior fossa anatomy.

Post LP symptoms.

Eleven of the patients complained of headache when questioned at the time of the second scan (24 hrs after LP). The headache was predominantly frontal in 3 patients, occipital +/- neckache in 3 patients and generalised or poorly localised in 5 patients. Associated features of nausea or dizziness were more frequently seen when the headache was generalised or occipital.

All patients had 10mls. of CSF removed at the time of lumbar puncture. Six of the 8 patients who lost more than 20mls. of cranial CSF following lumbar puncture developed headache compared with only 5 of the remaining 12 patients who lost less than 20mls of cranial CSF (Figure 21). The two patients who had a reduction in cranial CSF volume of 77.7mls and 158.6mls complained of severe headache, neck ache, nausea and vomiting and were incapacitated by headache for 3-4 weeks after the LP. The patient who had lost 158.6mls also spontaneously complained of cough headache and severe neck ache when sneezing. Both these lumbar punctures had been carried out on the same day by a less experienced locum SHO. The patient with the increase in CSF volume of 8.8mls was asymptomatic.

Two of the 5 patients who had SE40/500 sagittal structural scans pre and post LP, in order to measure the position of the cerebellar tonsils, developed headache, but there was no evidence of downward displacement of the cerebellum following lumbar puncture in any of the 5 patients.

Discussion.

This study demonstrates that within 24 hours of lumbar puncture the total cranial CSF can decrease by up to 158.6mls. or 62% of the initial cranial CSF volume. The changes are in fact probably an underestimate

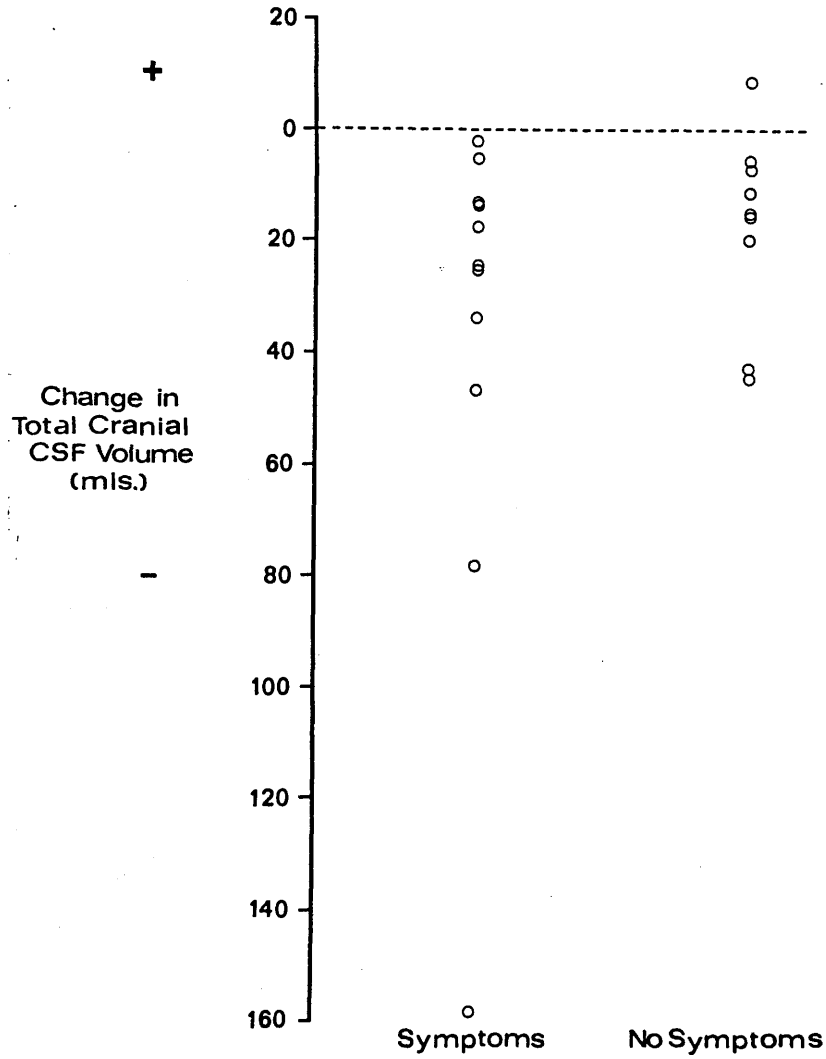

Figure 21. Relationship between CSF volume change after LP and symptoms (headache).

of the volume of cranial CSF volume lost since the scans are necessarily performed in recumbency and cranial CSF is likely to be reduced by standing. The intracranial pressure is less when upright and CSF is displaced into the head from the spinal subarachnoid space on lying down.[39,214]

The incidence of headache in this study (55%) was slightly higher than the incidence in other studies[148,209] and is probably related to the relatively large guage of needle used (18 guage).[206] When one considers the anatomy of the meninges, it is interesting that most of the CSF appears to be lost from the cortical sulci especially from the lateral convexities of the cerebral hemispheres. There is normally no subdural space as the arachnoid is held to the dura by the surface tension of the thin layer of fluid between these two membranes. The cerebral hemispheres are attached to the arachnoid and dura by fine fibrous arachnoid trabeculae and blood vessels. The subdural space overlying the temporo-parietal regions are less well able to withstand "negative" pressure as they do not contain the larger more robust bridging vessels that are present in the midline. If the CSF is predominantly lost from the temporo-parietal convexities the dural veins may tear resulting in subdural haematomas, a rare but well recognised complication of lumbar puncture. This may be due to a combination of factors; preferential loss of CSF from the cortical sulci in this region, compensatory venous vasodilatation and the reduction in intracranial pressure.

The mechanisms causing post-lumbar puncture headache are still debatable. Is it simply due to a reduction in pressure causing traction on the basal vessels or could it be due to compensatory cerebral vasodilatation?. Avezatt and Eijndhoven[9] have shown that the CSF compartment can cope with a volume load by volume storage and by volume compensation. By volume storage, they refer to "buffering" of the change in volume due to the elastic properties or compliance of the arachnoid and dural tissues. Volume compensation is where the change in CSF volume is balanced by a reciprocal change in one of the other two volume compartments (blood volume or brain volume). It therefore seems likely that the response to a CSF volume deficit may be by similar mechanisms, namely compliance of the system with a resultant reduction in the volume pressure relationship and volume compensation due to an increase in cerebral blood volume. The reciprocal relationship between cerebral blood volume and CSF volume is widely accepted (Modified Monro-Kellie

doctrine) and is supported by the changes in cranial CSF volume found during hypercapnia and hypocapnia (Chapter 4.4). As brain volume is unlikely to change significantly, most of the volume compensation must be accomodated by the vascular compartment, possibly by compensatory arterial vasodilatation or dilatation of the cerebral venous drainage pathways. The intracranial blood volume is approximately 150mls but less than 50% of this is within the brain substance and the remainder is in the subarachnoid space and subdural sinuses. While the changes occurring in intracerebral and extracerebral blood volume due to raised intracranial pressure have been studied by Portnoy and Chopp[176] the changes that occur in intracranial blood volume as a result of reduced intracranial pressure are uncertain. The increase in intracranial blood volume may be due to arteriolar vasodilatation or dilatation of the intracranial veins or venous sinuses. As the cerebral vessels contain pain sensitive nerve endings but the brain and dura do not, headache may be due to vasodilatation secondary to the reduction in CSF volume rather than the reduction in CSF pressure causing traction on basal vessels. The subject with the largest reduction in CSF volume following CO_2 inhalation in chapter 4.4. (Table 8 [4]) developed headache and he also had the largest increase in mean CBF and the second largest increase in pCO_2. This may support the hypothesis that headache is induced by vasodilatation. If there was predominantly arterial vasodilatation this may account for the "throbbing" character of post-lumbar puncture headache in the majority of patients, often likened to those of alcohol "hangover " headaches.[4] This is supported by the observations that the headache often settles following ergotamine tartrate[92] and follwoing compression of the carotid artery in the neck.[174] Alternatively, increase in intensity of headache during bilateral jugular compression may support cerebral venous vasodilatation. These possibilities have been discussed at length by Wolff[222] who finally concluded that the headache was due to "dilatation of and traction on pain sensitive structures". The evidence for a caudal shift of the brain[204] and traction on vessels as a cause of post lumbar puncture headache is lacking. The present studies did not demonstrate tonsillar descent through the foramen magnum in the cases where MRI was performed pre and post-lumbar puncture, or in two other patients referred with severe post-lumbar puncture headache outwith this study.

4.6. SUMMARY

This chapter set out to investigate if there are any diurnal or hormone related changes in total cranial CSF volume and to quantify the changes in CSF volume that occur in response to alterations in intracranial blood volume or as a result of CSF removal by lumbar puncture.

There is a tendency for total cranial CSF volume to decrease in the late afternoon but this just failed to reach a statistically significant level. Despite this, it is probably advisable to perform repeated CSF volume measurements at the same time each day. There is a highly significant increase in total cranial CSF volume premenstrually compared with the CSF volume measured at midcycle. The increase in CSF volume is found premenstrually in women with a regular menstrual cycle irrespective of whether they take oral contraceptives. A significant change in CSF volume is not demonstrated in post-menopausal females or in males. The premenstrual increase in CSF volume may be related to progesterone induced effects on the renin-angiotensin-aldosterone system affecting fluid retention but whether this results in increased CSF production or decreased CSF absorption remains uncertain. Contrary to what is generally believed this would suggest that the brain volume is decreased premenstrually or the intracranial blood volume is reduced premenstrually. If these two compensatory or reciprocal changes do not occur the intracranial pressure must be increased premenstrually when compared with the mid cycle intracranial pressure. Unfortunately, data on cerebral blood volume, brain volume and intracranial pressure changes over the menstrual cycle are not available. On critical review there is no evidence to support the widely held belief that brain swelling occurs premenstrually.

Changes in intracranial blood volume induced by 7% CO_2 inhalation and hyperventilation with 60% O_2 are reflected by reciprocal changes in total cranial CSF volume. The CSF volume decreased in all subjects during hypercapnia and increased in all subjects during hypocapnia. The mean change in total cranial CSF volume during hypercapnia was 9.36mls and during hypocapnia was 12.7mls. The range of CSF volume change in these normal subjects is from -23.7mls. to +26.7mls.. The mean changes in CSF volume during hypercapnia and hypocapnia are comparable with the

expected changes in cerebral blood volume in response to a similar stimulus. This study provides direct confirmation of the modified Monro-Kellie hypothesis.

CSF volume measurements performed before and 24 hours after lumbar puncture demonstrate that a continued loss of CSF occurs frequently and on occasion this can amount to a loss of more than 150mls. of cranial CSF. When cranial CSF was reduced by more than 20mls. post lumbar puncture headache occurred more frequently (75% of patients). There is some evidence that if the lumbar puncture is performed by a doctor with little practical experience of this procedure, the loss of CSF is greater. Post lumbar puncture headache may in part be due to the volume of CSF lost or due to the presumed compensatory increase in cerebral blood volume. There does not appear to be a measurable descent of the posterior fossa structures following lumbar puncture.

Physiological and possibly hormonal changes in total cranial CSF volume occur but interpretation of the results are hindered by the lack of information about how these factors influence intracranial blood volume and intracranial pressure. Further basic physiological research on intracranial pressure may help to explain some of these findings in more depth.

CHAPTER FIVE

PATHOLOGICAL CHANGES IN CSF VOLUME.

5.1. Introduction.

5.2. Dementia.

5.3. Normal Pressure Hydrocephalus.

5.4. Obstructive Hydrocephalus.

5.5. Benign Intracranial Hypertension.

5.6. Summary.

PATHOLOGICAL CHANGES IN CSF VOLUME

5.1. INTRODUCTION

The MRI measurement and reproducibility of cranial CSF volume in normal subjects has been assessed as have some of the physiological changes in CSF volume that occur as a result of "dynamic" or short term changes in intracranial volume. The aim of the present chapter is to apply the method of CSF volume measurement to certain neurological and neurosurgical disorders where the accurate determination of cranial CSF volume may have important research or clinical implications.

CSF acts as a hydrostatic buffer to changes in brain volume as has been shown in chapter 3 where cranial CSF volume increases with age reflecting the degree of cerebral atrophy. CSF volume measurement may help to answer the controversial question of whether there are significant changes in brain volume or ventricular volume in patients with dementia when compared with age related subjects with a normal memory and intellect.

The volume of the cerebral ventricles is increased in patients with normal pressure hydrocephalus and in obstructive hydrocephalus but quantitation of ventricular volume is often difficult and inaccurate. Cranial CSF volume measurements by MRI may be valuable in the diagnosis, and management of patients with hydrocephalus. CSF volume studies were performed on patients with normal pressure hydrocephalus and obstructive hydrocephalus to assess if measurement of total cranial, cortical sulcal and ventricular CSF volumes and the ventricular:cortical sulcal ratio would provide useful information on the natural history, severity and chronicity of these conditions and to investigate what happens to the cranial volumes following ventricular decompression.

CSF volumes were also measured in patients with benign intracranial hypertension; firstly,to determine if the ventricular and total cranial CSF volumes were decreased, remained normal or increased; secondly, to study the changes in CSF volume associated with medical management and lastly, to examine the theories of the possible mechanisms causing benign intracranial hypertension.

5.2. DEMENTIA

Introduction.

Dementia is characterised by a progressive deterioration in memory , comprehension, behaviour and personality due to a diffuse or multi-focal disorder of the cerebral hemispheres. The severity and rate of deterioration will vary from weeks to years depending on the underlying disease. The most common cause is Alzheimer's disease(50%),[138] followed by multi-infarct dementia and then by other nutritional, metabolic, traumatic, infective, degenerative and neoplastic conditions. Most of the dementing diseases are irreversible and result in generalised or more focal cerebral atrophy. Neuro-radiological investigations over the last 20 years have been aimed at excluding a treatable cause for dementia and identifying cerebral infarctions where present. The relationship between dementia and ventricular size or the degree of cortical atrophy has also interested clinicians,[3,76,115,116,184] radiologists[45,77,85,111] and pathologists.[21,57,109,167] In Alzheimer's disease there is good pathological evidence of a marked reduction in neurones not only in the cortex[110] but also from subcortical systems such as the nucleus basalis of Meynert, the basal forebrain and the hippocampus.[145,202] This in turn is reflected by cortical sulcal atrophy or ventricular enlargement.

Some authors have demonstrated a relationship between increasing intellectual impairment and increasing ventricular size[77,184] while others suggest that as the degree of overlap on CT between demented and non-demented groups is so large that it is of poor discriminating value.[115] The CT ventricular volume measurements were considered to be a more sensitive indicator of brain volume[77] and Albert et al.[3] claimed that a single computerized measure of fluid volume on the slice at the maximum width of the bodies of the lateral ventricles correctly separates patients with dementia from age matched controls in 88.9% of cases.

Since the MRI method of measuring CSF volume is more accurate than CT, and since the measurements can be subdivided into intracerebral and extracerebral components, and results can be compared with the normal subjects already studied, it should be possible to investigate more objectively, the total, cortical sulcal and ventricular CSF volumes and

the ventricular:cortical sulcal ratio in dementia (at present excluding patients with Normal Pressure Hydrocephalus).

Subjects.

Healthy Elderly Controls.

Twenty five healthy subjects over the age of 50 were studied (Table 11a). There were 9 males and 16 females aged from 50 yrs to 91 years. These subjects did not have any neurological or cardiovascular disorders in the past and were alert and orientated in time, place and person.

Patients with Dementia.

Twelve patients with a clinical diagnosis of dementia were studied (Table 11b). The patients were divided into these two categories clinically using the criteria of the "Cambridge Mental Disorders of the Elderly Examination (CAMDEX)".[186] Seven of the patients had Alzheimer's disease and 5 had multi-infarct dementia. There were 4 males and 8 females, aged from 54-89 years. All patients over the age of 71 years had dementia which became clinically apparent after the age of 65 years. Cases 7 and 10 had relatively mild dementia compared with the other cases.

Methods.

All healthy elderly subjects gave written informed consent and written informed consent was also obtained from patients with dementia or from their relatives. This study was passed by the hospital ethical committee.

CSF volume studies were performed as outlined in Chapter 3. Total cranial CSF volume was calculated from the 240 mm thick sagittal images (Figure 22a) and the ventricular volumes were calculated from thinner slices with the slice select set to fall between the lateral border of the lateral ventricles and the medial border of the sylvian fissures. After the CSF volume sequences were complete, a structural scan(SE80/2000) was performed to identify any space occupying lesions or infarcts (Figure 22b).

Subj	Age (Yrs)	Sex	Total Cranial CSF Volume (mls)	Ventric. CSF Volume (mls)	C.Sulcal CSF Volume (mls)	V:CS Ratio
1.	50	F	134.6	13.4	107.4	0.12
2.	51	F	136.8	20.3	106.9	0.19
3.	52	F	164.6	19.4	131.7	0.15
4.	53	M	157.8	19.7	125.6	0.16
5.	55	F	141.1	22.0	109.8	0.20
6.	56	F	107.1	10.8	83.6	0.13
7.	57	F	116.5	11.3	92.0	0.12
8.	57	F	142.7	14.8	117.9	0.13
9.	60	F	127.6	9.7	107.9	0.09
10.	60	M	183.3	17.0	157.7	0.11
11.	60	M	194.3	23.4	145.3	0.16
12.	61	M	255.9	26.1	202.9	0.13
13.	61	M	148.0	12.3	122.2	0.10
14.	62	F	118.9	11.2	95.4	0.12
15.	63	F	286.5	16.3	256.5	0.06
16.	64	M	214.8	26.9	171.1	0.16
17.	66	F	199.8	35.7	143.8	0.25
18.	70	F	189.7	17.4	156.3	0.11
19.	72	M	231.7	42.9	168.5	0.25
20.	72	F	262.7	41.4	194.4	0.21
21.	72	M	364.0	47.0	290.9	0.16
22.	74	F	142.7	20.4	113.4	0.18
23.	82	M	226.6	23.8	183.7	0.13
24.	90	F	463.7	43.5	399.1	0.11
25.	91	M	442.7	67.6	353.0	0.19

Figure 11a. CSF volume measurements in elderly normal subjects.

Subj	Age (Yrs)	Sex	Total Cranial CSF Volume (mls)	Ventric. CSF Volume (mls)	C.Sulcal CSF Volume (mls)	V:CS Ratio	Diagnosis
1.	54	M	183.5	35.4	117.6	0.30	Vascular
2.	57	M	334.5	42.6	270.3	0.16	Alzheimer's
3.	65	F	215.2	35.4	171.4	0.21	Alzheimer's
4.	67	M	402.1	61.6	321.1	0.18	Alzheimer's
5.	68	F	320.0	46.3	251.8	0.18	Alzheimer's
6.	71	F	237.7	32.0	186.4	0.17	Alzheimer's
7.	73	F	134.2	27.8	89.4	0.31	Vascular
8.	75	F	185.5	32.8	137.2	0.24	Vascular
9.	79	F	302.8	36.5	248.9	0.15	Alzheimer's
10.	79	F	367.1	42.6	280.4	0.15	Alzheimer's
11.	83	F	306.7	44.8	238.4	0.19	Vascular
12.	89	M	379.0	49.1	312.4	0.16	Vascular

Figure 11b. CSF volume measurements in patients with Alzheimer's dementia and vascular dementia.

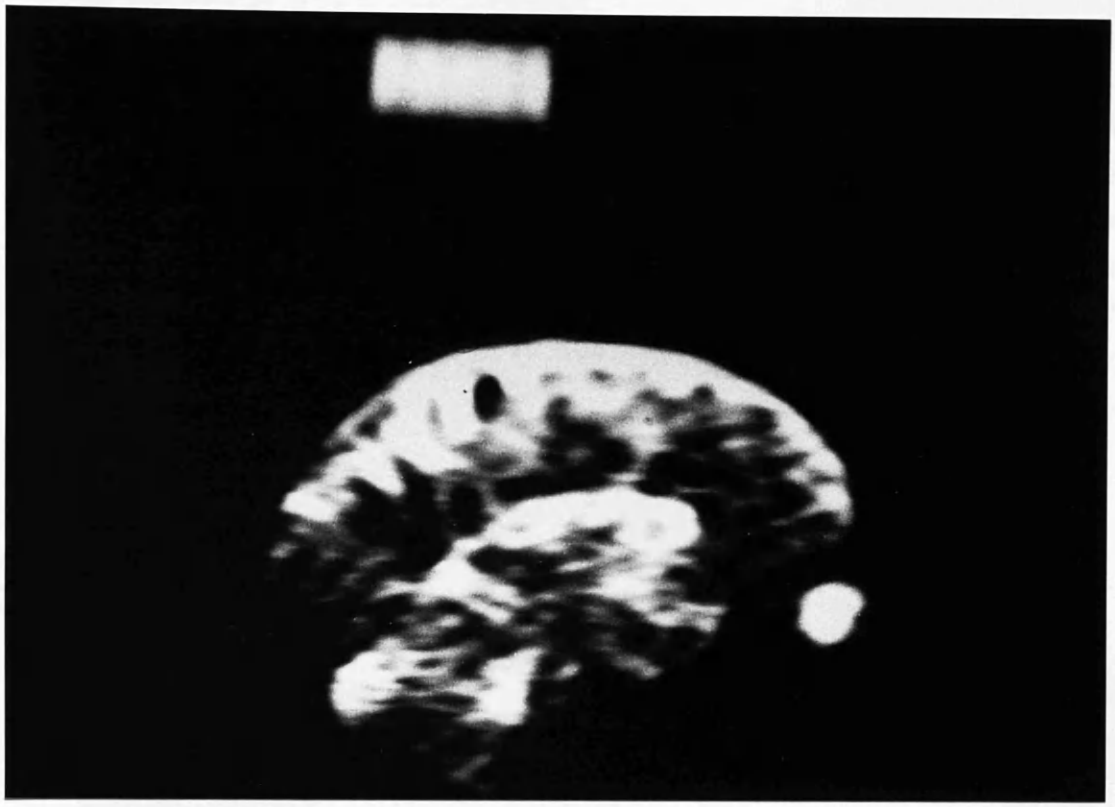

Figure 22a. Total cranial CSF image(240mm) in patient with dementia.

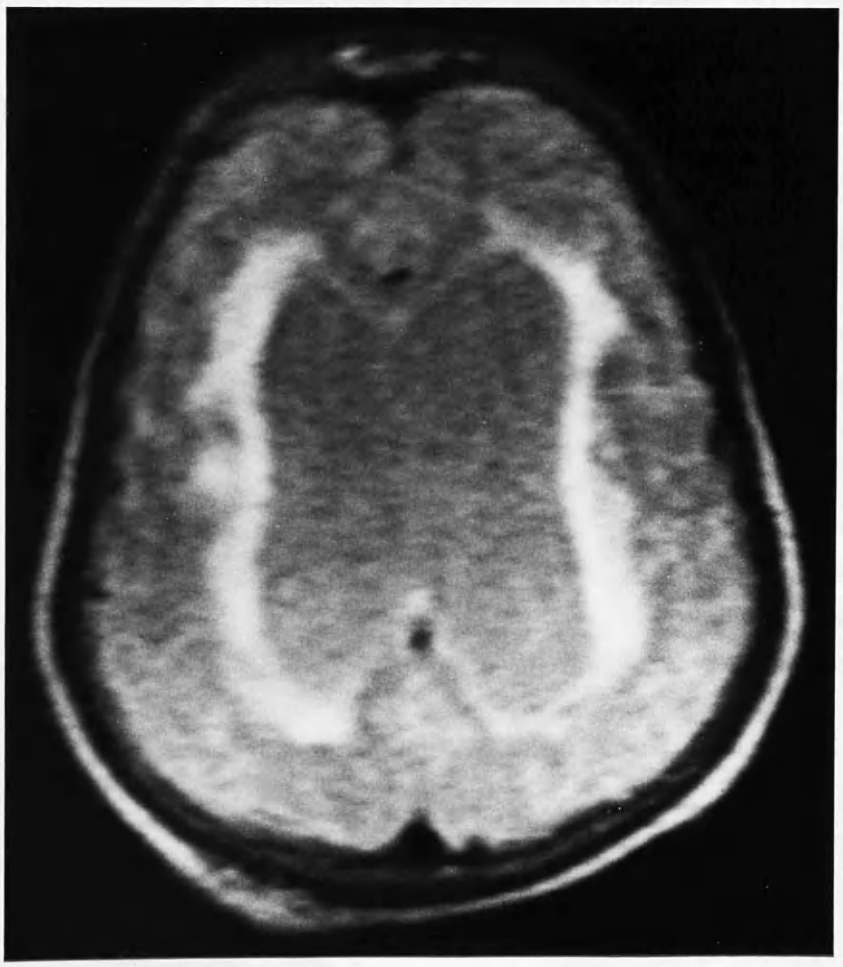

Figure 22b. Diffuse periventricular high signal areas in patient with dementia.

Results.

Healthy Elderly Controls.

Total cranial CSF volumes ranged from 107.1mls to 463.7mls in females and from 157.8mls to 442.7mls in males (Table 11a.). There was an increase in total cranial CSF volume with age which was highly significant ($p < 0.001$.) A linear regression best fitted these points, with a slope of 6.02x for females($R=0.76$) and of 7.94x for males($R=0.90$). Once more there was a wide scatter around the regression lines. Ventricular and cortical sulcal volumes also increased significantly with age, however there was not a significant change in V:CS ratio in males or in females.

Patients with Dementia.

Individual results for patients with dementia are shown in Table 11b. Because of the small number of patients in this study, the wide normal range for CSF volumes and the multiple variables involved in each patient, such as length of history, severity of dementia, other past medical history and medication, it would not be meaningful to perform formal statistical analyses on this group, but there are several trends which may be important. Patients with Alzheimers disease tended to have more total cranial CSF than patients with vascular dementia. Two male patients (Table 11b [2],[4]) with dementia had total cranial CSF volumes well above those of non-demented controls and both these patients had Alzheimer's disease. The other 2 males had vascular dementia and their total CSF volumes would be regarded as normal. The differences between the total cranial CSF volume in women with dementia were not significantly different from normal subjects. The ventricles were enlarged in patients with dementia aged under 70 years when compared with controls (Figure 23). However those aged over 70 years had ventricles of a similar volume as non-demented controls; i.e. the cases with "early onset" dementia (less than 65 years at onset) had larger ventricular volumes than age matched controls whereas those with "late onset" dementia(over 65 years at onset), particularly vascular dementia, had ventricular volumes similar to those of control subjects. Cortical sulcal volumes tended to be greater in those with Alzheimer's dementia starting before the age of 65 years (Table 11b [2],[3],[4] and [5]) (Figure

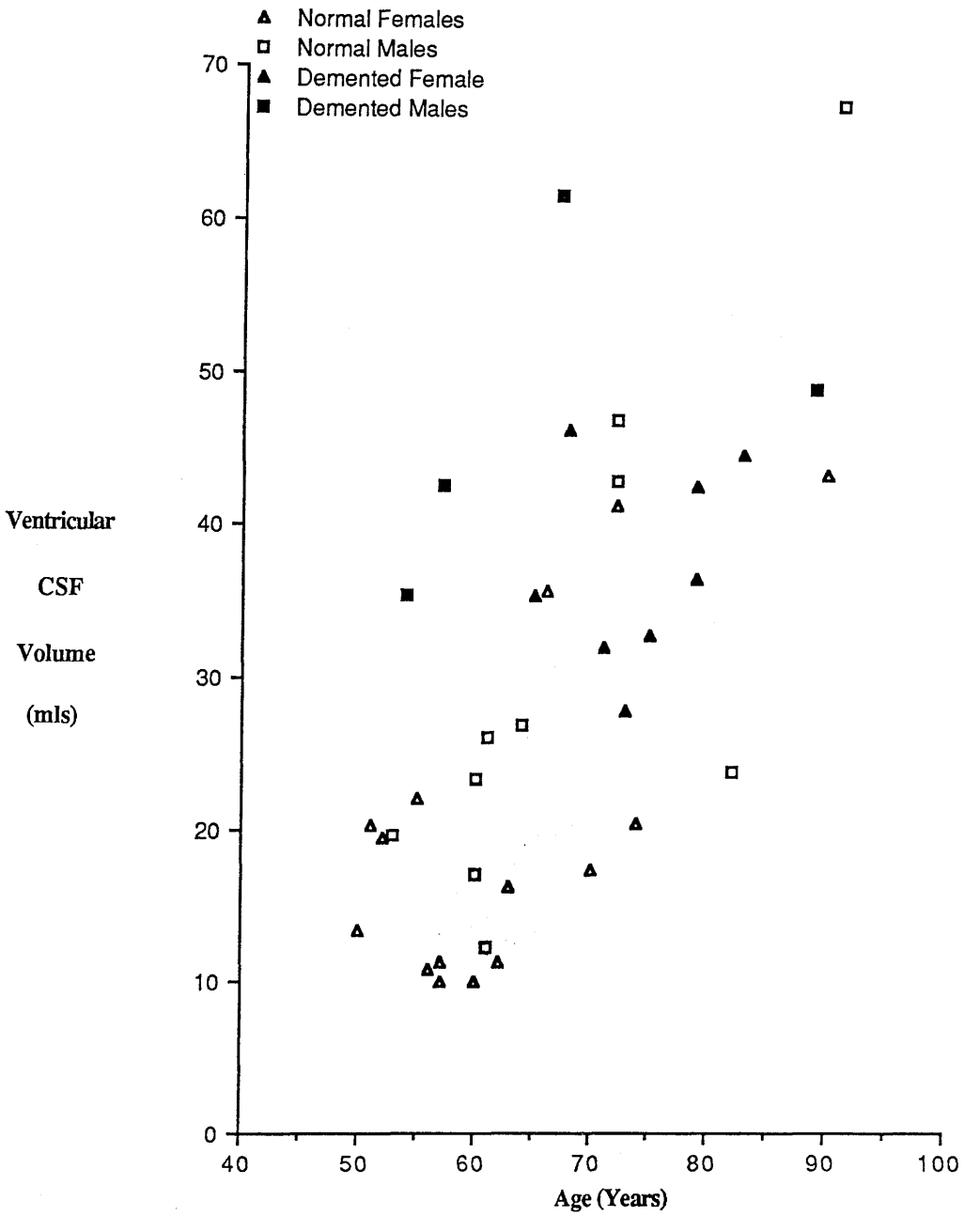

Figure 23. Ventricular CSF volume measurements in patients with dementia and in healthy elderly subjects.

24). The V:CS ratio was not greater than 0.31 in any patient and 0.25 in any of the elderly control subjects. The V:CS ratio was not significantly different between patients with dementia and controls.

All of the patients classified as having vascular dementia had discrete and periventricular high signal areas on the structural SE80/2000 images and 5 of 7 patients with Alzheimer's disease had periventricular high signal areas +/- discrete cerebral hemisphere high signal areas (Figure 22b). There was not an obvious association between the severity of the dementia and the presence of high signal areas.

Discussion.

Cortical atrophy and ventricular dilatation are both known to occur with advancing age.[21,31] This is supported by the findings in chapter 3 and the results of the normal individuals over the age of 50 years, where atrophy is reflected by an increase in total CSF volume of approximately 6-8mls per year. Therefore, the significance of ventricular dilatation or cortical atrophy in patients with dementia is more difficult to analyse. Hubbard and Anderson[109] performed post-mortem measurements of ventricular volume and "pericerebral" space in patients with senile dementia and in age matched controls and found that ventricular enlargement was an unreliable marker for clinical and pathologically proven Alzheimer's disease, being present in less than 60% of patients when compared with patient controls. Tomlinson et al.[205] found moderate to severe ventricular enlargement in 40% of brains from normal elderly individuals and x-ray CT studies of Gado and Hughes[77] were unable to demonstrate significant differences between elderly normal subjects and patients with dementia. Nevertheless, the results of the present study support findings of Hershey et al.,[103] who described enlarged ventricles on MRI more commonly in patients with dementia than in non demented control subjects, and of Albert et al.[3] who demonstrated that ventricular dilatation may be a frequent early finding in patients with Alzheimer's disease who are younger than 65 years. The cortical sulcal CSF volumes also seem to be increased in this group reflecting a generalised cortical atrophy in patients with "early onset" Alzheimer's disease. The separation of Alzheimer's disease by age of onset is almost certainly artificial, yet there are apparent

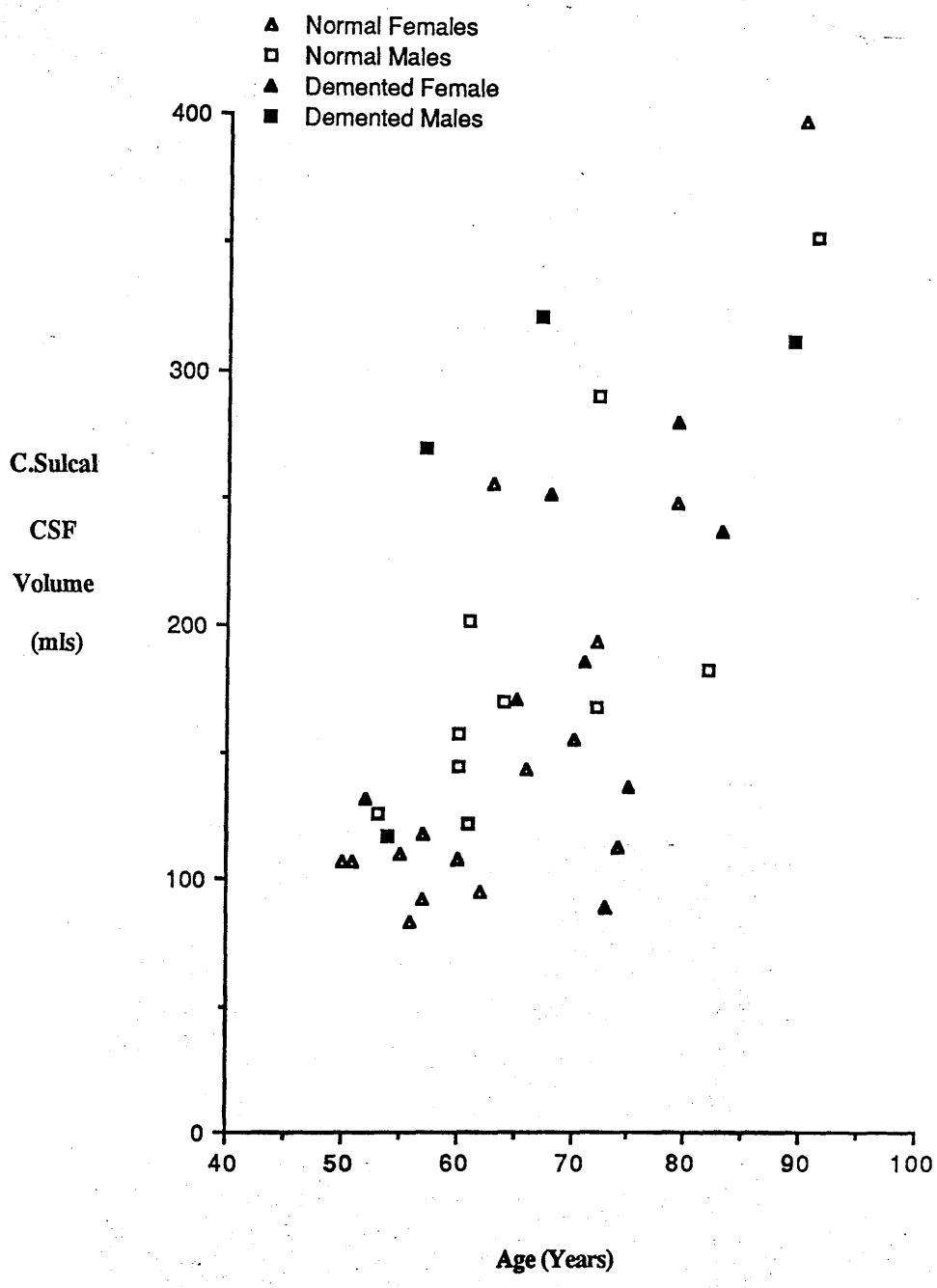

Figure 24. Cortical Sulcal CSF volumes in patients with dementia and in healthy elderly subjects.

neuro-chemical and neuropathological differences between "early onset" Alzheimer's and the "late onset" Alzheimer's group. In the group with an early age of onset there is a global reduction in cerebral cholinergic markers, while in the "late onset" group cholinergic receptors are reduced predominantly in the temporal lobes while they are preserved in the frontal areas.[26] These neuro-chemical receptor changes are reflected in loss of large cortical neurones and subcortical neurones in the locus coeruleus and the basal nucleus of Meynert, most marked in younger patients.[145,202] Hubbard and Anderson[110] demonstrated neuropathological evidence of generalised cerebral atrophy only in the "early onset" patients with Alzheimer's disease, using a technique that produced volumetric data.

The results of the V:CS ratios in patients with dementia and in healthy control subjects are potentially very important. Not one patient had a V:CS ratio greater than 0.31. This is of diagnostic value when normal pressure hydrocephalus is also considered as a possible diagnosis (See Chapter 5.3).

While discrete and periventricular high signal areas were found in all patients with vascular dementia, they were also seen in several patients with Alzheimer's disease and have been identified in normal controls,[103] and are therefore of limited diagnostic value. The confluent smooth periventricular high signal areas may simply reflect a deficient ependymal lining.[87]

Patients with dementia are difficult to image using MRI and to obtain adequate CSF volume images, it is certainly an advantage to have the reference phial in an insulated container fixed in position in the head coil rather than strapped to the patients head. It is also important to have the patient's head firmly restrained to minimise movement artefact while in the imager. Despite this some images may have significant movement artefact and should be repeated or abandoned. Where there is background "head movement" artefact an error in volume measurement can be produced resulting in a spuriously low total, ventricular, posterior fossa and cortical sulcal CSF volume although the V:CS ratio should remain fairly accurate(Chap 2.6).

The discriminatory value of ventricular volume and cortical sulcal volume measurement in separating patients with Alzheimer's from normal individuals remains to be adequately assessed but at present it does not appear to be of great diagnostic or prognostic importance.

5.3. NORMAL PRESSURE HYDROCEPHALUS.

Introduction.

Normal Pressure Hydrocephalus (NPH) is a clinical syndrome characterised by progressive memory failure, ataxia or apraxia of gait, and/or urinary urgency or incontinence. It must be associated with inappropriately large ventricles (hydrocephalus) for the degree of cortical atrophy, without evidence of obstruction to CSF flow within the ventricular system. The "mean" resting intracranial pressure is normal(<12mmHg), however there may be intermittently raised pressure or B waves.[200] It has been postulated that reduced CSF absorption by the cranial arachnoid villi is the main underlying abnormality. Although the mechanism remains uncertain,[22,69,95,220] it is generally believed that the reduced CSF absorption produces a transmantle pressure difference between ventricular and supra-cortical CSF.[44,106] The pressure difference in turn causes selective damage to periventricular white matter and this produces the characteristic clinical symptoms.[72,86]

The natural history of this clinical syndrome is unknown as most patients diagnosed as suffering from NPH undergo ventriculo-peritoneal shunting. Since the first report of clinical improvement after V-P shunting,[2] there have been numerous studies on the success rate of V-P shunting. In 1984, Borgesen[23] reviewed the literature and concluded that 42-67% of patients with NPH will improve after shunting but the complication rate is high (19-44%). The selection of patients who are likely to benefit from V-P shunting is therefore very important. CT brain scanning has been the initial step in confirming the clinical diagnosis as this demonstrates the size of the ventricles and cortical sulci. Gunasakera[91] and Crockard[46] observed that the patients with moderate cortical atrophy on CT did not respond to V-P shunting, however other authors[89,114,136,137] found that this was by no means a good prognostic factor and have documented several cases with ventricular dilatation and cortical atrophy who did improve after shunting. CT can also demonstrate whether there are periventricular low density areas in keeping with a transmantle pressure difference. The periventricular low density has been thought to be related to a reduced conductance to outflow of CSF and has been shown to resolve after shunting.

Borgesen[24] claimed that periventricular low density was associated with an improved clinical state in all cases still alive at one year follow up!. This apparently remarkable prognostic indicator has been found to be of diagnostic but not prognostic significance by other authors.[18] Vassilouthis[210] suggested that invasive procedures were not necessary in order to diagnose Normal Pressure Hydrocephalus and decision to operate should be based on the clinical and CT appearances only. Other methods suggested for identifying patients who are likely to respond to operation are; isotope cisternography,[25,62,144] subarachnoid infusion tests,[163] 24 hour lumbar pressure monitoring,[172,199] cerebral blood flow measurement[32,150] and the CBF response to CO2 inhalation[155] or removal of CSF.[203] Vorstrup et al.,[211] using SPECT (single photon emission computed tomography), have recently however have found blood flow tests alone can not predict those who are likely to benefit from surgery. Borgesen and Gjerris claim that measuring conductance to outflow of CSF by lumbo-ventricular perfusion can identify patients with NPH who are likely to benefit from surgery with a potential predictive success rate of 100%.[24] Others find ventriculo-cisternal or ventriculo-lumbar perfusion unreliable and subject to significant errors unless one can control perfusion time, craniospinal blood volume as well as intracranial pressure.[146] It is still often difficult to diagnose NPH, and to select patients who may benefit from surgery.[171]

Measurement of CSF volume by MRI in patients suspected of having NPH has potentially a very valuable role in the diagnosis, management and research of this disorder of CSF dynamics. The aim was firstly to determine whether the CSF volume sequences could differentiate between patients with clinical and CT evidence of possible NPH and normal subjects or those with dementia from other causes. Secondly, those patients who fulfilled the clinical criteria but were considered by the consultant in charge to be unsuitable for operation, (because a worthwhile clinical response was considered unlikely) were re-scanned after an interval in order to follow the natural history. Thirdly, patients with NPH who subsequently had a V-P shunt inserted were rescanned to assess the results of this procedure on the total cranial CSF volume and the distribution of intracranial CSF. Finally, the results of CSF analyses were compared with the clinical outcome in patients who did and those who did not have a V-P shunt operation to establish whether there may be any specific measures that might predict

a satisfactory outcome. As MRI is very sensitive to changes in water content of the brain and cortical biopsies in patients with NPH have demonstrated a marked increase in extracellular space,[75] SE80/2000 structural scans were also acquired to identify if there was evidence of periventricular "oedema" or multiple infarctions and to establish if this resolved after shunting.

Subjects.

Inclusion criteria for NPH.

1. Progressive dementia and ataxia/apraxia
   +/- urinary urge or incontinence.
2. Ventricular enlargement with
   little cortical atrophy demonstrated by CT.

Fifteen patients with NPH were studied and the clinical findings and results of investigations are shown in Table 12. There were 11 females and 4 males. Ages ranged from 59 to 78 years (mean 68.9 years). The severity of symptoms and the results of initial investigations are outlined in table 12. Thirteen patients had a mild or moderate "frontal type" of dementia, consistent with NPH. Two patients with "severe" dementia had a more global deficit. All patients had ataxia graded as mild (+) when the patient was unsteady but could walk unaided, moderate (++) if the patient required a walking aid and severe (+++) if the patient could not stand without assistance. Ten patients had either occasional episodes of incontinence (+) or were regularly incontinent of urine (++). All CT scans were reported as showing enlarged ventricles and being consistent with NPH rather than generalised atrophy. However in one case (Table 12 [13]) there was significant cortical atrophy, particularly of the frontal lobes and this scan was retrospectively thought to be more in keeping with generalised atrophy rather than NPH. Isotope cisternography was performed in 2 patients and 24-48 hour pressure monitoring was carried out in 8 patients (lumbar pressure monitoring(5); subdural pressure monitoring(1) ; intraventricular pressure monitoring(2). In 7 cases pressure monitoring was considered unneccessary or potentially hazardous as the clinical diagnosis was beyond doubt.

Eleven of the patients had a ventriculo-peritoneal shunt inserted on the strength of symptoms and these investigations.

Subj	Age (yrs)	Sex	Dementia	Ataxia	Incontinence	CT Scan	Isotope Cisternogram	Pressure Monitoring
1.	59	F	+	++	-	NPH		normal
2.	61	F	+	++	+	NPH		B waves
3.	61	F	+	++	-	NPH		
4.	64	M	+	+++	+	NPH		
5.	64	F	++	++	+	NPH		
6.	65	F	++	+++	+	NPH	NPH	B waves
7.	68	M	++	+++	++	NPH		
8.	70	M	++	++	+	NPH		B waves
9.	71	F	++	+++	+	NPH		B waves
10.	72	F	+++	+	+	NPH	NPH	normal
11.	73	M	+++	++	+	NPH		
12.	74	F	+	++	-	NPH		B waves
13.	76	F	++	+++	+	NPH		
14.	77	F	+	++	+	NPH		normal
15.	78	F	+	++	+	NPH		

Table 12. Symptoms, clinical severity and investigations in patients with Normal Pressure Hydrocephalus.

Healthy Control Subjects.

The 25 healthy subjects imaged for comparison in Chapter 5.2. were again used for comparison. There were 15 females and 10 males. Ages ranged from 50 years to 91 years(mean 64.4 years). These subjects did not have any past neurological or cardiovascular past history of note and were alert and orientated and did not have disturbance of gait or urinary symptoms.

Patient Controls with Dementia.

The 12 patients with dementia of other cause as outlined in Chapter 5.1 were also used for comparison. Their diagnoses and severity are as outlined in table 11b. There were 4 males and 8 females. Their ages ranged from 54 years to 89 years (mean 71.7 years).

These were patients with dementia of Alzheimers type and patients with vascular (multi-infarct) dementia. Patients were categorised using the CAMDEX (Cambridge Mental Disorders of the Elderly Examination) criteria.[186]

Written consent for MRI was obtained from the patient in mild cases and from the next of kin in more severe cases of dementia.

Methods.

A coronal pilot scan was obtained and then two CSF volume sequences were performed; the first with a 240mm slice thickness (Figure 25a) and the second with a narrower slice to include the ventricles but excluding the overlying and underlying cortical sulci. Following this a T_2 weighted(SE 80/2000) MRI of the head which produced sixteen 8mm thick contiguous slices was performed to assess the presence or degree of periventricular oedema.

Results.

CSF Volume Measurements.

The individual results for total, ventricular and cortical sulcal CSF volumes and ventricular:cortical sulcal ratios are shown in Table 13. The 240mm CSF volume image was fairly characteristic, with enlarged ventricles and relatively less cortical sulcal CSF. Another feature frequently seen in patients with NPH was a smooth concave cut-off of CSF at the foramen magnum (Figure 25a) which

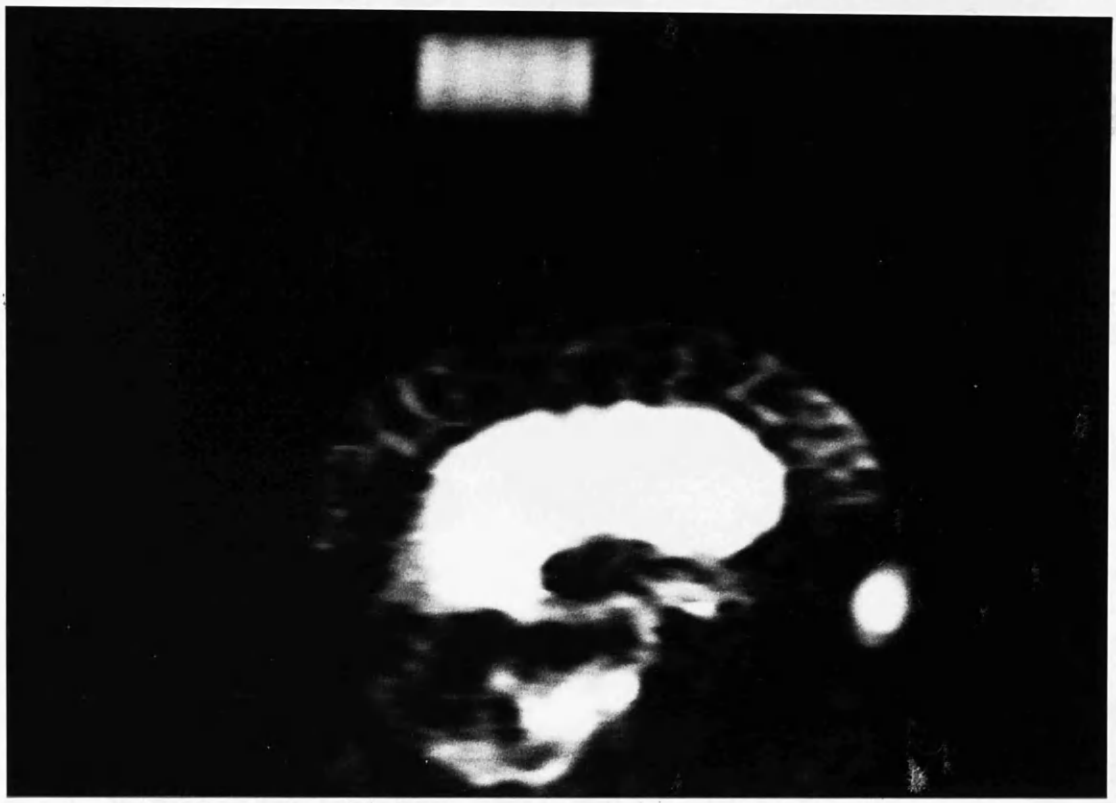

Figure 25a. Total cranial CSF image(240mm) in patient with NPH, with "concave" cut off at the foramen magnum.

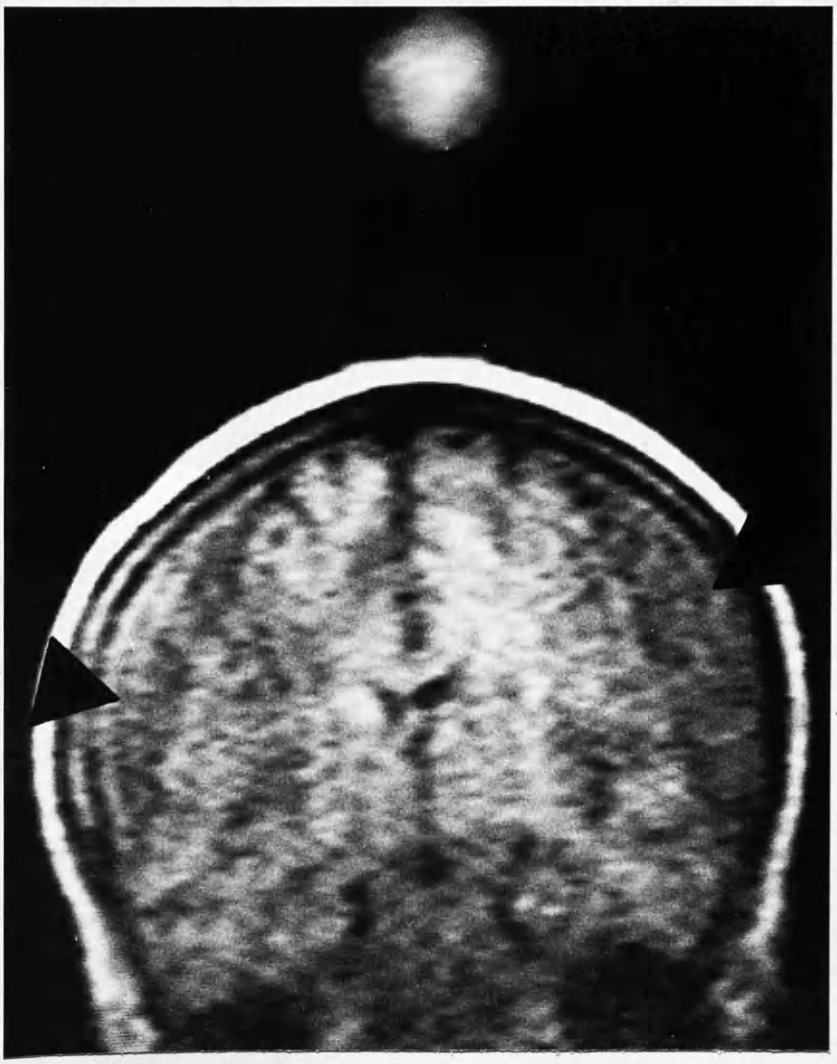

Figure 25b. Coronal pilot image showing bilateral subdural haematomas following insertion of V-P shunt.

Subj	Total CSF (mls)	Ventric CSF (mls)	C.Sulcal CSF (mls)	V:CS Ratio	Operation	Total CSF (mls)	Ventric CSF (mls)	C.Sulcal CSF (mls)	V:CS Ratio
	I----------Pre-operative----------I					I-Post-operative / Follow-Up Scan-I			
1.	436.4	202.7	222.3	0.91	No	459.3	219.4	222.7	0.99
2.	483.7	178.2	279.5	0.64	Yes	394.6	119.0	261.5	0.46
3.	175.8	46.1	119.2	0.39	No	190.1	60.2	112.1	0.54
4.	277.0	167.3	92.6	1.81	Yes**	341.0	116.3	205.1	0.57
5.	327.6	104.3	194.0	0.54	Yes	287.0	77.0	192.4	0.40
6.	313.3	92.2	202.1	0.46	Yes	223.4	50.4	156.4	0.32
7.	389.0	99.5	268.6	0.37	Yes	244.8	80.4	143.7	0.56
8.	268.2	156.7	69.3	2.26	Yes	261.2	142.8	84.5	1.69
9.	268.7	188.7	59.2	3.19	Yes	232.6	162.7	49.4	3.29
10.	378.6	116.5	233.8	0.50	VPM	269.1	76.5	171.5	0.45
11.	265.7	72.8	166.2	0.44	Yes*	378.5	85.7	253.1	0.34
12.	302.5	71.0	208.4	0.34	Yes	313.4	44.2	248.9	0.18
13.	561.8	115.5	401.4	0.29	Yes	272.0	42.5	186.4	0.22
14.	309.3	74.5	198.0	0.38	VPM	295.4	69.3	201.1	0.34
15.	262.5	136.8	97.9	1.40	Yes	247.4	97.8	126.8	0.77

Table 13. Results of initial CSF volume measurements, changes with time and the effect of insertion of V-P shunt in NPH.

Yes = post-operative repeat scan at one week.
VPM = ventricular pressure monitoring (but no V-P shunt performed).
No = No operation performed
* = follow up study at 3 months.
** = follow up study at 1 year.

contrasted with the acute " V shaped" cut-off found in normal individuals (Figure 4b) and in patients with dementia of other types. This characteristic feature may be of diagnostic importance.

Total cranial CSF volumes ranged from 175.8 to 561.8 mls. and there was no clear age or sex difference. Ventricular CSF volumes ranged from 46.1 to 202.7 mls. and were all greater than the ventricular volumes of subjects of the same sex and similar ages. Cortical sulcal CSF volumes ranged from 59.2 to 401.4 mls. reflecting marked cortical atrophy in some patients. This was certainly the case in one patient (Table 12 [13]), where in retrospect the CT scan did indeed demonstrate significant cortical atrophy particularly of the frontal lobes and this scan was not thought to be suggestive of NPH.

The most useful discriminatory measure in separating patients with NPH from normal individuals and from patients with dementia of other cause was the ventricular:cortical sulcal ratio (V:CS ratio) (Figure 26). All, except patient [13], had a V:CS ratio greater than 0.34, demonstrating that the ventricular dilatation was greater than one would expect for the degree of cortical atrophy. V:CS ratios greater than 1.00 ([4],[8],[9],[15]) reflected patients' low cortical sulcal CSF volumes.

Relationships between symptom severity and investigations.

There was no relationship between the severity of the dementia, ataxia or the presence of incontinence and the total, ventricular or cortical sulcal CSF volumes. Large V:CS ratios were not more common in patients with severe ataxia. There was no correlation between the presence or absence of B waves on pressure monitoring and the severity of symptoms, and no relationship between the presence of B waves and larger CSF volumes or a larger V:CS ratio.

All patients had peri-ventricular high signal areas on the SE80/2000 images. All had smooth confluent periventricular high signal areas but 7 patients also had discrete focal high signal areas in the cerebral hemispheres and in 3 patients(7,11,14) there were also discrete high signal areas (long T_2 lesions) in the cerebellum persumably reflecting old asymptomatic infarcts.

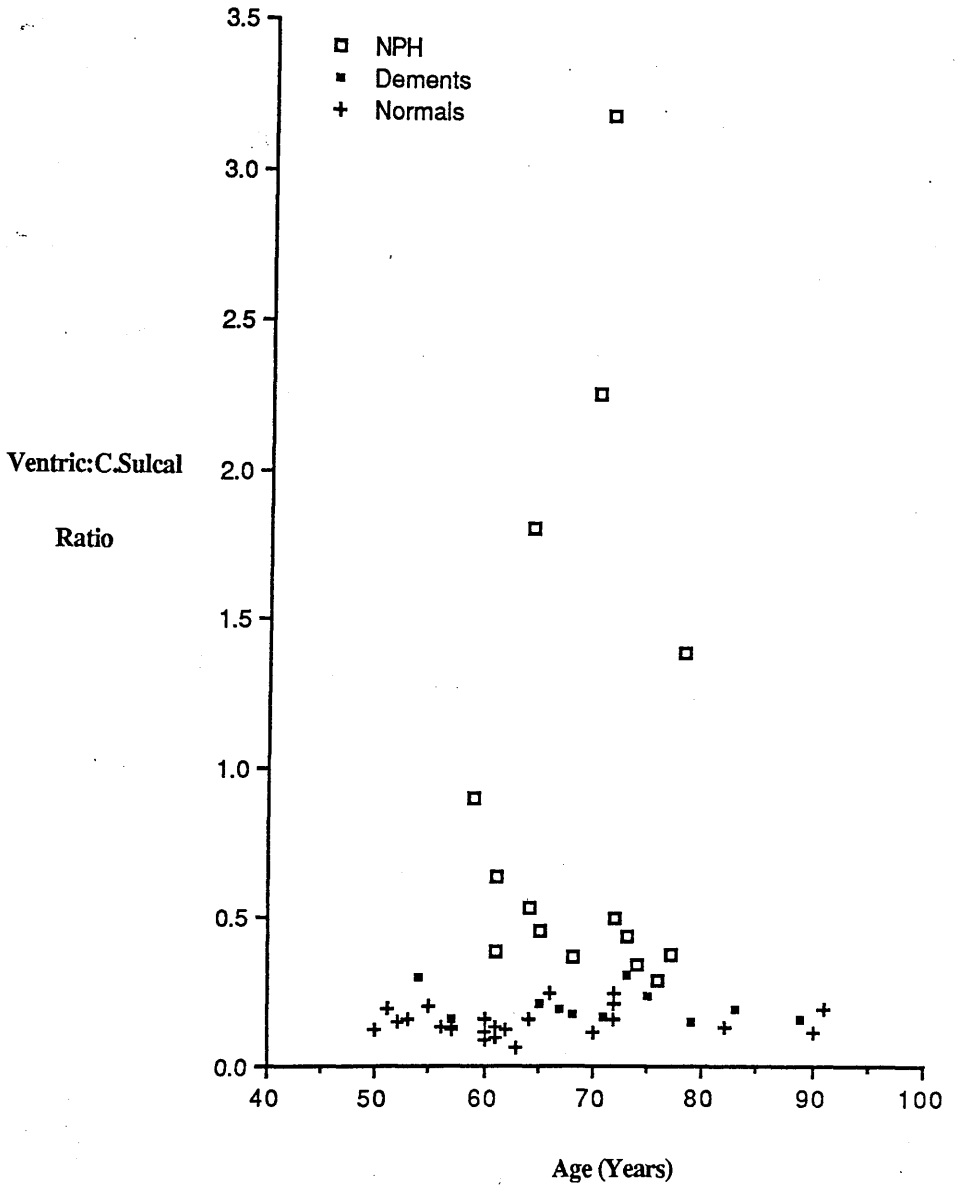

Figure 26. Ventricular:Cortical Sulcal ratios in patients with NPH, dementia and in healthy elderly subjects.

Operative and non-operative follow-up.

The follow-up results in these patients are outlined in Table 13. Eleven of the patients had insertion of a ventriculo-peritoneal shunt, two patients had 24-48 hour ventricular pressure monitoring without subsequent V-P shunting and two patients did not have an operation. CSF volumes were repeated one week after V-P shunting in 9 patients, after 3 months in one patient ([11]), and after 1 year in one case ([4]). CSF volume studies were repeated after one week in the two patients who had ventricular pressure monitoring (VPM) ([10],[14]). CSF volume sequences were repeated after 6 months in one patient who did not undergo operation ([1]) and after one year in another ([3]).

Total cranial CSF volume reduced by between 7 mls and 289.8 mls in 8 of the 9 patients re-scanned one week after V-P shunting. In one patient ([12]) the total cranial CSF volume increased by 10.9 mls. This patient had removal of V-P shunt 13 days after the second scan because of suspected shunt infection and on re-insertion one month later the total volume reduced by 10.7 mls. Following ventricular pressure monitoring (VPM), both patients had a reduction in total cranial and ventricular CSF volumes and a reduction in V:CS ratio.

Ventricular CSF volume reduced in all cases, to a variable degree after insertion of the V-P shunt (range 13.9-73.0 mls.). Following 24-48 hour VPM, the volume of the ventricles decreased by up to 40mls. Cortical sulcal CSF volumes fell in 6 patients after V-P shunting (four of whom had post-operative MRI evidence of subdural collections) and in one patient following VPM. The cortical sulcal CSF volumes increased in 5 patients following V-P shunting and in one patient after VPM. Ventricular:cortical sulcal ratios reduced in 7 of the nine cases who were shunted and re-imaged after one week, and in both of the patients who underwent ventricular pressure monitoring without insertion of a V-P shunt. The V:CS ratio increased in 2 patients after insertion of a V-P shunt and both these patients had MRI evidence of subdural collections. The V:CS ratio also increased in the two remaining patients who did not have ventricular pressure monitoring or shunt insertion.

The reduction in total and ventricular CSF voulmes would suggest that the ventriculo-peritoneal shunt is draining satisfactorily but

if the cortical sulcal CSF volume or the V:CS ratio increases, subdural collections should be suspected. As the total cranial CSF volume is reduced there must be a compensatory increase in blood or brain volume. The two patients re-scanned after 3 months and a year respectively had an increase in the total cranial CSF but the V:CS ratios were decreased. The two patients who did not have operation had increased total cranial and ventricular CSF volumes and an increased V:CS ratio when re-imaged after some time.

The presence of discrete high signal areas in the cerebrum or cerebellum may reflect a vascular basis for the symptoms however, unlike Shukla et al.,[192] the present study has demonstrated that patients with discrete periventricular high signal areas do not have any worse an outcome than patients without discrete high signal areas, assuming the diagnosis of NPH is correct. There was no obvious reduction in the periventricular high signal areas post-operatively after one week or indeed on longer follow up several months later.

Complications.

Five of the 11 patients who had V-P shunting had post-operative complications. These required further surgical intervention in 2 cases. MRI is very sensitive at identifying subdural haematomata (Figure 25b) and these were found in 4 patients following V-P shunt insertion ([6],[7],[9],[13]) where the total cranial CSF volume reduced in each case by 89.9mls., 144.2mls., 36.1mls. and 289.8mls. respectively. The latter patient required evacuation of the subdural collections. Cases [7] and [9] were the only patients where the V:CS ratio increased post-operatively and this may have reflected displaced cortical sulcal CSF due to subdural haematomas. Patient [12] developed a shunt infection and the system was removed and replaced one month later.

Outcome.

Three patients ([1],[3],[14]) who did not have operation, continued to deteriorate with worsening of dementia but without noticeable worsening of their gait or incontinence. Patient 10 had a slight improvement in gait following ventricular pressure monitoring.

There was a discernible improvement in 64% of patients following V-P shunting. In these cases the most clinically obvious improvement was in gait and in no case did higher function or continence improve without there being an clear improvement in gait. Patients [4] and [15] made dramatic post-operative improvement in gait, memory and continence. Both these patients could walk without assistance post-operatively. Patients [8] and [11] had an improvement in gait and mental acuity and patients [2],[6], and [12] had some improvement in gait. Patients [7] and [13] did not obtain any benefit from operation and cases [5] and [9] worsened post-operatively.

Discussion.

There is not a universally accepted investigation or combination of investigations which can act as a "goldstandard" for NPH that would effectively confirm the diagnosis beyond doubt. This has lead to an unprecedented research approach which has tried to equate the findings of "investigations" with "outcome" following surgery to determine if any particular investigation could predict which patients are most likely to benefit from surgery. This approach assumes that the operation will be effective in all cases who have the condition and ineffective in those who do not, and pays little regard to the general health status of the patient, complications from operation or shunt related complications such as shunt infections or non-functioning shunts. Alternatively, if a V-P shunt is successful or unsuccessful, pathological diagnosis is desirable if adequate conclusions are to be reached regarding the benefits of shunting for the various causes of hydrocephalus. Despite these intrinsic difficulties, the CSF volume studies may provide diagnostic or prognostic information.

Natural History.

It is difficult to draw any conclusions regarding the natural history of NPH from such small numbers, however in the 2 patients who did not have operation the total cranial CSF volume increased by between 8-11%/ year and the ventricular and V:CS ratio also increased. This percentage increase in total CSF per year was greater than that of the 25 age related normals (females 6%/yr., males 7.9%/yr.). The increase in total CSF volume was associated with a slowly progresssive deterioration in higher function but without worsening of the ataxia or developing

incontinence. Hughes et al.[112] found that 50% of patients with NPH remained clinically unchanged for 36 months. The patient who had ventricular pressure monitoring had a reduction in all cranial CSF volume compartments and in the V:CS ratio, despite not being shunted, had an improvement in his gait following this procedure but without improvement in his higher cortical function. Improvement in symptoms of NPH following lumbar puncture has been previously recognised and may be due to an increase in the frontal and temporal grey matter blood flow after CSF removal.

Diagnosis.

A ventricular:cortical sulcal ratio of greater than 0.34 separated all patients with NPH from normals and patients with dementia of other cause, with the exception one patient ([13]), who on retrospective interpretation of the CT scan was felt to have hydrocephalus ex vacuo (generalised atrophy) rather than NPH and who continued to deteriorate despite having a V-P shunt. The selection of patients for further investigation or V-P shunting would be more reliable if CSF volume analyses and in particular V:CS ratios and cortical sulcal CSF volumes were analysed. In the only studies that compared CT features with CSF dynamics,[23,128] the absence of cortical sulci greater than 3mm. on CT was the only feature that correlated with a decreased CSF absorption. Patients with V:CS ratios of more than 1.00, or cortical sulcal volumes less than 100mls. showed the most dramatic improvement assuming the patient did not have a post-operative subdural. The findings are in agreement with those of Black[17] who demonstrated that 85% of patients with large ventricles and little cortical atrophy on CT had a good outcome post-operatively. The loss of the " V shaped " cut-off of CSF at the foramen magnum, in favour of a smooth concave margin may well reflect either adhesions at the foramen magnum which could be of aetiological importance or alternatively may represent a functional disturbance of flow of CSF through the foramen magnum with increase in signal as the CSF is not as pulsatile. The only other time this appearance on the CSF volume sequence has been seen, apart from NPH, is in a patient with a previously unsuspected Chiari type 1 malformation. All SE80/2000 images in these patients demonstrated periventricular high signal areas. These were generally smooth and confluent but 7 also had discrete focal areas separated from the periventricular high signal. The smooth areas are thought to be due to deficient ependyma with

increased water content or decreased lipid content (demyelination) of the periventricular white matter[87] and the discrete focal lesions probable represent demyelination of vascular infarctions.

Prognosis.

Patients with V:CS ratios of more than 1.00, or cortical sulcal volumes less than 100mls. showed the most dramatic improvement assuming the patient did not have a post-operative subdural. The periventricular high signal areas did not resolve in the week after shunting or indeed in 10 cases followed up between 3 months and 1 year after shunting. The discrete high signal areas may represent microvascular infarts due to hypertensive vascular disease which is commonly associated with NPH.[192] It may be that there is a reduction in intensity of the periventricular high signal areas rather than the distribution. This was not visually obvious but multi-echo sequences such as the ME6 (Carr-Purcell sequences) would be required to calculate the T1 and T2 relaxation times of the periventricular white matter. Discrete high signal areas were not more common in patients who did less well post-operatively and they have been found in elderly normal subjects and in patients with dementia. Periventricular high signal areas do not therefore appear to offer any pre-operative indication of those patients who are likely to benefit from surgery in contrast to the claims of Borgesen[24] regarding CT periventricular low density.

The volume of the ventricles decreased in all the patients re-imaged one week post-operatively. There was no clear relationship between the magnitude of reduction in ventricular size and the clinical outcome. Black et al.[19] demonstrated that only 1 of 11 patients improved when the ventricles appeared the same size after shunting. Thus if ventricular volume does not alter after V-P shunting, the prognosis is likely to be worse. Black[18] also stressed the importance of developing V-P shunts that can be adjusted to suit individual pressures thus avoiding under-draining and over-draining with subdurals. A new type of shunt has been developed which aims to provide CSF drainage at the same rate as CSF secretion within a physiological ICP range.[190] A reduction in total cranial or ventricular CSF volume following V-P shunt confirms that the shunt has been functioning but if the V:CS ratio increases post-operatively or the volume of total cranial CSF falls markedly, one should be suspicious of overdraining of CSF resulting in subdural haematomas. Follow-up CSF volume scans may suggest shunt blockage or

non-functioning shunts and subdural collections are easily identified on the coronal pilot scan. There is no doubt that the CSF volume studies will be of value in accurately following the natural history of un-operated NPH, in the diagnosis of NPH by V:CS ratio and in the management and subsequent follow-up of patients. It is also clear that MRI is more sensitive at identifying the presence of subdural collections which although not always associated with a poor outcome may be influencing what may have been an excellent outcome. One cannot fully assess the prognostic importance of pre-operative investigations unless complications of operation are excluded. MRI and the CSF volume sequences in particular will make the follow up of patients with NPH more accurate and objective.

5.4. OBSTRUCTIVE HYDROCEPHALUS

Introduction.

Obstructive hydrocephalus, can be defined as an obstruction to the normal flow of CSF from the ventricular system to the cranial subarachnoid spaces, resulting in dilatation of the ventricles and an elevation of intracranial pressure. Patients generally present with headache suggestive of raised intracranial pressure and papilloedema, possibly with associated posterior fossa or cerebral signs depending on the aetiology, site, and size of lesion causing the obstruction. Cranial CSF volumes may therefore have a role to play, firstly, in the assessment of hydrocephalus for diagnostic, management and research purposes and secondly, to measure the success of post-operative ventricular decompression and to establish what happens to the CSF volume compartments following surgery; i.e. by how much does the ventricular system return towards normal and does brain volume increase after surgery as the raised intracranial pressure is relieved.

Subjects.

Twelve patients with symptoms of raised intracranial pressure and x-ray CT evidence of an obstructive hydrocephalus were studied. The aetiology of the obstruction varied from aqueduct stenosis to posterior fossa mass lesions and extensive craniopharyngioma (Table 14). Six females and 6 males aged from 21 to 70 years were studied. Eight of the patients had a CSF diversion procedure alone, one patient had a V-P shunt insertion and partial resection of a secondary cerebellar tumour deposit and one patient had subtotal removal of an cerebellar astrocytoma. Nine patients had CSF volume studies repeated 4-10 days post-operatively (mean 7 days). Seven of the 9 patients had insertion of right V-P shunt alone, one had V-P shunt with partial excision of a cerebellar secondary deposit and one had subtotal excision of a cerebellar anaplastic astrocytoma without V-P shunting. The individual diagnoses and types of operation are given in table 14. One patient was too uncomfortable post-operatively to lie in the imager and repeat scanning was abandoned. The other two patients were seriously ill, one had an extensive inoperable tumour in the brain

Subj	Age (yrs)	Sex	Total CSF (mls)	Ventric CSF (mls)	C.Sulcal CSF (mls)	V:CS Ratio	Total CSF (mls)	Ventric CSF (mls)	C.Sulcal CSF (mls)	V:CS Ratio
			I----------Pre-operative----------I				I----------Post-operative----------I			
1.	21	m	927.3	748.3	147.7	5.07	931.0	222.0	684.2	0.32
2.	26	m	96.7	44.9	38.6	1.16	129.1	15.3	98.5	0.16
3.	27	f	131.0	82.2	43.9	1.87	-	-	-	-
4.	27	f	102.1	42.9	51.1	0.84	85.2	8.9	67.5	0.13
5.	29	f	157.0	89.7	51.7	1.74	154.6	24.0	106.5	0.23
6.	30	f	348.0	199.0	140.0	1.42	318.0	137.7	170.9	0.81
7.	32	m	149.4	37.6	95.5	0.39	117.3	7.7	98.1	0.08
8.	43	m	170.6	103.8	60.7	1.71	144.4	63.9	56.7	1.13
9.	48	f	172.0	59.3	92.4	0.64	-	-	-	-
10.	56	m	237.1	67.1	142.5	0.47	218.3	44.2	152.4	0.29
11.	61	m	396.4	168.5	181.7	0.93	389.8	22.8	340.6	0.07
12.	70	f	172.0	59.9	109.3	0.55	-	-	-	-

Table 14a. Pre and Post-Operative CSF volume measurements in patients with Obstructive Hydrocephalus.

Subject	Diagnosis	Operation.
1.	Aqueduct Stenosis	Ventriculo-Peritoneal Shunt
2.	Brain Stem Tumour	Ventriculo-Peritoneal Shunt
3.	Pineal Region Tumour	Ventriculo-Peritoneal Shunt
4.	Bilateral Acoustic Neuromas	Ventriculo-Peritoneal Shunt
5.	Cerebellar Secondary Deposit	Ventriculo-Peritoneal Shunt and Partial Excision
6.	Aqueduct Stenosis	Ventriculo-Peritoneal Shunt
7.	?Aqueduct Stenosis	Ventriculo-Peritoneal Shunt
8.	Cerebellar Anaplastic Astrocytoma	Subtotal Excision.
9.	Brain Stem Glioma	No Operation/ Patient Died
10.	Cranio-pharyngioma	Ventriculo-Peritoneal Shunt
11.	Aqueduct Stenosis	Ventriculo-Peritoneal Shunt
12.	Cerebellar Haematoma	No Operation/ Patient Died

Table 14b. Individual diagnoses and type of operation performed.

stem and the other with a cerebellar haematoma was too unwell to undergo surgery. These two patients subsequently died.

Methods.

Two sagittal CSF volume sequences (IRCP 300/400/5000) were performed. The first had a slice select of 240mm, thus giving an image of the total cranial CSF volume. The second scan had a slice select set to a diameter that would include the ventricles and exclude overlying and underlying cortical sulci. The diameter was chosen using a coronal pilot scan (SE 40/20) and varied from patient to patient. In order that the thinner CSF volume sequence included all ventricular CSF, there was inevitably also inclusion of some CSF from the Sylvian fissures in patients with grossly dilated ventricles. This introduced a slight error in measurement which would overestimate ventricular volume and reduce cortical sulcal CSF volume, thus producing an overestimate of the ventricular: cortical sulcal ratio. This error was minimised by precise positioning of the patient, using overhead lasers, prior to imaging and careful delineation of the region of interest taken to include the cerebral ventricles on the thinner sagittal CSF volume image.

Results.

Total cranial CSF volumes ranged from 96.7mls. to 927.3mls. and the ventricular CSF volumes were increased in every patient (37.6mls.-748.3mls.). The V:CS ratio was also increased in all patients (0.47-5.07), reflecting the dilatation of the ventricles with relative reduction in cortical sulcal CSF volume as a compensatory mechanism, to maintain a normal intracranial volume. In patients where the obstruction was known or presumed to have been present for some time (Table 14a. [1],[6],[10], and [11]), the cortical sulcal volumes were within the accepted normal range. Total cranial and ventricular CSF volumes were markedly increased in 3 patients with hydrocephalus due to definite aqueduct stenosis. In the remaining 9 patients the total cranial CSF volumes were not grossly increased (Table 14a). When the total cranial CSF volume, the ventricular CSF volume and the V:CS ratio were increased, patients had more prolonged symptomatic histories

but less severe symptoms and did not have papilloedema. In contrast, when the total cranial CSF volume was not significantly increased for the patients age, yet the cortical sulcal CSF volume was significantly decreased and the cortical sulcal ratio was high (> 0.8), patients had more acute symptomatic histories and severe papilloedema. Two of the patients in this later group had emergency operations because of signs of coning (Table 14 [5] and [8]).

Nine of the 12 patients had post-operative imaging performed one week after surgery. There was a significant clinical improvement in all patients where the total cranial CSF volume decreased following operation. The volume of the cerebral ventricles reduced considerably after V-P shunting in all cases demonstrating that the operations had been sucessful. The range of reduction in ventricular CSF volume ranged from 22.9mls. to 526.3mls. Cortical sulcal volumes increased post-operatively in 8 of the 9 patients (range 2.6mls.- 536.5mls.), but decreased by 4mls. in the patient who had subtotal resection of a cerebellar astrocytoma. Ventricular:cortical sulcal ratios reduced considerably following V-P shunting in all patients with 6 decreasing to less than 0.3 (Figure 27). In three cases the ventricular:cortical sulcal ratio remained more than 0.3.; these cases included the patient who underwent subtotal cerebellar resection and two of the patients with aqueduct stenosis. Moderate bilateral subdural haematomas developed post-operatively in the one patient with definite aqueduct stenosis (Table 14 [1]) and the subdural collections were reflected by the dramatic reduction in ventricular CSF volume and V:CS ratio following insertion of the V-P shunt. The remaining 8 patients made a good post-operative symptomatic recovery.

Discussion.

The CSF volume sequences were helpful in that they demonstrated dilated ventricles in all cases when compared with the normal control population, thus confirming the presence of hydrocephalus. The ventricular:cortical sulcal ratio was also increased in each patient when compared with healthy subjects. Markedly raised total, ventricular and ventricular;cortical sulcal ratios were found in patients with a more prolonged history, while in contrast, patients who had decreased

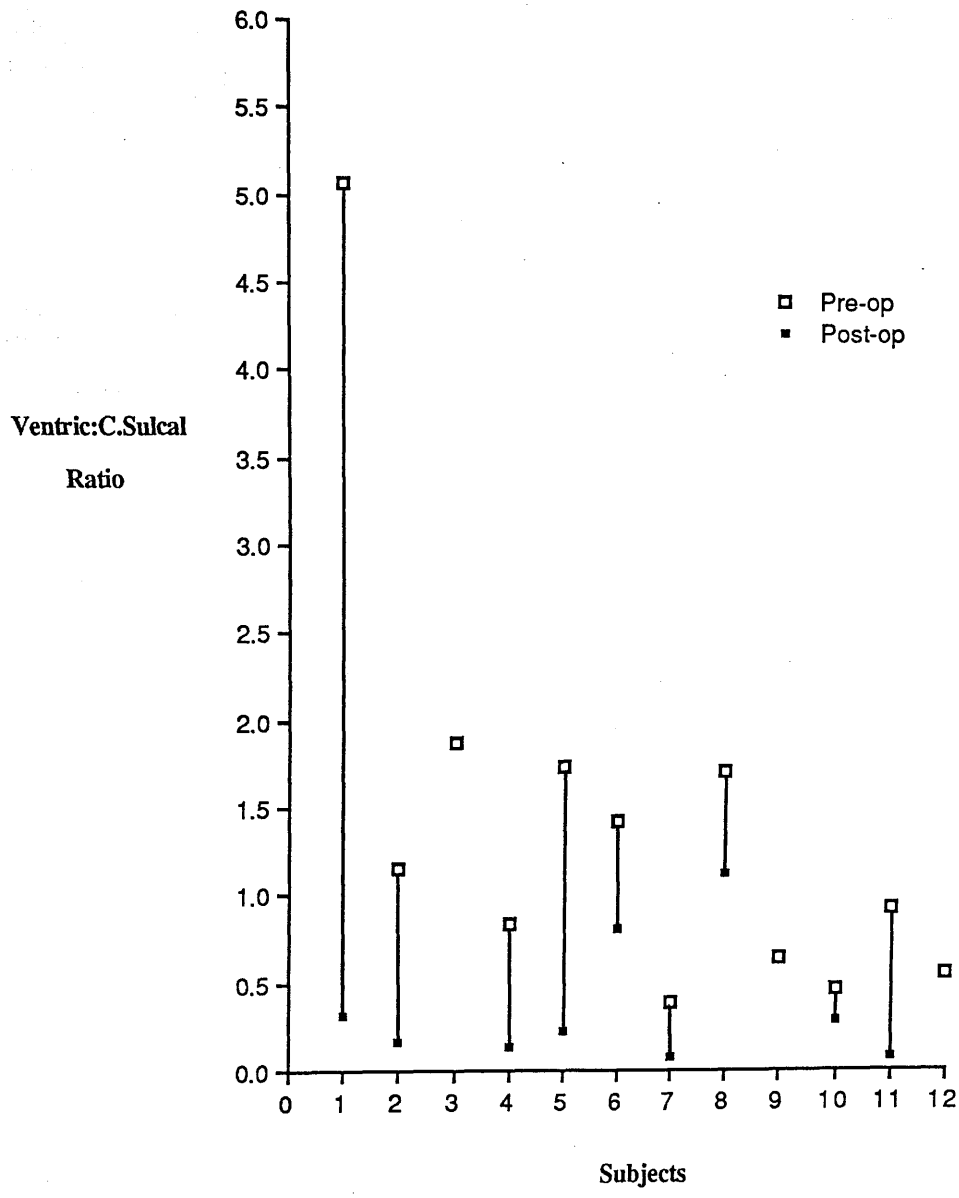

Figure 27. Changes in V:CS ratio following V-P shunting in patients with Obstructive Hydrocephalus.

cortical sulcal CSF volumes and an increased V:CS ratio (> 0.8) had more recent onset of symptoms and severe papilloedema. These measures may be a helpful factor for staging or grading severity and chronicity and in the follow-up of less severely affected patients when the timing of operation may be important.

Cortical sulcal volumes increased post-operatively in all but one patient. This patient had subtotal resection of a cerebellar astrocytoma and it is likely that the CSF was contaminated with blood. This would result in a reduction in signal from CSF and an underestimate of the true volume (Chapter 2.7.). The reduction in intracranial pressure with relief of compression of the cortex against the dura over the convexity was reflected in the decrease in V:CS ratio post-operatively. However the mechanism whereby the CSF manages to reach the cortical sulci following V-P shunting alone (without primary operation on the lesion causing ventricular obstruction) remains unclear. It is possible that this may occur at the time of operation or less likely from tracking of CSF from the ventricles around the shunt or directly through the interstitial spaces of the brain. Alternatively, as the intracranial pressure reduces, CSF may be displaced into the head from the spinal sub-arachnoid spaces or CSF may still be secreted from choroid plexus or ependyma distal to the site of obstruction. As intracranial pressure is reduced so absorption of CSF will also be reduced as this is pressure dependent.[152]

The type of operation and timing of surgery in patients with obstructive "high pressure" hydrocephalus and a posterior fossa mass is often debated. Operations directed at the primary cause of the obstruction may make ventriculo-peritoneal shunting unnecessary, thus avoiding possible complications such as subdural haematoma, post-operative upward herniation of the tumour through the tentorium cerebellum (if the obstructing lesion is situated in the anterior cerebellum), dissemination of malignant cells into the peritoneum or shunt infection or malfunction. Alternatively, ventriculo-peritoneal shunting may be necessary as an emergency procedure if the patient's condition is rapidly deteriorating and there are signs of coning, as an elective procedure before proceeding to the definitive operation, or as a palliative procedure. The decision concerning the best surgical management will depend on the clinical assessment and the radiological or MRI appearance of the obstructing lesion. CSF volumes measurements

may be of value when balancing the pros and cons of these procedures. In patients with obstructive hydrocephalus, ventricular CSF volume will increase and cortical sulcal and posterior fossa CSF will be displaced into the spinal subarachnoid space or will be absorbed more quickly due to the elevation in intracranial pressure. A normal or reduced cortical sulcal volume in the presence of a high V:CS ratio suggests that there is urgency as the remaining compensatory CSF reserve is minimal and coning may quickly ensue.

5.5. BENIGN INTRACRANIAL HYPERTENSION.

Introduction.

The term "Benign Intracranial Hypertension" (BIH) was coined by Foley in 1955[74] to describe patients with raised intracranial pressure without an intracranial mass lesion. He purposely excluded patients with "Otitic Hydrocephalus" due to lateral sinus thrombosis. Of the 60 patients with BIH without an obvious antecedent infection, described by Foley, over 90% were female.

Some studies have demonstrated a reduction in lateral ventricular size and a narrowed slit-like third ventricle in women with BIH.[52,179] It has been suggested that this is due to brain swelling, because of excess of intracerebral extracellular fluid, resulting in raised intracranial pressure. Others favour CSF obstruction and they suggest that the high percentage of small ventricles is simply a reflection of the predominantly young female population studied and support this theory with studies of patients with BIH who have normal or enlarged ventricles on x-ray CT scanning. As Magnetic Resonance Imaging is highly sensitive to changes in brain water content and can identify changes of cerebral oedema before they become evident on CT scanning, it may be useful in the diagnosis of BIH if it is due to increased intracerebral extracellular fluid content. In addition, if the brain is diffusely swollen one might expect the total cranial CSF volume or cortical sulcal volume to be reduced as a compensatory mechanism ;unless there is also increased outflow resistance due to increased venous sinus pressure. CSF volume measurement by MRI provides a more accurate measure of ventricular CSF volume and also enables the measurement of total cranial and cortical sulcal CSF volume for the first time in this condition. In order to investigate the possibility of reduced cranial CSF volume a number of patients with definite and probable BIH were studied and compared with the volume measurements in normal controls of similar sex and age.

Subjects.

Patients were considered to have "definite" BIH only if they had all of the following features:

a) Headaches +/- visual symptoms (obscurations or diplopia)

b) Papilloedema with enlarged blind spots

c) X-ray CT scan and MRI excluding a space occupying lesion.

d) Raised intracranial pressure (>18cm CSF) on single LP pressure recording or 24hr. lumbar pressure monitoring.

Patients were considered to have "probable" BIH if they had headaches with a normal CT scan, an elevated single lumbar pressure recording but without evidence of papilloedema and enlarged blind spots. Eight patients with definite and 8 patients with probable BIH were identified over an 18 month period. The mean age of patients in the "definite" group was 28.1 years compared with 25.9 years in the "probable" BIH group. There were 14 females (aged 14-46 years; mean 27 years) and 2 males aged 25 and 51 years. Seven of the women had definite BIH and 7 fulfilled the criteria for "probable" BIH. All the females were over their ideal weight for height, 13 were greater than 10% over their ideal and 9 could be defined as "obese" (greater than 20% over ideal weight for height). The 25 year old man with definite BIH had angiographically proven partial superior sinus thrombosis and the 50 year old male with probable BIH had significant systemic hypertension. MRI scans were performed before lumbar puncture/pressure monitoring and either before or shortly after starting treatment and while still symptomatic.

Follow-up.

Seven of the patients (6 with "definite" BIH and 1 with "probable" BIH) were re-imaged after an interval of 3-15 months (mean 11.7 months). Two patients were mildly symptomatic and neither had papilloedema. Of the remainder 2 were still on treatment and 3 were asymptomatic and not taking medication.

Methods.

CSF volumes were measured as described in Chapter 3. A 240mm thick slice and a narrower slice, to enclose the ventricles but exclude overlying and underlying cortical sulci, were acquired.

After "image non uniformity" correction, the total, cortical sulcal and ventricular CSF volumes were measured and the ventricular:cortical sulcal ratio was calculated. Additional scans (SE80/2000 - 8mm axial slices) were performed to exclude a space occupying lesion.

Results.

The total cranial CSF volumes in women ranged from 54mls to 147.9 mls. and the total cranial, ventricular and cortical sulcal volumes and the V:CS ratios were smaller in the "probable" group than the "definite" group but this may reflect the age differences between the groups ("probable" mean age 25.9yrs.; "definite" mean age 28.1yrs.). The individual results are shown in Table 15. The scatter plots of female patients with BIH compared with normal female volunteers demonstrate that some of the patients with "definite" or "probable" BIH have significantly less total cranial and ventricular CSF than aged matched controls but this is by no means always the case and there is significant overlap between normals and patients with BIH (Figure 28 & 29). The best distinguishing factors between patients with BIH and normals in this study was the ventricular volume. However even this measurement failed to separate approximately 40% of patients who had ventricular CSF volumes within the limits of our healthy subjects. The mean total cranial CSF in "obese" females was less than the mean volume of the women who were overweight but non "obese", however the mean age was also less in this group.

The male with acute partial superior sagittal sinus thrombosis had a large ventricular volume and ventricular:cortical sulcal ratio (41.9mls and 0.59 respectively). On follow up scanning 12 months later ventricular volume had decreased to 23.3mls and the V:CS ratio had fallen to 0.18. The 50 year old male with "probable" BIH had CSF volume measurements that fell within the normal range.

Follow Up.

Total cranial CSF volumes increased in all patients who were rescanned after a variable interval of time on treatment (3 to 17 months) (Table 16). One of the two women who continued to be symptomatic (Table 16; [2]) had a minimal reduction in ventricular

Definite Benign Intracranial Hypertension.

Subj	Age (yrs)	Sex	Total CSF (mls)	Ventric CSF (mls)	C.Sulcal CSF (mls)	V:CS Ratio	>20% overweight
1.	15	f	98.6	3.9	87.9	0.04	
2.	16	f	67.7	6.9	48.3	0.14	
3.	25	f	147.9	13.0	119.7	0.11	*
4.	28	f	64.5	7.8	50.2	0.16	*
5.	35	f	114.6	8.9	90.8	0.10	*
6.	37	f	141.7	7.8	121.1	0.06	
7.	41	f	54.0	3.6	46.9	0.08	*
8.	25	m	123.7	41.9	70.6	0.59	

Probable Benign Intracranial Hypertension

Subj	Age (yrs)	Sex	Total CSF (mls)	Ventric CSF (mls)	C.Sulcal CSF (mls)	V:CS Ratio	>20% overweight
9.	14	f	62.9	3.8	48.2	0.08	*
10.	15	f	61.9	4.8	50.7	0.09	*
11.	22	f	54.8	4.2	44.1	0.09	*
12.	23	f	108.9	3.6	95.7	0.04	*
13.	28	f	62.4	4.2	45.9	0.09	*
14.	33	f	105.2	8.6	78.6	0.11	
15.	46	f	83.2	3.3	68.0	0.05	
16.	53	m	163.8	9.7	140.8	0.07	

Table 15. Cranial CSF volume measurements in patients with definite and probable Benign Intracranial Hypertension.

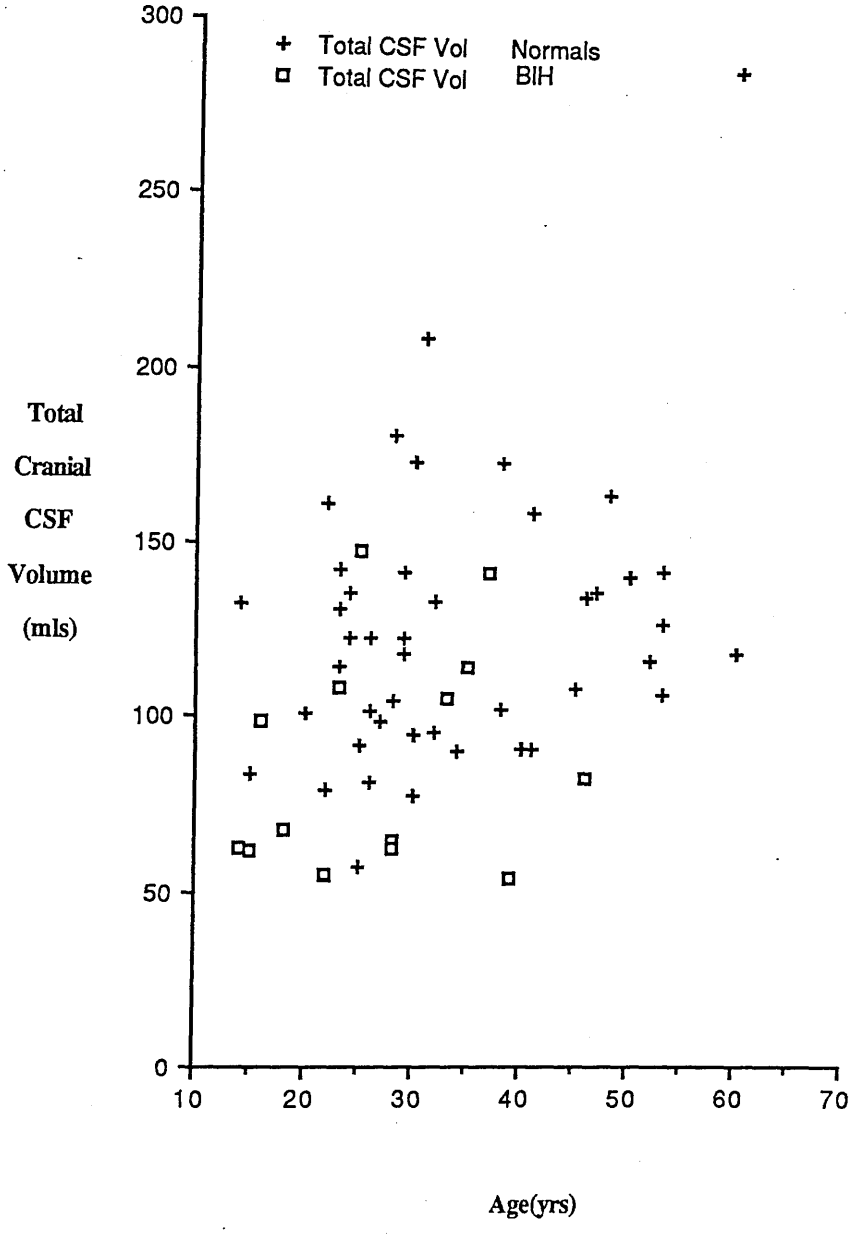

Figure 28. Total cranial CSF volume measurements in patients with BIH and in healthy subjects.

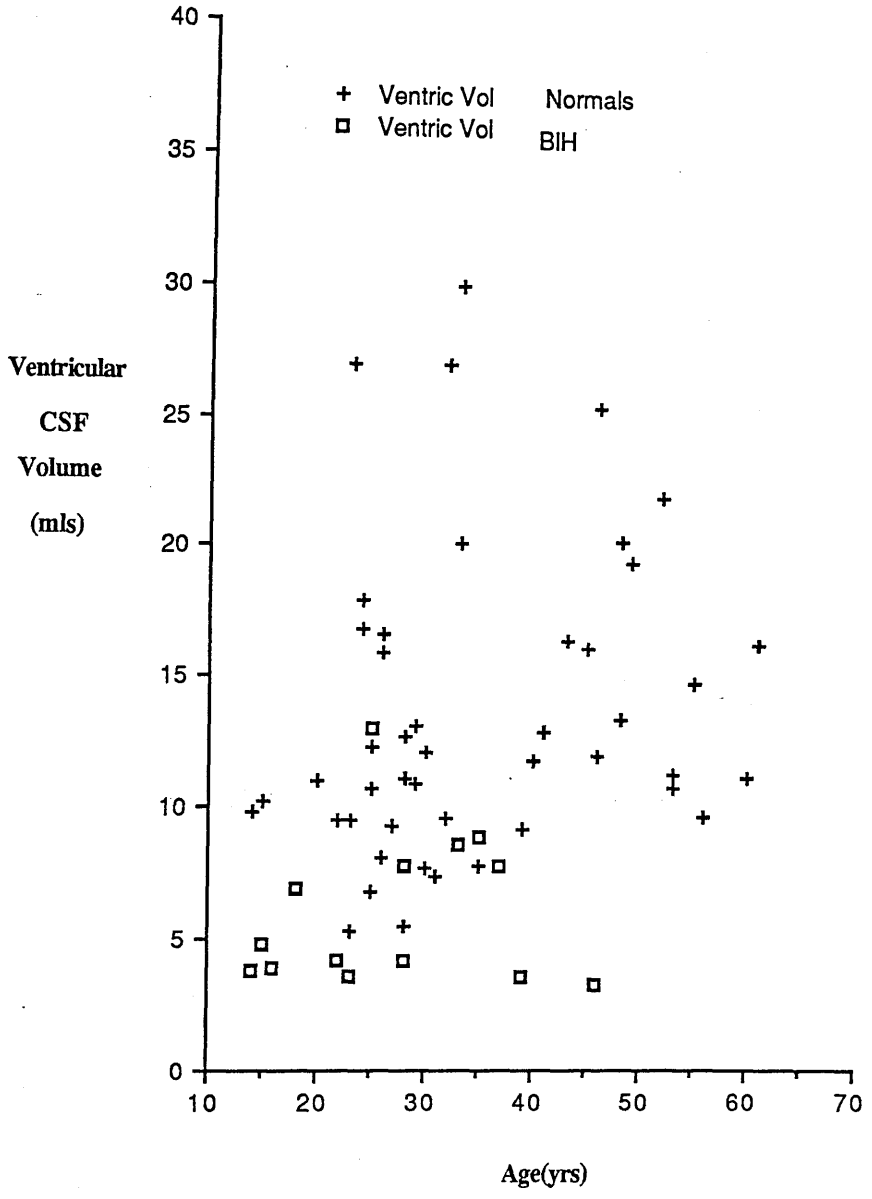

Figure 29. Ventricular CSF volume measurements in patients with BIH and in healthy subjects.

Benign Intracranial Hypertension.

Subj	Age (yrs)	Sex	Interval between scans (mths)	Total CSF (mls)		Ventric CSF (mls)		C.Sulcal CSF (mls)		V:CS Ratio	
				1st	2nd	1st	2nd	1st	2nd	1st	2nd
1.	15	f	17	98.6	126.2	3.9	7.3	87.9	101.2	0.04	0.07
2.	16	f	3	67.7	85.2	6.9	6.8	48.3	70.0	0.14	0.10
3.	28	f	15	64.5	119.6	7.8	18.1	50.2	90.2	0.16	0.20
4.	33	f	14	105.2	133.1	8.6	12.1	78.6	102.9	0.11	0.12
5.	37	f	8	141.9	144.9	7.8	8.1	121.1	105.8	0.06	0.08
6.	41	f	11	54.0	135.8	3.6	10.1	46.9	110.8	0.08	0.09
7.	25	m	14	123.7	180.7	41.9	23.3	70.6	131.5	0.60	0.18

Table 16. Cranial CSF volume measurements before and after treatment in patients with Benign Intracranial Hypertension.

CSF volume while the ventricular volumes in the remaining five increased. This symptomatic patient had a reduction in V:CS ratio while the others had an increased V:CS ratio.

Structural Images (SE80/2000).

All patients had normal high definition SE 80/2000 images. There was no evidence of localised or generalised increase in signal to suggest increased water content and in particular the periventricular white matter did not have the abnormal appearance that is often seen in obstructive or "normal pressure" hydrocephalus where CSF diffuses into the extracellular spaces in the periventricular regions.

Discussion.

Three possible mechanisms are hypothesised for the development of raised intracranial pressure in benign intracranial hypertension: Firstly, CSF volume is increased due to a reduction in absorption of CSF or an increase in production of CSF; secondly, there is an increase in brain volume due to cerebral oedema; and lastly there is increased intracranial blood volume.

A)Increased CSF volume.

Johnston and Paterson suggested that there is reduced CSF absorption because of increased cerebral venous sinus pressure.[120] The increase in venous pressure causes an increase in CSF volume which is accommodated in distended subarachnoid spaces, and results in raised intracranial pressure. To support this they quote the work of Barcaw and Greer[12] who demonstrated delayed flow of CSF on isotope cisternography and reduced absorption of isotopes in two of three patients with BIH suggesting an abnormality of CSF absorption in BIH. The observations of Davidoff LM[55] that the cortical sub-arachnoid spaces are commonly distended with CSF and the frequent association of BIH with disturbances of clotting mechanisms also support reduced CSF absorption and thus presumably increased total CSF volume. Finally, venous sinus thrombosis eg during pregnancy or associated with oral contraceptive use or with transverse sinus thrombosis associated with middle ear infection ("Otitic Hydrocephalus") is a well recognised cause of raised intracranial pressure without evidence of a space occupying lesion. In a minority of cases there may be an overproduction of CSF by the choroid plexus and cases of BIH have been reported in association with choroid plexus

papilloma and with Vitamin A toxicity, both of which may increase CSF production. However, overproduction of CSF is considered to be a very rare cause of BIH.

The present study demonstrates that the total cranial and ventricular CSF volumes are either normal or decreased in idiopathic BIH. Where partial sagittal sinus thrombosis results in raised intracranial pressure the ventricular CSF volume may be increased.

B)Increased brain volume.

Cerebral swelling has been implicated as a cause of BIH particularly when this occurs in young women and is often associated with obesity and menstrual irregularities. This is supported by studies that demonstrate smaller lateral ventricular size/volume in BIH than in comparable controls.[179] The third ventricle is often almost obliterated, a sign also found in patients with diffuse head injury where it acts as a reliable marker for cerebral oedema. The often quoted cerebral oedema found in a brain biopsy study of patients assumed to have BIH is used to support this theory.[189] However, it is worth noting that the cases described by Sahs and Joynt were of "brain swelling of unknown cause" and not classical BIH as described by Foley.[74] Foley did not find evidence of oedema at post-mortem in 3 patients with BIH who died from other causes. In their paper, Sahs and Joynt[189] described 3 cases in detail. One patient was a 17 year old male who had a recent right otitis media, headache and seizures, the second was a female with a filling defect in the ventricle which turned out to be a fresh clot and the third patient was a 58 year old woman with proven superior sagittal sinus thrombosis. All had undergone ventriculography some days prior to cerebral biopsy and there would almost certainly have been some herniation of the brain through the burr hole site because of the raised intracranial pressure. Local oedema may then have occurred because of this. Finally, the brain swelling was examined only by light microscopy and described as extensive and both intracellular and extracellular. Such changes, if present, would result in abnormalities on EEG, and yet the EEG is not abnormal in BIH.[74] MRI is very sensitive to changes in brain water content and animal models of vasogenic and cytotoxic oedema show dramatic changes in signal compared with that from normal brain.[13] Increased signal from white matter indicating an increased water content is frequently seen on MR images in patients with cerebral tumours, obstructive hydrocephalus, normal pressure hydrocephalus, head injury

and even in elderly normal subjects where there is increased extracellular fluid space between axons.[87] The normal EEG and MRI findings and the normal brain biopsy findings of Foley would strongly suggest that there is no intracellular or extracellular cerebral oedema.

C)Increased Blood Volume.

There is good evidence to support an increase in cerebral blood vloume in BIH. In 1937, Dandy[52] initially hypothesised an increased blood volume in BIH and since then Mathew[151] and Raichle[178] have confirmed this by radio-isotope techniques. In 1975, Mathew serially measured regional cerebral blood flow and cerebral blood volume using intra-arterial ^{133}Xe and ^{99m}Tc radio-isotopes and a gamma camera in two patients with BIH. They demonstrated a gross increase in cerebral blood volume in the acute stages of BIH. Raichle[178] used intra-carotid injection of ^{15}O-labelled carboxyhaemoglobin in 8 patients and stimulated X-ray fluorescence[170] in 9 patients with BIH in order to measure cerebral blood volume. They also found a significant increase in CBV and concluded that the increase was predominantly due to dilatation of the intraparenchymal blood vessels. Lastly, oestrogens in oral contraceptives are known to cause loss of smooth muscle vascular tone[84] which may result in an increase in CBV. There are well known associations between BIH and oral contraceptives, pregnancy and imbalance of sex hormones[169] and CSF oestrone levels have been found to be raised in obese young women with BIH.[63]

Significance of the present study

The results of the present study support the findings of others[52,179] who demonstrated a reduction in ventricular CSF volume, in the acute phase, in many but not all patients with established BIH and an increase in ventricular CSF volume in all asymptomatic patients on treatment for BIH. However, the male with partial superior sagittal sinus thrombosis had enlarged ventricular volumes in the acute phase which then settled to within normal limits as the symptoms settled. This may reflect a different mechanism from those females with idiopathic BIH. Bering[16] suggested that where there was a blockage to CSF drainage, the intraventricular pulse pressure rose causing dilatation of the ventricles, similar to NPH. For the first time, it has now been possible to measure the total and cortical sulcal volumes in BIH and this study shows that the total and cortical sulcal CSF volumes are

either the same or smaller than age matched controls. This does not support the hypothesis that the cortical sulcal spaces are distended.[55] Superficially it would appear to lend support to the theory that the brain is swollen. However there is no evidence of increased intracellular or extracellular water content within the white matter of the brain in SE 80/2000 images in contrast to the findings frequently seen in acute head injury with diffuse axonal injury due to shearing forces, or in obstructive hydrocephalus. The lack of symptoms suggesting intracellular oedema and the normal EEG and MRI appearances in BIH would strongly suggest that the brain is not oedematous either intracellularly or extracellularly.

Could small ventricles predispose to the development of BIH?

There does appear to be a relationship between small ventricles and BIH and it has been assumed that the small ventricles are the result of increased pressure due to cerebral oedema. However, alternatively could young women with small ventricles be predisposed to developing BIH? There are striking similarities between BIH and altitudinal sickness.[39] Altitudinal or acute mountain sickness presents with headache and nausea caused by raised intracranial pressure. It is more common in women and is inversely correlated with age.[97] A well conducted study by Cummins[47] of 10 climbers in the Himalayas, 3 of whom had intracranial pressure monitoring ,demonstrated that it was the climbers that had small ventricles on CT scans performed at sea level before the climb that developed symptoms, signs and elevated ICP recordings above 15,500ft. Headaches of acute mountain sickness are prevented by prophalactic acetazolamide and gradual acclimatization, and respond quickly to evacuation to lower altitude and oxygen. Occasionally steroids are neccessary.[71] These factors cause a reduction in cerebral blood volume and therefore cerebral vasodilatation rather than cerebral oedema could be the underlying mechanism.[188] It is known that CO_2 retention with respiratory acidosis can lead to raised intracranial pressure and papilloedema.[156] If cerebral vasodilatation is severe and prolonged frank cerebral oedema with widespread petechiae and gross haemorrhage can result. Plateau waves during REM sleep probably occur as a result of changes in the cerebral circulation with acute increase in CBV.[113,183]

In the studies outlined in chapter 4.4., subjects with a small resting

total cranial CSF volume tended to have smaller changes in cranial CSF volume, following CO_2 and O_2 inhalation, than those patients with larger resting total cranial CSF volumes. This would suggest that subjects with small cranial CSF volumes may be less able to respond to intracranial vasodilatation by volume storage and volume compensation. Subjects with small ventricles and low total cranial volumes may possibly be at increased risk of developing raised intracranial pressure and thus BIH. Sklar et al.[194] demonstrated that the elastic slope that related the logarithm of intracranial pressure to volume is significantly lower in patients with BIH, than in patients with large ventricles. This may also help to explain why BIH is uncommon in the elderly and in males where the total and ventricular CSF volumes are larger and why BIH may resolve spontaneously with time, as ventricular and total cranial CSF volumes increase with normal aging.

Could BIH be due to increased cerebral blood volume?

Increased cerebral blood volume can result in raised intracranial pressure. Could the brain be engorged, as suggested by Dandy?[52] Brain engorgement and brain oedema are different processes. Brain engorgement, due to increased cerebral blood volume, as a result of relative or complete obstruction of the cerebral venous sinuses or dilatation of the arteries eg due to hypercapnia, therefore raised intracranial pressure and brain swelling may occur without brain oedema. This could account for the normal MRI findings yet smaller ventricles than average.

Finally, could the obesity be related to the CSF volume findings? Dilated ventricles and possibly cortical atrophy are known to occur in patients with anorexia nervosa and we found an unexpected degree of cerebral atrophy in a subject who had been thyrotoxic suggesting that the atrophy could be related to catabolic rate. It is possible that the inverse is also true and obesity is related to small total and ventricular CSF volumes. Reid et al.[180] found that persisting small ventricular volume correlated with persisting symptoms and signs and with persisting obesity. Weisberg[215] found that 90% of patients with BIH whose symptoms lasted more than 12 months were obese, compared with only 33% of those whose symptoms settled within 3 months. There does therefore appear to be a relationship between obesity, ventricular volume and symptomatic BIH.

This study has demonstrated small or normal total cranial and

ventricular CSF volume in patients with idiopathic BIH and has not been able to demonstrate intracerebral oedema in any patient. This would suggest that there must be an increase in cerebral blood volume. The primary initiating factor in development of BIH still remains obscure but may well be multifactorial. It is possible that young obese women, perhaps with small ventricles at the outset and poor CSF compensatory reserve to changes in blood volume, have an increase in cerebral blood volume which in turn produces brain engorgement and increased venous outflow pressures resulting in the symptoms and signs of raised intracranial pressure.

It is important to realise that while the majority of patients with BIH may have small ventricles, a significant proportion are within the normal range. Normal CSF volume measurements therefore do not exclude this diagnosis, and it is possible that by ignoring this point, patients with "probable" BIH may be missed because investigations are taken no further. Indeed this may well have influenced the "probable" group in this study. The CSF volume sequences are unlikely to be of diagnostic importance in the individual cases of BIH, in view of the overlap, but they may still have an important role to play in determining the underlying physiological processes and should be used in conjunction with other haemodynamic investigations for BIH.

5.6. SUMMARY

The aim of this chapter was to determine if measurement of the cranial CSF volume had potentially important research uses or implications for diagnosis or management of certain neurological disorders where the CSF volumes or dynamics were altered.

In the preliminary study of patients with dementia cranial CSF volumes were frequently increased when compared the age related healthy subjects with normal intellect and memory. In particular, the ventricular volumes were often greater in patients with dementia, especially if the dementia started before 65 years of age (patients under 70 when examined). There were no clear differences between the CSF volumes of patients with dementia that had started after 65 years of age (patients over 70 when examined) and those of intellectually normal elderly subjects. These findings would be consistent with post-mortem studies of brain atrophy of patients with Alzheimer's disease and could reflect the global reduction in cholinergic receptors in early onset Alzheimer's disease compared with the more focal decrease in cholinergic markers in late onset Alzheimer's disease. All patients with dementia in this study had a V:CS ratio less than 0.33. This was retrospectively found to be useful in separating patients with dementia of Alzheimer's type or multi-infarct dementia from patients with NPH. Statistical confirmation of these preliminary observations, in patients with dementia, would require a much larger study with patients categorised for age, sex, type of dementia, severity of disease, length of history and other relevant past history. From the initial pilot study , it would appear that there was a significant overlap between normal subjects and patients with dementia. Movement artefacts on the scans of demented patients often made interpretation of the scan difficult and measurement of CSF volumes less accurate.

The value of CSF volume measurements are potentially most important in the diagnosis and management of patients with NPH. The V:CS ratio was increased in all patients with definite NPH (> 0.34). This simple non invasive investigation may not only confirm the clinically suspected cases of NPH but also may be important in predicting which patients should respond best to V-P shunting (V:CS ratio greater than 1.00). In cases where diagnostic uncertainty remains objective assessment of the total cranial, ventricular and cortical sulcal CSF volume and the V:CS

ratio should help to identify which patients have continuing CSF haemodynamic disturbances. Further work is neccessary to confirm these findings and to compare the diagnostic and predictive value of CSF volume measurements with other more established, more invasive but poorly substantiated predictive tests.

In obstructive hydrocephalus it is not suggested that CSF volume measurements replace the more informative diagnostic tests of CT or structural MRI scanning, however they are useful in quantitating the degree of hydrocephalus. This study also demonstrates that when the total cranial and cortical sulcal volumes are small and the V:CS ratio is greater than 0.8, the hydrocephalus is of recent onset. These findings may identify the cases where early surgery is advisable. In more chronic cases, total cranial and cortical sulcal CSF volumes are normal or increased and in these cases it may be possible to perform serial CSF volume measurements to help decide when surgery is indicated.

The present study has confirmed that the ventricles are generally smaller in patients with BIH than in the general population. The total cranial and cortical sulcal CSF volumes however are frequently normal. Structural MRI scans fail to demonstrate evidence of cerebral oedema and therefore the increased intracranial pressure is most likely due to increased intracranial blood volume. In some cases with definite BIH the ventricular volumes were within the accepted normal range for age and therefore the CSF volume measurements are unlikely to be of diagnostic value. However, total cranial and ventricular CSF volumes increase as symptoms settle after treatment with e.g. weight reduction and diuretics, and it is possible that serial measurements may be more valuable in monitoring resolution of intracranial hypertension than repeated lumbar punctures. Further work will be required to substantiate this.

There are several other neurological or neurosurgical conditions, that have not been covered in this thesis, where measurement of cranial CSF volume may have research potential. More work is required on the relationship of cranial CSF volume to intracranial pressure and intracranial blood volume in conditions where intracranial pressure in elevated such as BIH, obstructive hydrocephalus and head injury. This thesis has been directed at the possible clinical value of accurate CSF volume measurement in man. Future research into the MRI method of measuring CSF volume could equally well be carried out on animal models.

APPENDICES

A. - Basic principles of Magnetic Resonance Imaging.

B. - In vitro relaxation time measurements using the Bruker NMR Spectroscope.

BASIC PRINCIPALS OF MAGNETIC RESONANCE IMAGING (MRI).

It is not possible or neccessary in this thesis to go into the scientific basis of MRI in depth, but an introduction to the basic principles and terms used is helpful. For further information a list of key references is given at the end of this short basic introduction.

Theory.

(Nuclear) Magnetic Resonance Imaging is a method of imaging nuclei that have an uneven number of protons and neutrons and also have the capability to resonate or "spin". The most abundant and the most important nuclei that have these characteristics are hydrogen ions (^1H). Each charged proton that possesses "spin" will produce its own magnetic field and act as a small bar magnet. These are randomly oriented in the body. When placed in a strong magnetic field these magnetic dipoles align in the direction of the main static magnetic field(B_o). The protons can align in "parallel" in a low energy state, or "anti-parallel" in a high energy state. The hydrogen ions "spin" at a particular frequency (Larmor Frequency) depending on the field strength. Hydrogen ion nuclei are abundant in the body (1023 ^1H/cm3 in water) and can not be considered separately. The sum of the individual microscopic directional spins will create a macroscopic magnetic moment(M).

A radiofrequency pulse(RF pulse) at Larmor frequency is applied perpendicular to the static magnetic field B_o (and the magnetic moment (M) of the tissue being imaged). The duration of the pulse can be adjusted to tilt the nuclei through 90^o or 180^o from its previously alignment. During this process the H ions absorb energy. When the RF pulse is stopped, the H ions will relax back to their previous position emitting energy as they do so. This emitted energy is detected by a RF receiver coil.

The time taken for a group of nuclei to return from the longitudinal direction after a 180^o pulse is known as the longitudinal or spin-lattice relaxation time (T_1). This time constant is related to the transfer of energy from excited spinning protons to neighbouring larger molecules that are not resonating.

When the RF pulse is discontinued, the local magnetic field is not

uniform as the individual magnetic fields of neighbouring H ions interact with each other and cause "dephasing" of these spins. As a result the signal received by the RF receiver coil will diminish rapidly with time. The time taken for this to occur is known as the transverse or spin-spin relaxation time (T_2).

The size of the signal picked up by the RF receiver coil will be dependent on the number of nuclei involved (proton density) and the relaxation times of the tissue. The T_1 and T_2 relaxation times are dependent on temperature, magnetic field strength and the tissue in which the H ion is bound. In liquids nuclei are relatively free, therefore T_1 and T_2 will be long. In solids, the nuclei are closer and therefore spin interference effects are greater and consequently T_1 and T_2 will be short.

Pulse Sequences.

Pulse sequences can be designed to provide an image that gives more information about the T_1 of the tissue, than the T_2 (T_1 weighted image) or alternatively more information about the T_2 (T_2 weighted).

Inverse Recovery (IR) pulse sequences can be considered to be T_1 weighted. IR sequences start with a 180° pulse followed by a 90° pulse after a time interval (TI) or "Delay Time". This pair of pulses is then repeated after a defined time interval(TR) or Repetition Time.

Spin Echo (SE) pulse sequences can be considered to be more T_2 weighted when the TR is relatively long compared with the T_1. SE sequences start with a 90° pulse followed by a 180° pulse. If the time interval between the 90° and 180° pulse is x msec, an "echo" will occur x msec after the 180° pulse. The time fom the 90° pulse to the "echo" is called the Echo Time (TE).

The Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence has a 90° pulse followed by a train of 180° pulses at times TE/2, 3/2 x TE, 5/2 x TE etcetera. The T_2 relaxation curves of grey matter, white matter or CSF can be calculated from this sequence.

Abreviations used in the thesis:

NMR Nuclear Magnetic Resonance ("Bruker" Spectrometer (0.14T))

MRI Magnetic Resonance Imager ("Picker" Resistive System (0.15T)

T Tesla:measure of magnetic field strength.(1T = 10 KiloGauss)

SE Spin Echo Sequence

IR Inverse Recovery Sequence

CPMG Carr-Purcell-Meiboom-Gill Sequence

T_1 Spin Lattice or Longitudinal Relaxation Time

T_2 Spin-Spin or Transverse Relaxation Time

TR Repetition Time

TE Echo Time

TI Delay Time

RF Radio-Frequency

CSF Cerebro-Spinal Fluid

pCO_2 Partial pressure of CO_2 (in CSF or blood)

pO_2 Partial pressure of O_2 (in CSF or blood)

IN VITRO RELAXATION TIME MEASUREMENTS USING THE BRUKER NMR SPECTROSCOPE.

In vitro measurements of T_1 and T_2 relaxation times were performed in a Bruker PC6 (Minispec) Nuclear Magnetic Resonance (NMR) non imaging spectroscope (Figure 5). This is a tabletop microprocessor-controlled analyser with a 0.14T permanent magnet that operates at 6.0 MHz. The magnetic field strength is very similar to that of the Magnetic Resonance Imager(0.15T), which operates at 6.4 MHz. and relaxation times in vitro and in vivo should produce comparable results.

a) Magnet Module.

The magnet module consists of the permanent magnet, magnetic field correction coils, magnet-temperature control circuits and heaters and the probe head and radiofrequency (RF) transmitter/receiver coil.

b) Control Module.

The control module contains the power supply, the RF circuitry neccessary for generating the correct RF pulse (6 MHz) and the microprocessor. The microprocessor controls the operation depending on the program punched in on the keypad by the operator. Automated T_1 and T_2 measurements of samples can be obtained from the NMR spectroscope and results are provided on a direct readout, digital display.

c) Pulse Sequences.

T_1 is determined by an Inverse Recovery (IR) pulse sequence using 16 averages and eight variable settings for delay time (TI). T_2 is measured by a Carr-Purcell-Meiboom-Gill (CPMG) sequence with 10 echos and 9 averages. In both circumstances, the repetition time (TR) must be greater than five times the final T_1 value.

d) Method.

The "sample" , is placed in 7.5mm sample tubes and inserted into the magnet module via a port on the top of the unit. It is important that the centre of the sample is at the centre of the coil as the sensitive volume is only +/- 0.6cm. from the centre of the coil. The most reproducible results are obtained if the sample volume is approximately $7mm^3$.

The operator can set a suggested T_1 or T_2 value on the control module and decide the attenuation, number of scans and the relaxation delay time in seconds . A measurement of sample T_1 or T_2 and the degree of error is calculated automatically and printed. These measurements were repeated several times in order to obtain the most accurate recording of T_1 or T_2 with the smallest error.

REFERENCES

REFERENCES.

1. Adamkiewicz A. Die Lehre vom Hindruck und die Pathologie Hirnkompression Sitzungsher. Kaiserl Akad der Wissensch 1883; 88: 11-98. From: Lundberg N. The Saga of the Monro-Kellie Doctrine. In: Ishii S, Nagai H, Brock M eds. Intracranial Pressure V. Berlin: Springer-Verlag, 1983; 68-75.
2. Adams RD, Fisher CM, Hakim S, Ojemann RG, Sweet WH. Symptomatic occult hydrocephalus with "normal" cerebrospinal fluid pressure. N Engl J Med 1965; 273: 117-26.
3. Albert M, Naeser MA, Levine HL, Garvey AJ. Ventricular size in patients with presenile dementia. Arch Neurol 1984; 41: 1258-63.
4. Alksne JF. Headache associated with changes in intracranial pressure. In: Dalessio DJ. ed. Wolff's Headache and other head pain. 4th ed. New York: Oxford University Press, 1980; 301-13.
5. Allen PS, Castro ME, Treiber EO, Lunt JA, Boisvert DPJ. A proton NMR relaxation evaluation of a model of brain oedema fluid. Phys Med Biol 1986; 31(7): 699-711.
6. Anderson M. Normal Pressure Hydrocephalus. Br Med J 1986; 293:837-8
7. Ansell B, Clarke E. Epilepsy and menstruation. The role of water retention. Lancet 1956; 271: 1232-7.
8. Avezaat CJ, Eindjhoven JHM van. Cerebrospinal fluid and pulse pressure and craniospinal dynamics. A Theoretical, clinical and experimental study. Thesis Erasmus University Rotterdam, A Jongbloed en Zoon, The Hague 1984; 63.
9. Avezaat CJ, Eijndhoven JHM van. How does the craniospinal system cope with a disturbance of its volume. In: Miller JD, Teasdale GM, Rowan JO, Galbraith SL, Mendelow AD. eds. Intracranial Pressure VI. Berlin: Springer-Verlag, 1986: 99-104.
10. Baldy RE, Brindley GS, Ewusi-Mensah I et al. A fully-automated computer assisted method of CT brain scan analysis for the measurement of cerebrospinal fluid spaces and brain absorption density. Neuroradiology 1986; 28: 109-17.
11. Banna M. The ventriculo-cephalic ratio on computed tomography. J Can Assoc Radiol 1977; 28: 205-10.
12. Barcaw BL, Greer M. Transport of intrathecal ^{131}I RISA in benign intracranial hypertension. Neurology 1970; 20: 787-90.

13. Barnes D, McDonald WI, Johnson G, Tofts PS, Landon DN. Quantitative nuclear magnetic resonance imaging: characterisation of experimental cerebral oedema. J Neurol Neurosurg Psychiat 1987; 50: 125-33.

14. Barron SA, Jacobs L, Kinkel WR. Changes in size of normal lateral ventricles during ageing determined by computed tomography. Neurology 1976; 26: 1011-3.

15. Bergmann E von. Uber den Hirndruck. Lagenbecks Archiv fur klinische Chirurgie 1885; 32: 705-32. From: Lundberg N. The Saga of the Monro-Kellie Doctrine. In: Ishii S, Nagai H, Brock M. eds. Intracranial Pressure V. Berlin: Springer-Verlag, 1986:99-104.

16. Bering EA. Circulation of cerebrospinal fluid. J Neurosurg 1962; 19(1): 405-13.

17. Black PM. Idiopathic Normal Pressure Hydrocephalus. Results of shunting in 62 patients. J Neurosurg 1980; 53: 371-7.

18. Black PM, Conner ES. Chronic increased intracranial pressure. In: Ashbury A, McKhann G, McDonald WI. eds. Diseases of the Nervous System: Vol II Clinical Neurobiology. London: Heinemann Medical Books, 1986; 87: 1058-60.

19. Black PM, Tzouras A, Ojemann RG. CSF shunts in dementia, incontinence and gait disturbance. Clin Neurosurg 1985; 32: 632-57.

20. Blayo MC. Comparison of cisternal and lumbar CSF pH in high altitude natives. Eur J Physiol 1975; 356: 157-67.

21. Blinkov SM, Glezer II. The human brain in figures and tables. Cambridge: Plenum Press, 1968.

22. Bloch R, Talalla A. A mathematical model of cerebrospinal fluid dynamics. J Neurol Sci 1976; 27: 485-98.

23. Borgesen SE. Conductance to outflow of CSF in Normal Pressure Hydrocephalus. Acta Neurochir(Wein) 1984; 71: 1-45.

24. Borgesen SE, Gjerris JG. The predictive value of conductance to outflow of CSF in Normal Pressure Hydrocephalus. Brain 1982; 105: 65-86.

25. Borgesen SE, Westergard L, Gjerris F. Isotope cisternography and conductance to outflow of CSF in Normal Pressure Hydrocephalus. Acta Neurochir(Wein) 1981; 57: 67-73.

26. Bowen DM, White P, Spillane JA, et al. Accelerated ageing or selective neuronal loss as an important cause of dementia. Lancet 1979; i: 11-14.

27. Bradbury M. The concept of a blood-brain barrier. Chichester: Wiley Interscience Pubications. 1979: 1-37.
28. Bradley RD, Semple SJG. A comparison of certain acid-base characteristics of arterial blood, jugular venous blood and cerebrospinal fluid in man, and the effect on them of some acute and chronic acid-base disturbances. J Physiol(Lond) 1962; 160: 381-91.
29. Bradley WG, Yadley RA, Wycoff RR. The appearance of different forms of brain edema on NMR. Abstracted in Soc Mag ResMed. (San Francisco). 1983; 57-8.
30. Brocker RJ. Technique to avoid spinal tap headache. JAMA 1958; 68: 261-3.
31. Brody H. Aging of the vertebrate brain. In: Development and Aging in the Nervous System. Eds. Rockstein S, Sussman ML. Academic Press Inc. 1973; 7: 121-133.
32. Brooks DJ, Beaney RP, Powell M et al. Studies on cerebral oxygen metabolism, blood flow and blood volume in patients with hydrocephalus before and after surgical decompression using positron emission tomography. Brain 1986; 109(4): 613-28.
33. Brooks RA, Di Chiro G. Slice geometry in computer assisted tomography. J Comput Assist Tomogr 1977; 1: 191-9.
34. Bull JWD. The Robert Wartenberg Memorial Lecture. The volume of the cerebral ventricles. Neurology 1961; 11(1): 1-9.
35. Burger M. Abhandl sacks Acad Weis Leipwig. Math-naturur Kl 1957; 45: 1. From: Hirnwich WA. Neurochemical patterns in the developing and aging brain. In: Rockstein S, Sussman ML. eds. Development and Aging in the Nervous System. London: Academic Press Inc., 1973; 121-133.
36. Burrows G. On disorders of the cerebral circulation, London 1846. From: Lundberg N. The Saga of the Monro-Kellie Doctrine. In: Ishii S, Nagai H, Brock M. eds. Intracranial Pressure V. Berlin: Springer-Verlag, 1983; 68-75.
37. Cabanes J, Vazquez R. Quantitative isotope ventriculography: a comparative study. Surg Neurol 1977; 8: 209-15.
38. Castro ME, Boisvert DP, Treiber EO, Lunt JA, Allen PS. The effect of CSF albumin concentration on NMR relaxation parameters. Abstracted in Soc Mag Res Med (New York). 1984; 138-9.

39. Clarke C. What is the latest thinking on the prevention and treatment of altitudinal sickness. Br Med J 1987; 294: 1278.

40. Condon B, Patterson J, Jenkins A, et al. MR relaxation times of cerebrospinal fluid. J Comput Assist Tomogr 1987; 11(2): 203-7.

41. Condon B, Patterson J, Wyper D, et al. Intracranial CSF volumes determined using Magnetic Resonance Imaging. Lancet 1986; 1:1355-8.

42. Condon B, Patterson J, Wyper D, et al. A quantitative index of ventricular and extraventricular intracranial CSF volumes using MRI. J Comput Assist Tomogr 1986; 10: 784-92.

43. Condon B, Patterson J, Wyper D, Jenkins A, Hadley DM. Image non-uniformity in Magnetic Resonance Imaging: Its magnitude and methods for its correction. Br J Radiol 1987; 60(709): 83-7.

44. Connor ES, Foley L, Black PMcL. Experimental normal pressure hydrocephalus is accompanied by increased transmantle pressure. J Neurosurg 1984; 61: 322-7.

45. Creasey H, Schwartz M, Frederickson H, Haxby JV, Rapoport I. Quantitative computed tomography in dementia of the Alzheimers type. Neurology 1986; 36: 1563-8.

46. Crockard HA, Hanlon K, Duda EE, Mullan JF. Hydrocephalus as a cause of dementia: evaluation by computerised tomography and intracranial pressure monitoring. J Neurol Neurosurg Psychiat 1977; 40: 736-40.

47. Cummins BH. Measuring intracranial pressure in the Himalayas. Presented at the Soc British Neurological Surgeons. Abstracted in J Neurol Neurosurg Psychiat (In Press).

48. Cutler RWP. The cerebrospinal fluid. In: Swash M, Kennard C. eds. Scientific Basis of Clinical Neurology Edinburgh: Churchill Livingstone, 1985; 646-57.

49. Cutler RWP, Page L, Galicich J, Watters GV. Formation and absorption of cerebrospinal fluid in man. Brain 1968; 91: 707-20.

50. Dalton K. Influence of menstruation on glaucoma. Br J Ophthalmol 1967; 51(10): 692-5.

51. Dalton K. The premenstrual syndrome and progesterone therapy. 2nd ed. London: Heinmann Medical Books Ltd, 1984: 100-5.

52. Dandy WE. Intracranial pressure without brain tumour. Ann Surg 1937; 106: 492-513.

53. Darroch CJ, Staines A, Patterson J, Mendelow AD. The effect of carbon dioxide inhalation on systemic blood pressure and cerebral blood flow. IRCS Med Sci 1985; 13: 418-9.

54. Datlof S, Coleman PD, Forbes GB, Kreipe RE. Ventricular dilatation on CAT scans of patients with anorexia nervosa. Am J Psychiatry 1986; 143(1): 96-8.

55. Davidoff LM. Pseudotumour cerebri. Benign Intracranial Hypertension. Neurology 1956; 6: 605-15.

56. Davidoff LM, Epstein BS. The abnormal pneumoencephalogram. Ed.2. Philadelphia: Lea and Febiger, 1955.

57. Davis PJM, Wright EA. A new method of measuring cranial cavity volume and its application to the assessment of cerebral atrophy at autopsy. Neuropathol Appl Neurobiol 1977; 3: 341-58.

58. Davson H, Hollingsworth G, Segal MB. The mechanism of drainage of cerebrospinal fluid. Brain 1970; 93: 665-78.

59. Davson H, Welsh K, Segal MB. Physiology and pathophysiology of cerebrospinal fluid. Edinburgh: Churchill Livingstone, 1987; 6: 189-209.

60. Delaney P, Schellinger D. Computed tomography and benign intracranial hypertension. JAMA 1976; 236: 951-2.

61. De Souza SN, Dobbing J. Cerebral edema in developinf brain: Normal water and cation content in developing rat brain and postmortem changes. Exp Neurol 1971; 32: 431-8.

62. Di Chiro G. New radiographic and isotopic procedures in neurological diagnosis. JAMA 1964; 188: 524-29.

63. Donaldson JO, Horak E. Cerebrospinal fluid oestrone in pseudotumour cerebri. J Neurol Neurosurg Psychiat 1982; 45: 734-6.

64. Doyle FH, Gore JC, Pennock JM, et al. Imaging the brain by nuclear magnetic resonance. Lancet 1981; ii: 53-7.

65. Droege RT, Wiener SN, Rzeszotarski MS. A strategy for MRI of the head: Results of a semi-empirical model. Radiology 1984; 153: 425-33.

66. Earnest MP, Heaton RK, Wilkinson WE, Manke WF. Cortical atrophy, ventricular enlargement and intellectual impairment in the aged. Neurology 1979; 29: 1138-43.

67. Ellis J. Changes in the cerebellum with aging. J Comp Neurol 1920; 32: 1-33.

68. Enzman DR, Lane B. Cranial computed tomography findings in anorexia nervosa. J Comput Assist Tomogr 1977; 1: 410-4.
69. Epstein CM. The distribution of intracranial forces in acute and chronic hydrocephalus. J Neurol Sci 1974; 21: 171-80.
70. Evans WA. Encephalographic ratio for estimating ventricular enlargement and cortical atrophy. Arch Neurol Psychiat (Chic) 1942; 47: 931-37.
71. Ferrazzini G, Maggiorini M, Kriemler S, Bartsch P, Oelz O. Successful treatment of acute mountain sickness with dexamethasone. Br Med J 1987; 294: 1380-2.
72. Fisher CM. Hydrocephalus as a cause of distrubance of gait in the elderly. Neurology 1982; 32: 1358-63.
73. Fishman RA. Cerebrospinal Fluid in Diseases of the Nervous System. Philadelphia: WB Saunders Co., 1980; 6: 253-325.
74. Foley J. Benign forms of intracranial hypertension-"Toxic" and "Otitic" hydrocephalus. Brain 1955; 78(1): 1-41.
75. Foncin JF, Redondo A, Le Beau J. Le cortex cerebral des malades atteints d'hydrocephalie a pression normale. Acta Neurol Path (Berlin) 1976; 34: 353-7.
76. Fox JH, Topel JL, Huckman MS. The use of computerized tomography insenile dementia. J Neurol Neurosurg Psychiat1975;38: 948-58.
77. Gado M, Hughes CP, Danziger W, Chi D. Aging, dementia and brain atrophy: A longitudinal computed tomography study. AJNR 1983; 4: 699-702.
78. Gawler J, Du Boulay GH, Bull JWD, Marshall J. Computed tomography (the EMI scanner): a comparison of pneumoencephalography and ventriculography. J Neurol Neurosurg Psychiat 1976; 39: 203-11.
79. Geigy Scientific Tables. Units of measurement, body fluids composition of the body, nutrition. Lentner C. ed. Ciba Geigy Pub. 1981; 165-77.
80. Glydensted C. Measurement of the normal ventricular system and hemispheric sulci in 100 adults with computed tomography. Neuroradiology 1977; 14: 183-92.
81. Gluck E, Radu EN, Mundt C, Gerhardt P. A computed tomographic prolective trohoc study of chronic schizophrenics. Neuroradiology 1980; 20: 167-71.
82. Go KG, Dijk P van, Luiten AL, et al. Interpretation of NMR tomograms of the brain. J Neurosurg 1983; 59: 574-84.

83. Go KG, Dijk P van, Luiten AL, Teelken AW. Proton Spin Tomography in brain edema. In: Go KG, Baethmann A. eds. Recent progress in the study and therapy of brain edema. New York: Plenum Pub. 1984; 283-91.

84. Goodrich SM, Wood JE. Peripheral venous distensibility and velocity of venous blood flow during pregnancy or during oral contraceptive therapy. Am J Obstet Gynecol 1964; 90: 740-4.

85. Gosling RH. The association of dementia with radiologically demonstrated cerebral atrophy. J Neurol Neurosurg Psychiat 1955; 18: 129-33.

86. Granholm L. An explanation of the reversible memory defect in hydrocephalus. In: Beks JWF, Bosch DA, Brock M. eds. Intracranial Pressure III. Berlin: Springer-Verlag, 1976: 173-6.

87. Grant R, Hadley D, Graham DI, Condon B, Teasdale GM. Magnetic Resonance Imaging and smooth periventricular high signal areas. Lancet 1987; i: 807-8.

88. Greenberg JH, Alavi A, Reivich M, Kuhl D, Uzzell B. Local cerebral blood volume response to carbon dioxide in man. Circ Res 1978; 43(2): 324-31.

89. Greenberg JO, Shenkin HA, AdamR. Idiopathic Normal Pressure Hydrocephalus: a report of 73 patients. J Neurol Neurosurg Psychiat 1977; 40: 336-41.

90. Grubb RL, Raichle ME, Eichling JO, Ter-Pogossian MM. The effects of changes in PaCO2 on cerebral blood volume, blood flow and vascular mean transit time. Stroke 1974; 5: 630-9.

91. Gunasekera L, Richardson AE. Computerised Axial Tomography in idiopathic hydrocephalus. Brain 1977; 100: 749-54.

92. Guttman SA. (Personal communication to Wolff) In: Dalessio DJ. ed. Wolff's Headache and other head pain. Ed 2. New York: Oxford University Press, 1966; 96-125.

93. Hadley DM, Jenkins A, Macpherson P, et al. Magnetic Resonance Imaging in acute sub-arachnoid haemorrhage: an in vitro and in vivo study. Proc Eur Soc Magn Reson Med Biol 1985: 306-17.

94. Hahn FJY, Rim K. Frontal ventricular dimensions on normal computed tomography. AJR 1976; 126: 593-6.

95. Hakim S, Adams RD. The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure: Observations on the cerebrospinal fluid haemodynamics. J Neurol Sci 1965; 2: 307-27.
96. Hall TC, Miller AKH, Corsellis L. Variations in the human Purkinjee cell population according to age and sex. Neuropathol Appl Neurobiol 1975; 1: 267-92.
97. Hansen JE, Evans WO. Hypothesis regarding the pathophysiology of acute mountain sickness. Arch Environ Health 1970; 21: 666.
98. Harvey FH. The significance of the amount of fluid surrounding the brain to the recognition of brain swelling (or atrophy at autopsy): A new and routinely applicable method of diagnosing abnormal brain size. J Forensic Sci 1980; 2: 287-96.
99. Harvey RW. The volume of the ventricles of the brain. Anat Rec 1911; 5: 301-5.
100. Haug G. Age and sex dependence of the size of the normal ventricles on computed tomography. Neuroradiology 1977; 14: 201-4.
101. Hawkes RC, Holland GN, Moore WS, Worthington BS. Nuclear Magnetic Resonance(NMR) tomography of the brain: a preliminary clinical assessment with demonstration of pathology. J Comput Assist Tomogr 1980; 4: 577-86.
102. Health and Public Policy Committee, American College of Physicians. The diagnostic spinal tap. Ann Intern Med 1986; 104(6): 880-5.
103. Hershey LA, Modic MT, Greenough G, Jaffe DF. Magnetic Resonance Imaging in vascular dementia. Neurology 1987; 37: 29-36.
104. Hill L. The physiology and pathology of the cerebral circulation. London 1896. From: Lundberg N. The Saga of the Monro-Kellie doctrine. In: Ishii S, Nagai H, Brock M. eds. Intracranial Pressure V. Berlin: Springer-Verlag, 1983; 68-75.
105. Hochwald GM, Sahar A. Effect of spinal fluid pressure on cerebrospinal fluid formation. Exp Neurol 1971; 32: 30-40.
106. Hoff J, Barber R. Transcerebral mantle pressure in normal pressure hydrocephalus. Arch Neurol 1974; 31: 101-5.
107. Hopkins AL, Yeung HN, Bratton CB. Multiple field strength in vivo T1 and 2 for cerebrospinal fluid protons. Magn Reson Med 1986; 3: 303-11.

108. Houndsfield GN. Computerized axial scanning. Br J Radiol 1973; 46: 1016-22.

109. Hubbard BM, Anderson JM. Age, senile dementia and ventricular enlargement. J Neurol Neurosurg Psychiat 1981; 44: 631-35.

110. Hubbard BM, Anderson JM. Age related variations in neuron content of the cerebral cortex in senile dementia of Alzheimer's type. Neuropath Appl Neurobiol 1986; 11: 369-82.

111. Huckman MS, Fox J, Topel J. The validity of criteria for the evaluation of cerebral atrophy by computed tomography. Radiology 1975; 116: 85-92.

112. Hughes CP, Siegel BA, Coxe WS, Gado MH, Coleman RE, Berg L. Adult idiopathic communicating hydrocephalus with and without shunting. J Neurol Neurosurg Psychiat 1978; 41: 961-71.

113. Hulme A, Cooper R. Cerebral blood flow during sleep in patients with raised intracranial pressure. Prog Brain Res 1968; 30: 70-81.

114. Jacobs L, Kinkel W. Computerized axial transverse tomography in normal pressure hydrocephalus. Neurology 1976; 26: 501-7.

115. Jacoby RJ, Levy R. Computed tomography in the elderly. 2.Senile dementia: diagnosis and functional impairment. Br J Psychiatry 1980; 136: 256-69.

116. Jacoby RJ, Levy R, Dawson JM. Computed tomography in the elderly. 1.The normal population. Br J Psychiatry 1980; 136: 249-55.

117. Jernigan TL, Zatz LM, Moses JA, Berger PA. Computed tomography in schizophrenics and normal volunteers. 1. Fluid Volume. Arch Gen Psychiatry 1982; 39: 765-70

118. Jernigan TL, Zatz LM, Naeser MA. Semi-automated methods of quantifying CSF volume on cranial computed tomography. Radiology 1979; 132: 463-6.

119. Johnston I. Reduced CSF absorption syndrome. Reappraisal of benign intracranial hypertension and related conditions. Lancet 1973; ii: 418-20.

120. Johnston I, Paterson A. Benign intracranial hypertension: CSF pressure and circulation. Brain 1974; 97: 301-12.

121. Johnston R. Cerebrospinal Fluid. In: Critchley AM, O'Leary JL, Jennett B. eds. Scientific Foundations of Neurology. London: Heinemann Medical Books Ltd. 1972; 281-8.

122. Kaszniak AW, Garron DC, Fox JH, Bergen D, Hackman M. Cerebral atrophy, EEG showing age, education, and cognitive functioning in suspected dementia. Neurology 1979; 29: 1273-9.

123. Kjos BO, Ehman RL, Brant-Zawadski M, Kelly WM, Norman D, Newton TH. Reproducibility of relaxation times and spin density calculated from routine MR imaging sequences: clinical study of the CNS. AJR 1985; 144: 1165-70.

124. Klipstein RH, Firmin DN, Underwood SR, Nayler GL, Rees RSO, Longmore DB. Colour display of quantitative blood flow and cardiac anatomy in a single magnetic resonance cine loop. Br J Radiol 1987; 60: 105-11.

125. Knudsen PA. Ventriklernes Storrelsesforhold: Anatomisk Normale Hjerner Fra Voksne Mennesker. Odense, Andelsbogtrykkeriet 1958. From: Bull JWD. The Robert Wartenberg Memorial Lecture. The volume of the cerebral ventricles. Neurology 1960; 11(1): 1-9.

126. Kohlmeyer K, Lehmkuhl G, Poutska F. Computed tomography of anorexia nervosa. AJNR 1983; 4(3): 437-8.

127. Koller WC, Glatt SL, Fox JH, Kaszniak AW, Wilson RS, Huckman MS. Cerebellar atrophy: relationship to ageing and cerebral atrophy. Neurology 1981; 31: 1486-8.

128. Kosteljanetz M, Ingstrup HM. Normal Pressure Hydrocephalus: Correlation between CT and measurements of cerebrospinal fluid dynamics. Acta Neurochir(Wein) 1985; 77: 8-13.

129. Kuhl DE,Reivich M, Alavi A, Nyary I, Staum MM. Local cerebral blood volume determined by three-dimensional reconstruction of radionuclide scan data. Circ Res 1975; 36: 610-9.

130. Kunkle EC, Ray BS, Wolff HG. Experimental studies on headache. Analysis of the headache associated with changes in intracranial pressure. Arch Neurol Psychiat(Chic) 1943; 49: 323-58.

131. Laffey PA, Peyster RG, Hathan R, Haskin ME, McGinlay JA. Computed tomography and ageing: Results in a normal elderly population. Neuroradiology 1984; 26: 273-8.

132. Laidlaw J. Catamenial epilepsy. Lancet 1956; 271: 235-7.

133. Lamb WM, Ulett GA, Masters WH, Robinson DW. Premenstrual tension: EEG, hormonal and psychiatric evaluation. Am J Psychiatry 1953; 109: 840-8.

134. Landau RL, Bergenstal DM, Lugibihl K, Kascht ME. The metabolic effects of progesterone in man. J Clin Endocrinol 1955; 15: 1194-215.

135. Last RJ, Tompsett DH. Casts of the cerebral ventricles. Br J Surgery 1953; 40: 525-43.

136. Laws ER Jr, Mokri B. Occult Hydrocephalus: results of shunting correlated with diagnostic tests. Clin Neurosurg 1977; 24: 316-33.

137. Le May M, New PFJ. Radiological diagnosis of occult normal pressure hydrocephalus. Radiology 1970; 96: 347-58.

138. Lindsay KW, Bone I, Callander R. Neurology and Neurosurgery illustrated. Edinburgh. Churchill Livingstone. 1986; 339-46.

139. Locke CE Jr. Studies of casts of the cerebral ventricles. Arch Neurol Psychiat(Chic) 1926; 15: 588-96.

140. Logothesis J, Harner R, Morrell F, Torres F. The role of estrogens in catamenial exacerbation of epilepsy. Neurology 1959; 9: 352-60.

141. Lups S, Haan AMFH. The cerebrospinal fluid. Amsterdam: Elsevier Pub Co. 1954; 15-17.

142. Machida H. Influence of progesterone on arterial blood and CSF acid-base balance in women. J Appl Physiol 1981; 51(6): 1433-6.

143. Magnaes B. Movement of cerebrospinal fluid within the craniospinal space when sitting up and lying down. Surg Neurol 1978; 10: 45-9.

144. Mahaley MS, Wilkinson RH Jr, Sivalingham S, Friedman H, Tyson W, Goodrich JK. Radionuclide blood levels during cisternography of patients with normal pressure hydrocephalus or Alzheimer's disease. J Neurosurg 1974; 41: 471-80.

145. Mann DMA, Yates PO, Marcyniuk B. Alzheimer's presenile dementia, senile dementia of Alzheimer's type and Down's syndrome in middle age from an age related continuum of pathological changes. Neuropath Appl Neurobiol 1984; 10: 185-207.

146. Martins AN, Newby N, Doyle TF. Sources of error in measuring cerebrospinal fluid formation by ventriculo-cisternal perfusion. J Neurol Neurosurg Psychiat 1977; 40: 645-50.

147. Martins AN, Wiley JK, Myers PW. Dynamics of the cerebrospinal fluid and the spinal dura mater. J Neurol Neurosurg Psychiat 1972; 35: 468-73.

148. Marton KI, Gean AD. The spinal tap: A new look at an old test. Ann Intern Med 1986; 104(6): 840-8.

149. Mathew NT, Meyer JS, Bell RL, Johnson PC, Neblett CR. Regional cerebral blood flow and blood volume measured with the gamma camera. Neuroradiology 1972; 4: 133-40.

150. Mathew NT, Meyer JS, Hartmann A, Ott EO. Abnormal cerebrospinal fluid-blood flow dynamics. Implications in diagnosis, treatment and prognosis in normal pressure hydrocephalus. Arch Neurol 1975; 32: 657-64.

151. Mathew NT, Meyer JS, Ott EO. Increased cerebral blood volume in benign intracranial hypertension. Neurology 1975; 25: 646-9.

152. McComb JG. Recent research into the nature of cerebrospinal fluid formation and absorption. J Neurosurg 1983; 59: 369-83.

153. McQuarrie I. Some recent observations regarding nature of epilepsy. Ann Intern Med 1932; 6: 497-505.

154. Mellanby AR, Reveley MA. Effects of acute dehydration on computerised tomographic assessment of cerebral density and ventricular volume. Lancet 1982; 16(2): 874.

155. Meyer JS, Tachibana H, Hardenberg JP, Dowell RE, Kitagawa Y, Mortel KF. Normal Pressure Hydrocephalus: Influences on cerebral haemodynamic and cerebrospinal fluid pressure - chemical autoregulation. Surg Neurol 1984; 21: 195-203.

156. Miller A, Bader RA, Bader ME. The neurologic syndrome due to marked hypocapnia with papilloedema. Am J Med 1962; 33: 309-18.

157. Miller JD, Adams JH. The pathophysiology of raised intracranial pressure. In: Adams JH, Corsellis JAN, Duchen LW. eds. Greenfield's Neuropathology. London: Edward Arnold Pub, 1984; 67.

158. Miller JD, Garibi J, Pickard JD. Induced changes in cerebrospinal fluid volume. Arch Neurol(Chic) 1973; 28: 265-9.

159. Miner LC, Reed DJ. Composition of fluid obtained from choroid plexus tissue isolated in a chamber in situ. J Physiol(Lond) 1972; 227: 127-39.

160. Momose KJ, Khellberg RN, Klinan B. High incidence of cortical atrophy of the cerebral hemispheres in Cushings disease. Radiology 1971; 99: 341-8.

161. Monro A. Observations on the structure and functions of the nervous system. Footnote 1:5, Edinburgh 1783. Quoted by Kellie G. An account of the appearance. Transactions of the medico-chirurgical society of Edinburgh 1824; 1: 84.

162. Naylen G, Hedlund S, Regnstrom O. Cerebral circulation studies with labelled red cells in healthy males. Circ Res 1961; 9: 667- 74.

163. Nelson JR, Goodman SJ. An evaluation of the cerebrospinal fluid infusion test for hydrocephalus. Neurology 1971; 21: 1037-53.

164. Nussbaum M, Shenker IR, Marc J. et al. Cerbral atrophy in anorexia nervosa. J Paediatr 1980; 96: 867-9.

165. Oppelt WW, Maren TH, Owens ES, Rall DP. Effects of acid-base alterations on cerebrospinal fluid production. Proc Soc Exp Biol Med 1963; 114: 86-9.

166. Ostheimer GW, Palahniuk RJ, Shnider SM. Epidural blood patch for post-lumbar puncture headache. Anaesthesiology 1974; 41: 307-8.

167. Pearl R. Variations and correlations in brain weight. Biometrika 1905; 4: 13-104.

168. Penn RD, Belanger MJ, Yasnoff WA. Ventricular volume in man computed from CT scans. Ann Neurol 1978; 3: 216-23.

169. Peterson M, Kelly JV. Pseudotumour cerebri in pregnancy. Case reports and review of the literature. Obstet Gynaecol Survey 1985; 40(6): 323-9.

170. Phelps ME, Grubb RL Jr, Ter-Pogossian MM. In vivo regional cerebral blood volume by X-ray fluorescence: validation of method. J Appl Physiol 1973; 35: 741-7.

171. Pickard JD. Adult Communicating Hydrocephalus. Br J Hosp Med 1982; 1: 35-44.

172. Pickard JD, Teasdale GM, Matheson M et al. Intraventricular pressure waves - The best predictive test for shunting in normal pressure hydrocephalus. In: Shulman K, Marmarou A, Miller JD, Becker DP, Hochwald GM, Brock M. eds. Intracranial Pressure IV. Berlin: Springer Verlag, 1980;498-500.

173. Pickering GW. 'Experimental observations on headache' Br Med J 1939; i: 4087.

174. Pickering GW. Lumbar puncture headache. Brain 1948; 71: 274-80.

175. Pollay M, Curl F. Secretion of cerebrospinal fluid by the ventricular ependyma of the rabbit. Am J Physiol 1967; 213: 1031-8.

176. Portnoy HD, Chopp M. Intracranial Fluid Dynamics. Interrelationship of CSF and vascular phenomena. In: Karger S ed. Concepts in Pediatric Neurology 3. Basel, 1983; 133-44.

177. Quinke HI. Die Lumbalpunction des Hydrocephalus. Berl Klin Wochenschr 1891; 929-65.

178. Raichle ME, Grubb RL Jr., Phelps ME, Gado MH, Caronna JJ. Cerebral haemodynamics and metabolism in pseudotumor cerebri. Ann Neurol 1978; 4: 104-11.

179. Reid AC, Matheson MS, Teasdale GM. Volume of the ventricles in benign intracranial hypertension. Lancet 1980; ii: 7-8.

180. Reid AC, Teasdale GM, Matheson MS, Teasdale EM. Serial ventricular volume measurements: further insights into the aetiology and pathogenesis of benign intracranial hypertension. J Neurol Neurosurg Psychiat 1981; 44: 636-40.

181. Reveley MA. Ventricular enlargement in schizophrenia: The validity of computed tomographic findings. Br J Psychiatry 1985; 147: 233-40.

182. Reveley MA, Murray RM. Cerebral ventricular enlargement in non genetic schizophrenia: a controlled twin study. Br J Psychiatry 1984; 144: 89-93.

183. Risberg J, Lundberg N, Ingvar DH. Regional cerebral blood volume during acute transient rise of the intracranial pressure. (Plateau waves). J Neurosurg 1969; 31: 303-10.

184. Roberts MA, Caird FI. Computerised tomography and intellectual impairment in the elderly. J Neurol Neurosurg Psychiat 1976; 39: 989-90.

185. Roberts MA, Caird FI, Grossart KW, Steven JL. Computed tomography in the diagnosis of cerebral atrophy. J Neurol Neurosurg Psychiat 1976; 39: 909-15.

186. Roth M. The association of clinical and neurological findings and its bearing on the classification an aetiology of Alzheimer's disease. Br Med Bull 1986; 42(1): 42-50.

187. Roy CS, Sherrington CS. On the regulation of the blood supply to the brain. J Physiol(Lond) 1890; 11: 85-108.

188. Rubin RC, Henderson ES, Ommaya AK, Walker MD, Rall DP. The production of cerebrospinal fluid in man and its modification by acetazolamide. J Neurosurg 1966; 25: 430-6.

189. Sahs AL, Joynt RJ. Brain swelling of unknown cause. Neurology 1956; 6: 791-802.

190. Sainte-Rose C, Hooven MD, Hirsch JF. A new approach in the treatment of hydrocephalus. J Neurosurg 1987; 66: 213-26.

191. Sarwar M, McCormick WF. Decrease in ventricular and sulcal size after death. Radiology 1978; 127: 409-11.

192. Shulka D, Singh BM, Strobos RJ. Hypertensive cerebrovascular disease and Normal Pressure Hydrocephalus. Neurology 1980; 30: 998-1000.

193. Sklar FH, Beyer CW, Hagler H, Ramanathan M, Clark WK. The pressure volume function of brain elasticity and its relationship with ventricular size. In: Shulman K, Marmarou A, Miller JD, Becker DP, Hochwald GM, Brock M. eds. Intracranial Pressure IV. Berlin: Springer-Verlag, 1980; 81-4.

194. Sklar FH, Beyer CW, Ramanathan M, Cooper PR, Clark WK. Cerebrospinal fluid dynamics in patients with pseudotumour cerebri. Neurosurg 1979; 5(2): 208-16.

195. Smallhout B, Kalenda Z. An atlas of capnography. Kerkebosch, The Netherlands, 1981: 5-11.

196. Smith AL, Neufeld GR, Ominsky AJ, Wollman H. Effect of arterial CO2 tension on cerebral blood flow, mean transit time and vascular volume. J Appl Physiol 1971; 31: 701-7.

197. Smith FW, Mallard JR, Reid A, Hutchinson JS. Nuclear Magnetic Resonance tomographic imaging in liver disease. Lancet 1981; i: 963-6.

198. Smith FW, Reid A, Hutchinson JS, Mallard JR. Nuclear Magnetic Resonance Imaging of the pancreas. Radiology 1982; 142: 677-80.

199. Symon L, Dorsch NWC. Use of long-term intracranial pressure measurement to assess hydrocephalic patients prior to shunt surgery. J Neurosurg 1975; 42: 258-73.

200. Symon L, Dorsch NWC, Stephens RJ. Pressure waves in so called low pressure hydrocephalus. Lancet 1972; ii: 1291-2.

201. Synek V, Reuben JR, Gawler J, Du Boulay GH. Comparison of measurements of the cerebral ventricles obtained by CT scanning and pneumoencephalography. Neuroradiology 1979; 17: 149-51.

202. Tagliavini F, Pilleri G. Neuronal counts in basal nucleus of Meynert in Alzheimer's disease and in simple dementia. Lancet 1983; i: 469-70.

203. Tamaki N, Kusunoki T, Wakabayashi T, Matsumoto S. Cerebral haemodynamics in normal pressure hydrocephalus. Evaluation by Xe^{133} inhalation method and dynamic CT study. J Neurosurg 1984; 61: 510-4.

204. Thorsen G. Neurological complications after spinal anaesthesia and results from 2,493 follow up cases. Acta Chir Scand 1947; 95(Suppl 121): 7-272.

205. Tomlinson BE, Blessed G, Roth M. Observations on the brains of non demented old people. J Neurol Sci 1968; 7: 331-56.

206. Tourtellotte WW, Haerer AF, Heller GL et al. Post-lumbar puncture headaches. Springfield III: Charles C Thomas 1964: 79-97.

207. Tripathi BJ, Tripathi RC. Vascular transcellular channels as a drainage pathway for cerebrospinal fluid. J Physiol(Lond) 1974; 239: 195-206.

208. Tripathi RC. The functional morphology of the outflow systems of ocular and cerebrospinal fluids. Exp Eye Res 1977; 25(Suppl): 65-116.

209. Vandam LD, Dripps RD. Long term follow up of patients who received 10,098 spinal anaesthetics. Syndrome of decreased intracranial pressure(Headache and ocular and auditory difficulties. JAMA 1956; 161: 586-91.

210. Vassilouthis J. The syndrome of normal-pressure hydrocephalus. J Neurosurg 1984; 61: 501-9.

211. Vorstrup S, Christensen J, Gjerris F, Sorensen PS, Thomsen AM, Paulson OB. Cerebral blood flow in patients with normal pressure hydrocephalus before and after shunting. J Neurosurg 1987; 66: 379-87.

212. Weed LH. Some limitations of the Monro-Kellie Hypothesis. Arch Surg 1929; 18: 1049-68.

213. Weed LH, Flexner LB. Further observations upon the Monro-Kellie Hypothesis. Bull Johns Hopk Hosp 1932; 50: 196-223.

214. Weed LH, Flexner LB, Clark JM. The effects of dislocation of cerebrospinal fluid upon its pressure. Am J Physiol 1932; 100: 246-61.

215. Weisberg L, Nice CN. Computed tomographic evaluation of increased intracranial pressure without localising signs. Radiology 1977; 122: 133-6.

216. Weiss MH, Nulsen FE. The effect of glucocorticoids on CSF flow in dogs. J Neurosurg 1970; 32: 452-8.

217. Welsh K. Secretion of cerebrospinal fluid by choroid plexus of the rabbit. Am J Physiol 1963; 205: 617-24.

218. Welsh K, Friedman V. The cerebrospinal fluid valves. Brain 1960; 83: 454-69.

219. Weston PG. Sugar content of the blood and spinal fluid in insane subjects. J Med Res 1916; 35: 199-207.

220. White DN, Wilson KC, Curry GR, Stevenson RJ. The limitation of pulsatile flow through the aqueduct of Sylvius as a cause of hydrocephalus. J Neurol Sci 1979; 42: 11-51.

221. Williams G, Bydder GM, Kreel L. The validity and use of computed tomography attenuation values. Br Med Bull 1980; 36: 279-87.

222. Wolff HG. Headache and other head pain. Ed 2, New York: Oxford University Press 1963: 96-125.

223. Wyper DJ, Lennox GA, Rowan JO. Two minute slope inhalation technique for cerebral blood flow measurement in man. 1. Method. J Neurol Neurosurg Psychiat 1976; 39: 141-6.

224. Wyper DJ, Lennox GA, Rowan JO. Two minute slope inhalation technique for cerebral blood flow measurement in man. 2. Clinical appraisal. J Neuro Neurosurg Psychiat 1976; 39: 147-51.

225. Wyper DJ, Pickard JD, Matheson M. Accuracy of ventricular volume estimation. J Neurol Neurosurg Psychiat 1979; 42(4): 345-50.

226. Young IR, Payne JA, Khenia S, Oliver AG, Bryant DJ, Bydder GM. Cancellation of tissue signals in inversion recovery and partial saturation sequences. Abstracted in: Soc Mag Res Med. (London) 1985: 120-1.

227. Zatz LM, Jernigan TL, Ahumada AJ. Changes on computed cranial tomography with ageing: Intracranial fluid volume. AJNR 1982; 6: 1-11.

228. Zervas NT, Liszczak TM, Mayberg MR, Black PMcL. Cerebrospinal fluid may nourish cerebral vessels through pathways in the adventitia that may be analogous to systemic vasa vasorum. J Neurosurg 1982; 56: 475-81.

229. Zeumer H, Hacke W, Hartwich P. A quantitative approach to measuring the cerebrospinal fluid space with CT. Neuroradiology 1982; 22: 193-7.

230. Zuckerman S, Palmer A, Hanson DA, The effect of steroid hormones on the water content of tissues. J Endocrinol 1950; 6: 261-76.