The Role of Surgery and B_2-Transferrin in The Management of Cerebrospinal Fluid Fistulae

Muftah S.M. Eljamel

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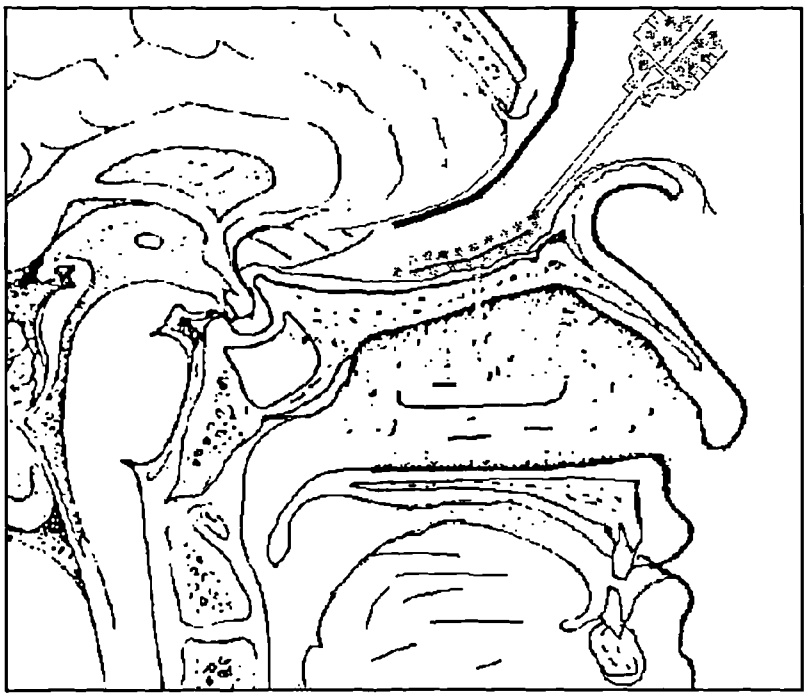

By
Muftah S.Eljamel ,MB,ChB,FRCS(I)

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Introduction

Cerebrospinal fluid (CSF) fistulae often manifest as CSF rhinorrhoea, CSF otorrhoea or CSF leakage through the skin. Less commonly, the fistula reveals itself as an aerocele (pneumocephalus) or recurrent intra-cranial infection. The increasing number of road traffic accidents (RTAs), inter-personal violence and more aggressive surgical approaches to the base of skull and intra-cranial diseases have increased the number of patients presenting with CSF fistulae. The literature on this subject remains controversial and at best inconclusive (Griffith 1990, Editorial, Br J Neurosurgery); most previous studies on CSF fistulae were retrospective cross-sectional surveys of selected group of patients, lacking long-term follow up data. This unsatisfactory position is the result of:

(1) The deficiencies in information on the long-term risks of CSF fistulae.

(2) The underestimation of the long-term risk of meningitis.

(3) The difficulty in the precise diagnosis and localization of the CSF fistulae.

(4) The reported high complication-rate of surgical dural repair.

Therefore, vital information, regarding the long-term prognosis of patients with CSF fistulae, is missing and a reliable diagnostic technique to confirm CSF leakage, is lacking.

Despite several reports of meningitis occurring many years after spontaneous cessation of CSF leakage, a more conservative line of management of CSF leaks has been gaining support.

However, recent advances in neuroradiology have made more precise localisation of CSF fistulae possible and recent advances in microsurgery, neuro-anaesthesia and intensive-therapy have made surgical dural repair a safer and more accurate technique.

The aim of this thesis is to provide vital information on the long-term prognosis of CSF fistulae and the effect of each modality of surgical treatment. This thesis also evaluates the accuracy and specificity of a new method of distinguishing CSF from other body fluids. This information is essential in formalizing the management of CSF fistulae and answering the following unsettled questions:

(1) What are the long-term risks of unrepaired CSF fistulae?. What is the actuarial risk of meningitis in these patients?

(2) What are the adverse prognostic factors for developing meningitis in patients with CSF fistulae?

(3) Does prophylactic antibiotic treatment play a role in the management of these patients?

(4) What are the long-term benefits of surgical dural repair?. Is it safe?. Have microsurgery and computed tomography made any difference to the operative morbidity and mortality?

(5) What are the adverse prognostic factors for recurrent CSF leaks?

(6) What is the role of reduction of facial fractures?. When should it be pererformed in patients with CSF leak?

(7) What are the effects of CSF drainage in patients with

CSF fistulae?

(8) What is the value of pre-operative localization of CSF fistulae?. Which is the safest and most accurate technique ?

To answer these controversial questions, I have reviewed 300 patients with suspected CSF fistulae, which is the largest study with long-term follow up in the literature. I will refer to these patients in the subsequent chapters as "this study". I have also examined the value of Paragon^{R} immunofixation in confirming CSF leakage. I have written this thesis in different chapters, each of which deals with one aspect of CSF fistulae. Chapter 1 summarizes the literature on the history, pathology, pathogenesis, classification and presentation of CSF fistulae. The long-term outcome of unrepaired CSF fistulae is presented in chapters 2 & 3. The subsequent two chapters deal with the role of surgery in the management of CSF fistulae. Chapter 6 contains the results of a study of $\underline{B}_2$-Transferrin (Paragon^{R} immunofixation) in the confirmation of CSF leakage. Finally, chapter 7 contains the results of pre-operative localization of CSF fistulae. The relevant literature is embodied in each chapter.

A summary of the conclusions is presented in chapter 8. A full list of references and a subject index are included at the end of the thesis for quick reference.

Chapter 1

History, Pathology, Pathogenesis, Classification and Presentation of CSF Fistulae

1-1 DEFINITIONS:

Fistulae are defined as abnormal connections between two epithelial surfaces. They are usually lined by granulation tissue, but they can become epithelialized. Cerebrospinal fluid (CSF) fistulae are abnormal defects in the dura, that allow the CSF to escape from the subarachnoid space. CSF fistulae, which occur through a skin wound, are very easy to localise and do not usually create any formidable problems to the surgeon. However, CSF fistulae, that occur at the skull base, can be difficult to find and formidable to treat. They often present with CSF leakage from the nose (Rhinorrhoea), less commonly with CSF leakage through the ear (Otorrhoea) and infrequently with an intracranial air (pneumocephalus or aerocele) or recurrent intra-cranial infections. Most CSF fistulae occur at the skull base as a result of or in relation to a tear or erosion of the dura overlying the cribriform plate, the frontal, the ethmoidal and / or the sphenoidal air sinuses (Figure 1-1 & 1-2).

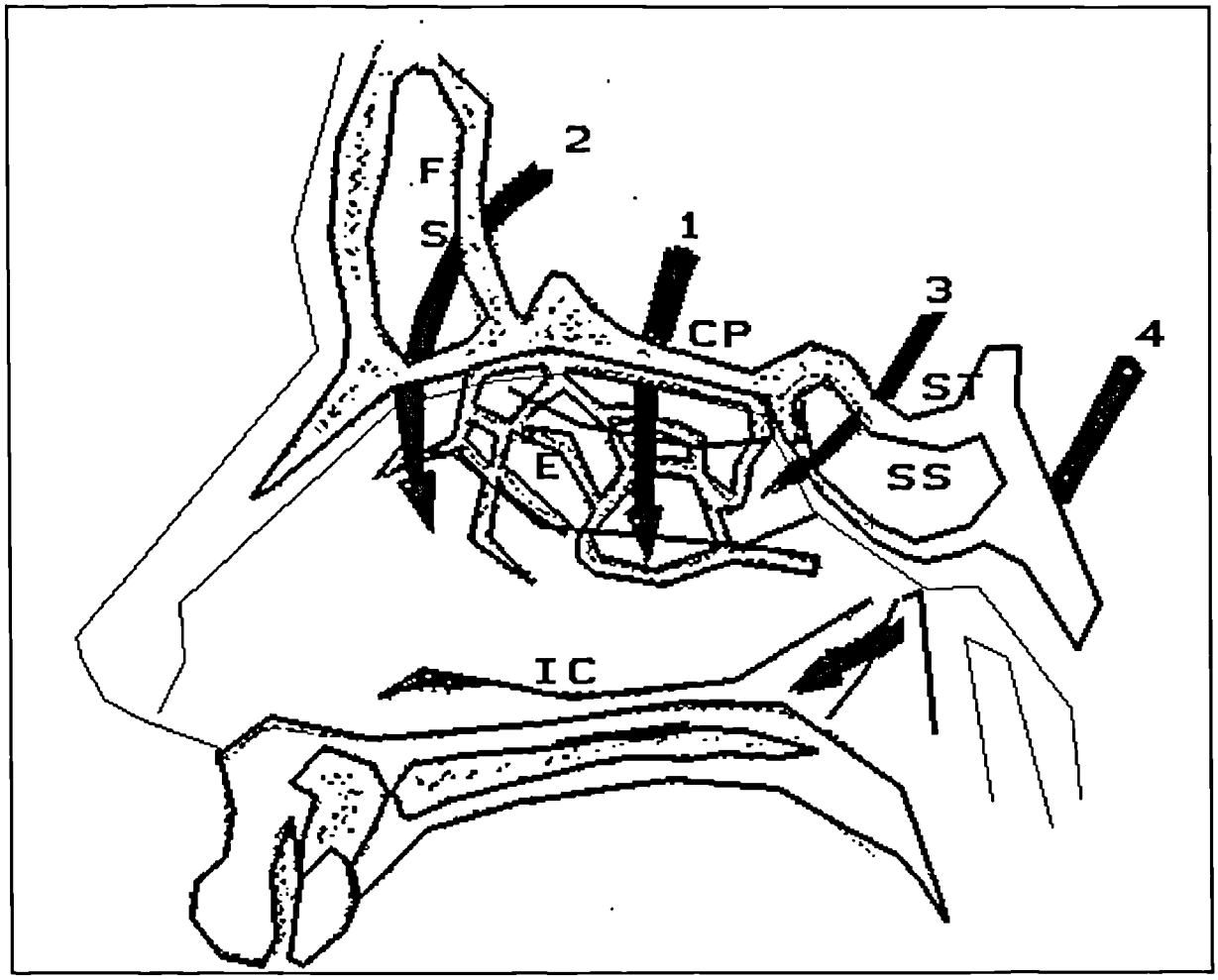
CSF Rhinorrhoea : is the term used to describe the leakage of cerebrospinal fluid from the nose and it was first used by St.Clair Thomson in 1899 .

CSF Otorrhoea : designates leakage of cerebrospinal fluid through the ear and it was first described by Escat in 1875.

Aerocele (Pneumocephalus): refers to intra-cranial air and it was first used by Wolff in 1914.

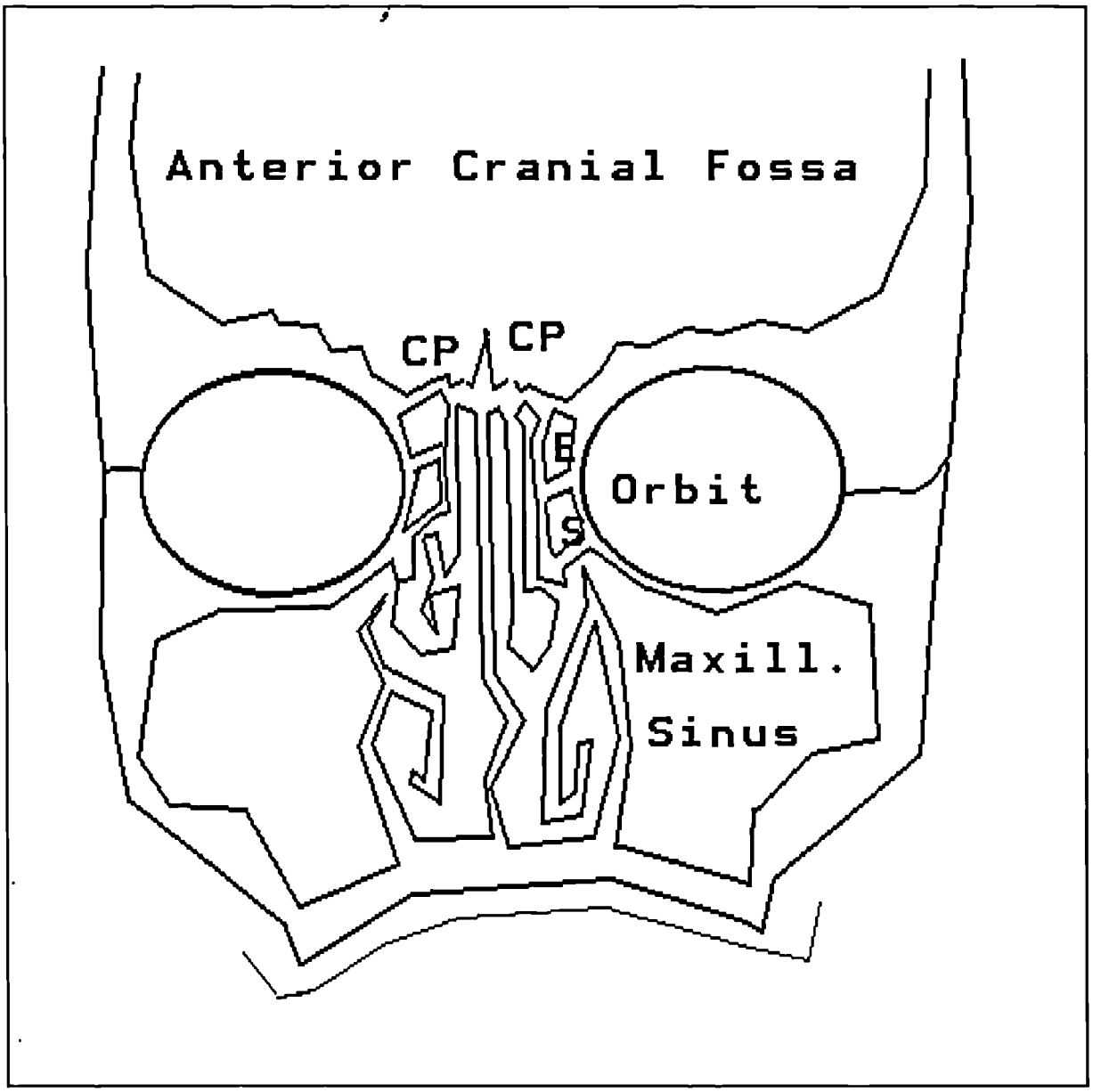
Paradoxical CSF Rhinorrhoea : is used to indicate leakage of CSF through the nose via the middle ear and the eustachian tube, when the tympanic membrane is intact.

Figure 1-1; Diagram showing the common sites of CSF leakage, Sagittal section through the cribriform plate and the paranasal air sinuses:



1- Cribriform plate (CP)
2- Frontal Sinus (FS)
3- Sphenoid Sinus (SS)
4- Petrous Bone
ST= Sella Turcica
E = Ethmoid
IC = Inferior Concha

Figure 1-2; Diagram of a coronal section through the anterior cranial fossa, cribriform plate and the paranasal air sinuses;



CP=Cribriform plate ES=Ethmoid sinus

1-2 HISTORY :

1-2,1 History of CSF Circulation:

Our knowledge of cerebrospinal fluid has been traced back to the Egyptians (Clarke & O'Mally 1968), but credit goes to the Roman physician, Galen (130-200 A.D.), for his observation, that the brain contained fluid filled cavities. Galen spoke of this fluid being excreted as mucus, under physiological conditions, into the nose through the ethmoid bone and hypophysis (Leyden 1660 & J.B. Bailliere 1854). Sylvius F. de la Boe (1641) described the aqueduct between the III and the IV ventricles and Willis (1676) emphasised that the passage of CSF from the intracranial space into the nose " via nervous processes and their membranes " occurring either through the cribriform plate or the sphenoid sinus. He also renounced that the nasal passage of CSF is an accessory outflow mechanism which is important when there is a surplus of intracranial CSF (Leyden 1660 & Caspar 1641). The interventricular foramen was described by Alexander Monro (1797) and the lateral foramina of the IV ventricle were described by Luschka (Luschka 1855) and Magendie (Magendie 1828). Furthermore, Magendie was the first to describe the modern account of CSF circulation in the ventricles and subarachnoid space.

1-2,2 History of CSF Fistulae ;

Although credit goes to Bidloo (Gissane & Rank 1939), for describing the first case of CSF rhinorrhoea, Miller was the first to describe such a case in the English literature. Miller's patient was a chronic hydrocephalic patient, who developed CSF rhinorrhoea (Miller 1828). Six years later King (1834) reported another case of CSF rhinorrhoea to the Westminster Medical Society in London.

The first case of CSF otorrhoea was described by Escat (1875) and Hans Chiari (1884) was the first to describe an intracranial aerocele, although Wolff (1914) was the first to use the term aerocele to indicate the presence of intra-cranial air.

St. Clair Thomson in 1899 was the first to use the term CSF rhinorrhoea to designate leakage of CSF through the nose, he compiled 20 cases of nontraumatic CSF fistulae and summarised the literature of the eighteenth century in a monograph entitled "The cerebrospinal fluid; its spontaneous escape from the nose", but he did not suggest any treatment (Thomson 1899).

1-2,3 History of Surgical Dural Repair;

Surgical treatment was first suggested by Grant (1923) and then by Dandy (1926). In the beginning of the nineteenth century, Grant said that " .. we felt that an attempt should be made to find and close the tear in the dura ... ", unfortunately in

Grant's patient the osteoplastic flap was made too high to find the CSF fistula and he encountered profuse bleeding from thesagittal sinus (Grant 1923). In the case reported by Dandy, the fistula was repaired successfully (Dandy 1926), and in the same year Cushing repaired successfully three other cases of dural fistulae (Cushing 1927). In 1927. Teachenor advocated that in all frontal sinus fractures, the frontal sinus should be drained and if CSF rhinorrhoea was present, the frontal sinus should be exenterated and the rent in the dura should be repaired (Teachenor 1927). Lawson said that in the fullness of time all CSF fistulae were fatal, unless the CSF leakage could be stopped surgically or by natural healing (Lawson 1934). Cairns reported the first series of patients with traumatic CSF rhinorrhoea treated surgically (Cairns 1937).

With the outbreak of the second world war in 1939, the incidence of traumatic CSF fistulae increased and the debate about their management intensified. Cairns and Calvert adopted the Grant-Dandy technique of extradural repair and they recommended that all patients with CSF rhinorrhoea should be given the benefit of surgery. This recommendation was based on an analysis of 128 cases of paranasal sinus fractures, of which there were 21 patients who developed CSF rhinorrhoea and 50 % of these developed meningitis (Cairns 1937 and Calvert 1942). However, the more widely used technique for repairing the dura is the intradural approach. It was first performed by Taylor in 1934 (Eden 1942), who quoted a very high operative mortality (30 %). Although, Dohlman has described a transnasal approach

to the repair of CSF fistulae through the cribriform plate, his technique was not widely adopted (Dohlman 1948).

Because of the limitations of radiology in localising the precise site of the CSF leakage, the high operative mortality and the high negative exploration rate, Adson & Uihlein and McKissock concluded that it would be wise to wait eight weeks before deciding on surgical repair as the CSF leaks often stopped spontaneously (Adson & Uihlein 1949 and McKissock 1952). However, Lewin (1954) elaborated this subject further and concluded that every patient with CSF rhinorrhoea, of whatever duration, should have a surgical exploration. This was based on his experience of 26 patients treated conservatively, of which two survived an attack of meningitis and four died as a result of meningitis (Lewin 1954, 1966). This more aggressive management policy was supported later by Morley & Hetherington (1957). At the beginning of the 1970's, a more conservative line of management was again advocated (Leech & Paterson 1973). This policy was based on a survey of 118 cases of CSF rhinorrhoea, in which the meningitis rate was 6 % in those who were treated conservatively and 1.5 % in those who underwent dural repair, the difference not being statistically significant. Furthermore, the authors reported a very high surgical morbidity rate of 25.4 %.

1-2,4 History of CSF Fistulae Diagnosis;

It is often difficult to differentiate between CSF and nasal secretions in cases of non-traumatic CSF fistulae and it is even harder in traumatic cases to differentiate between bloody CSF and blood. Biochemical tests have been used extensively to determine the nature of the fistulous fluid. Glucose is normally present in the cerebrospinal fluid and therefore testing the fistulous fluid for glucose seemed to provide the answer. Unfortunately, glucose is also present in the nasal and lachrymal secretions and a false positive rate for CSF of 45-75 % has been recorded using glucose-oxidase test papers (Gadeholt 1964, Kirsch 1967, Healy 1969 & Kosoy & others 1972). However, If the amount of fistulous fluid is sufficient allow quantitative analysis for glucose, then testing for glucose is more reliable and a value of 1.7 millimoles/litre (30 mg %) indicates that the fluid is CSF (Gadeholt 1964). A more specific technique has been developed recently to confirm the presence of CSF. The value of this technique will be presented in chapter 6.

Radiography is the most widely used technique to investigate CSF fistulae. Luckett was the first to detect pneumocephalus following skull fracture using radiography (Luckett 1913). Cairns predicted that anterior cranial fossa (ACF) tomography would be of value in fractures of the frontal sinus (Cairns 1937). Oblique views of the orbital roof to visualize the postero-superior wall of the frontal sinus and the roof of ethmoids were introduced in 1942 (Calvert 1942 and Johnson & Dutt 1944).

The predicted value of tomography was confirmed in 1952 (Tonnis & Frowein 1952 , Brandt 1959 and Jefferson & Lewtas 1963). Jefferson & Lewtas suggested that if tomography alone did not show the site of the CSF fistula, introduction of air into the subfrontal region, combined with anterior cranial fossa tomography might give more accurate information. The association of air fluid level in the paranasal sinuses and basilar skull fractures are well known (Reynolds 1961 & Robinson & others 1967). A method, using fluid-air displacement in conjunction with tomography, to localise the site of CSF leakage in the sphenoid sinus, has been described (Marc and others 1973). The importance of the lateral skull radiograph in the brow-up position of the head in detecting intra-cranial air was emphasised by North and Jennett (1972).

Cisternography, using intrathecal injection of substances which can be traced along the subarachnoid space and eventually through the CSF fistula, has been used to localise the site of CSF leakage by several authors. Subdural air encephalography was used mainly to demonstrate scars uniting the brain to the dura in post-traumatic epilepsy but also to show the site of CSF fistulae (Penfield & Norcross 1936, Hemmingson 1940, Lindgren 1941 and Mayr & de Reya 1951). The same technique was used in combination with anterior cranial fossa tomography to locate CSF fistulae (Jefferson and Lewtas 1963). The subdural air injection technique was further modified by injecting the air into the subarachnoid space instead of the subdural space to detect brain adhesions at the site of CSF fistulae (Tonnis & Loew 1948).

Intrathecal dye injection was also used to locate the CSF fistulae. Dohlman (1948) used blue stain cystachrome, Kirchner & Proud (1960) used sodium fluorescein and Gotham & others (1965) used indigo-carmine. Of the dye cisternographies, the fluorescein method has become the most widely used. It was refined by Messerklinger (1972) and Oberascher & Arrer (1986). It involves injecting 2 mls of 5 % sodium fluorescein intrathecally via a lumbar puncture and immediately placing three small sponges into each nostril. The sponges are left overnight and sent the next morning for analysis. The fluorescein is detectable by nasal endoscopy using blue filters and by electrophoretic & photometric analysis of the fluid in the sponges.

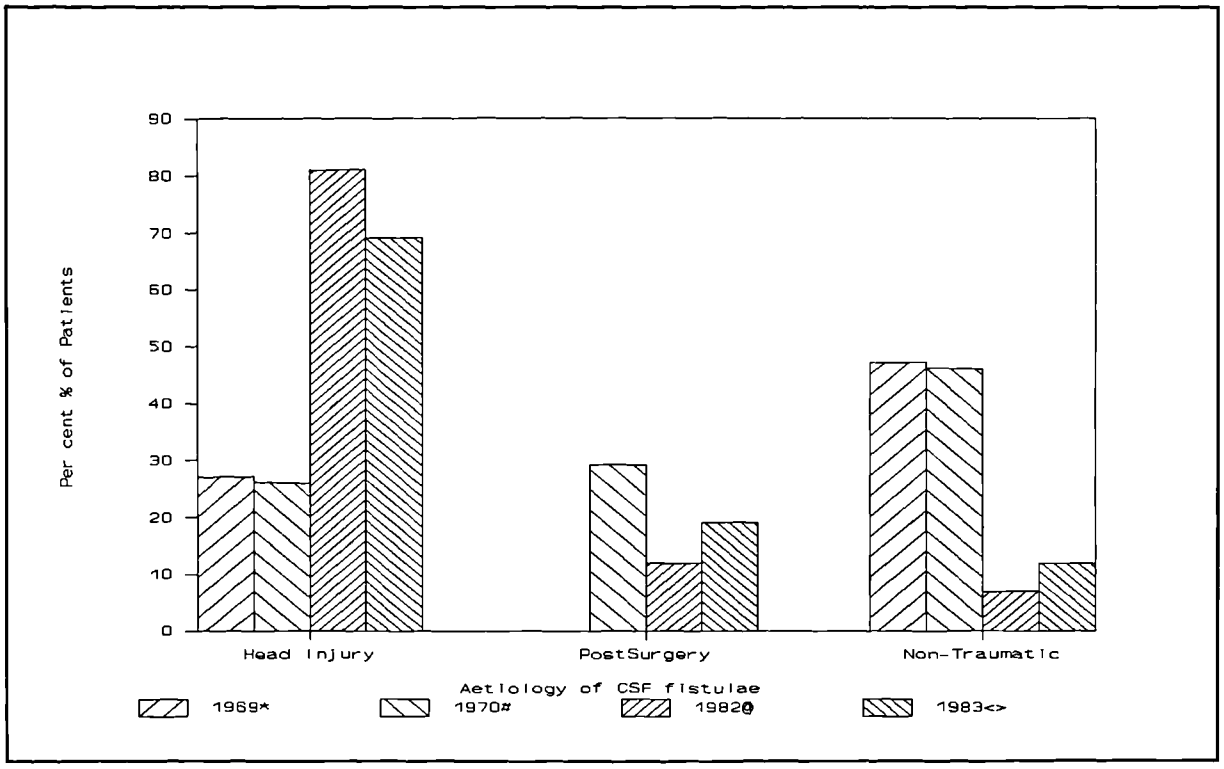
Radioisotope cisternography (RIC) was introduced by Di Chiro in 1964 and has been used in the differential diagnosis of hydrocephalus, to test shunt patency and to detect CSF leakage (Di Chiro 1964). Many other radionuclide substances have been used; ^{24}Na by Crow & others (1956), RISA by Di Chiro & others (1964), ^{111}I-HSA & ^{111}In-DTPA by Cooper & Herbert (1975), ^{169}Yb-DTPA, ^{131}I-HSA, ^{99m}Tc-DTPA and ^{99m}Tc-HSA (Maeda & others 1984). Radioisotope cisternography involves placing sponges in the patient's nose, intrathecal injection of the radioisotope and quantitative Scintigraphy of the patient's head and the nasal sponges after removal. Metrizamide computed tomographic cisternography (MCTC) was first introduced by Drayer & others to demonstrate CSF leakage (Drayer & Others 1977).

The patient is premedicated with 10 mg of diazepam 30 minutes before the examination, 5-6 millilitres of nonionic water-soluble contrast (metrizamide or lopamidol, in a concentration of 185-200 mg Iodine / millilitre) are injected intrathecally and cotton pledgets are placed in each nostril. If the CSF leakage is intermittent or inactive at the time of examination, the patient is asked to cough or perform a Valsalva manoeuvre so as to attempt to induce the CSF leakage (Menalfe & others 1982). Some authors have used an intrathecal saline infusion in order to show a slow or intermittent CSF leakage (Naidich & Moran 1980). After the intrathecal injection of contrast the patient is tipped head down (-60 °) in the prone position for 1-2 minutes before he is returned to -10 ° position and scanned using computed tomography. The Metrizamide-CT-Cisternography is considered to be positive if the contrast was visualised passing through a dural and / or a bony defect, the defect was identified and the contrast was detectable in one or more of the paranasal sinuses or the cotton pledgets (Menalfe & others 1982).

1-3 AETIOLOGY OF CSF FISTULAE;

All CSF fistulae have in common a breach in the dura through which CSF escapes from the subarachnoid space and by far the commonest cause of CSF fistulae is trauma. However, in the series compiled by St Clair Thomson (1899), there was only one case of traumatic origin in the 21 collected cases of CSF rhinorrhoea (Thomson 1899). However, in the recently reported series of CSF fistulae of mixed aetiology, trauma has become the most common cause of CSF fistulae (Figure 1-3).

Figure 1-3: The relative incidence of the different causes of CSF fistulae, over the years:



* Ray & Bergland (1969). # Brisman & others (1970).

@ Westmore & Whittam (1982) <> Park & others (1983).

The causes of CSF fistulae include:

(a) Congenital Anomalies.

(b) Head injuries.

(c) Surgical Trauma (Iatrogenic).

(d) Raised Intracranial Pressure & Tumours.

(e) Focal osteomyelitis.

(f) Idiopathic " Spontaneous ".

(a) Congenital Anomalies:

CSF fistulae occur rarely as a result of congenital anomalies. However, anatomical studies suggested seven possible sites of potential development of CSF fistulae, these are;

(1) The perineurial sheets of the olfactory nerves.

(2) The sella turcica.

(3) The perineurial sheets of the Facial (VII) and Vestibulo-Cochlear (VIII) nerves.

(4) The cochlear aqueduct.

(5) The vestibular aqueduct.

(6) The foramen caecum of the anterior cranial fossa.

(7) The subarcuate fossa of the petrous bone.

Only the first four sites have been documented in the literature to be associated with CSF fistulae and a case demonstrating the sixth site as the cause of a CSF fistula in one patient in the present study will be described later.

It has been postulated that as a result of the pulsatile CSF pressure the subarachnoid pouches present in these areas progressively become distended with CSF causing focal atrophy and ultimately rupturing through to form a CSF fistula (O'Connel 1964, Gabriele 1968, Calkins & others 1968, Brisman & others 1970 and Obrador 1972). Figure 1-4 & 1-5 show schematic presentations of these sites of potential focal atrophy.

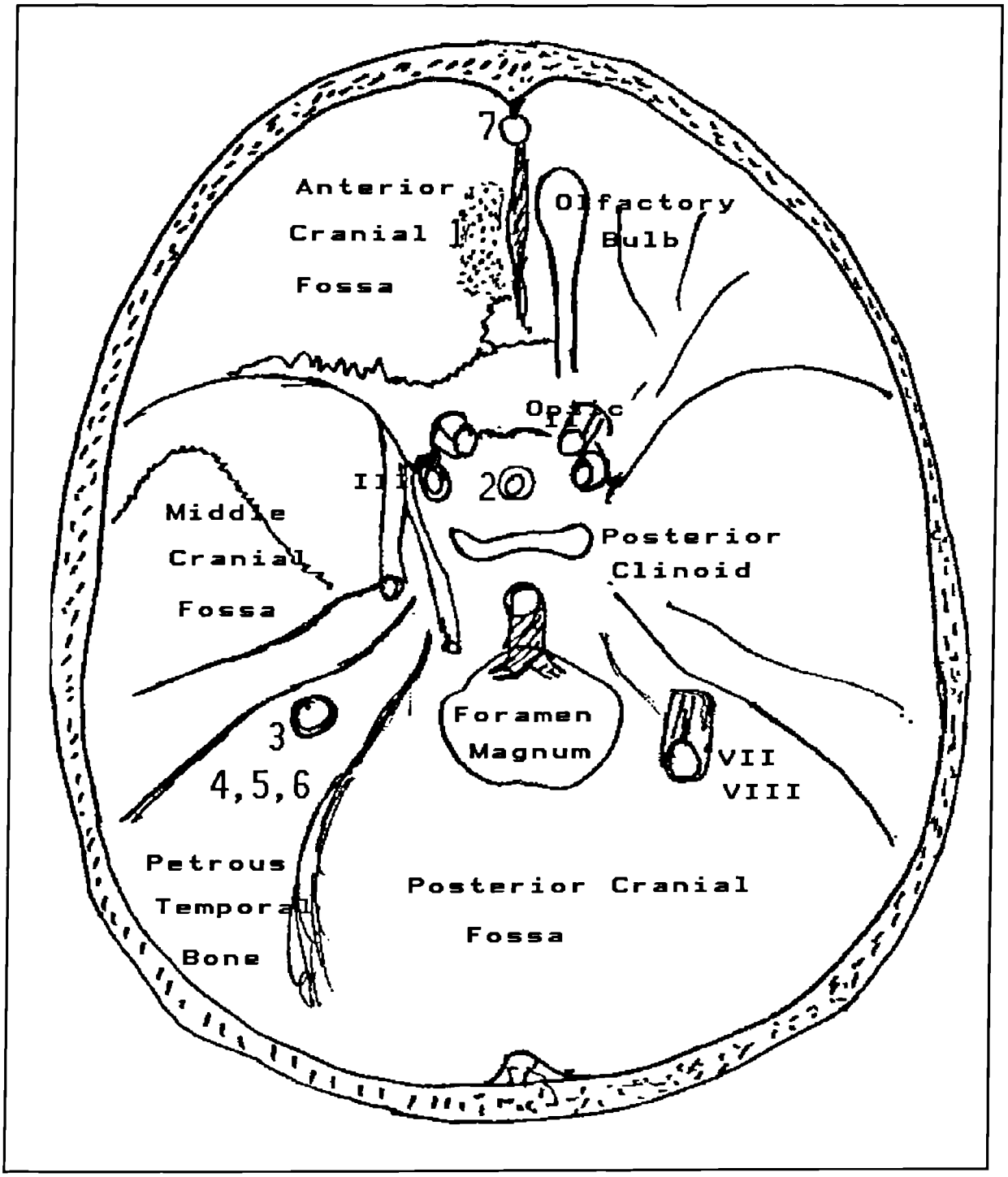
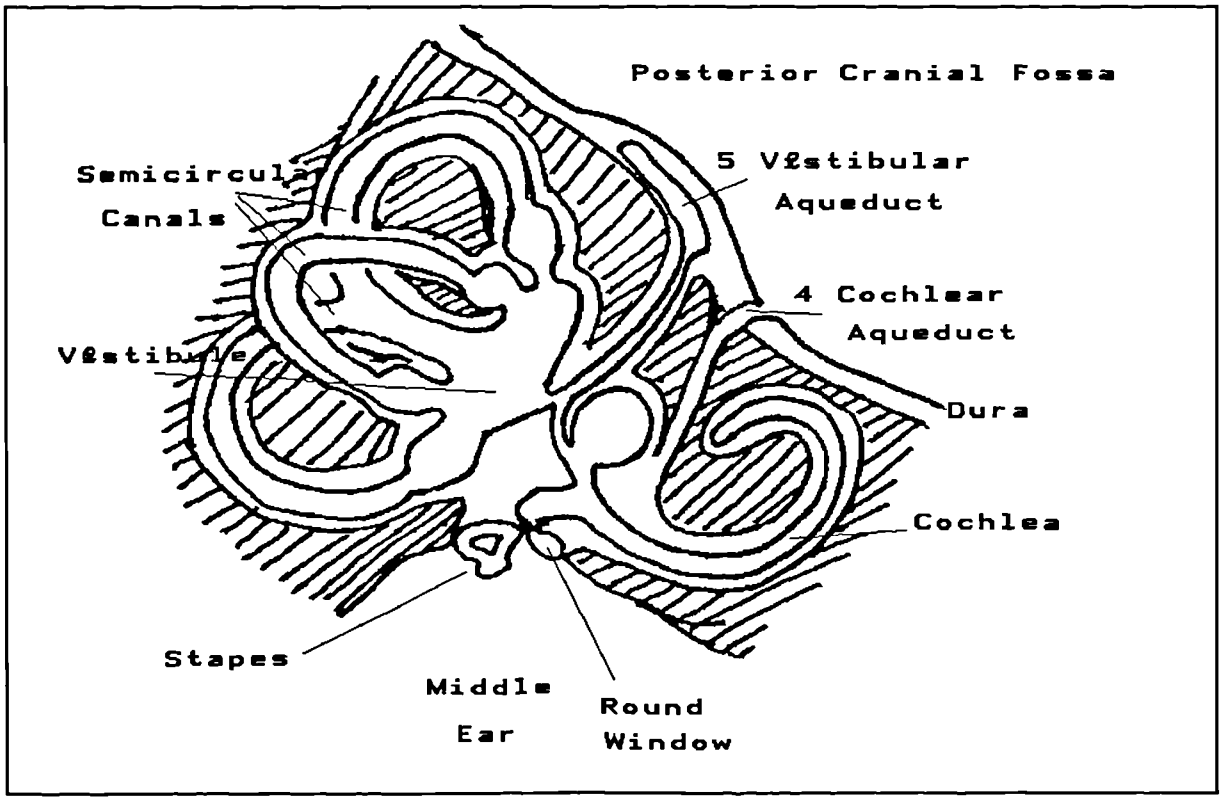


Figure 1-4: Diagram of a superior view of the skull base showing the potential sites of focal atrophy;

1- Cribriform plate. 2- Sella Turcica.
3- Internal auditory meatus. 4- Cochlear aqueduct.
5- Vestibular aqueduct. 6- Subarcuate fossa.
7- Foramen Caecum.

Figure 1-5; A diagram through the petrous temporal bone showing the potential sites for CSF FISTULAE;



4- The cochlear aqueduct. 5- The vestibular aqueduct.

Two cases of non-traumatic CSF rhinorrhoea, in which the olfactory bulb was atrophic have been described (O'Connel 1964 and Brisman & Others 1970). It has been suggested that the pulsatile CSF pressure caused the empty perineurial sheets of the olfactory nerves to become distended and eventually rupture into the nose forming a CSF fistula (O'Connel 1964). A similar mechanism has been postulated in the causation of nontraumatic CSF fistulae associated with the empty sella syndrome, in which the sella turcica appears to be empty apart from CSF (Gabriele 1958, Calkins & others 1968, Brisman & others 1970 and Obrador 1972).

An anatomical analysis of 138 normal human skulls revealed 27 defects in 20 sphenoid bones and there were remnants of the craniopharyngeal canal in 18 % of the sphenoid bones. Furthermore,in 5 % there were defects connecting the cranial cavity to the sphenoid sinus (Hooper 1971). These defects may be responsible for the development of some of the nontraumatic CSF fistulae through the sphenoid bone. In a series of 11 cases of nontraumatic CSF fistulae, five (45%) were through the cribriform plate and five were through the sphenoid sinus (Brisman & others 1970). In another report of 14 cases of nontraumatic CSF fistulae, four were related to the sella turcica, of which two were associated with an empty sella and two with pituitary adenomas (Bjerre & Others 1982).

Congenital CSF fistulae through the internal auditory meatus have been demonstrated (Kaufman & others 1969, Rockett & others 1969, Skolnik & Ferrer 1959, Ferrer 1960, Schultz & Stool 1970 and Clark & others 1978). A case of congenital mixed deafness, nontraumatic CSF fistula and ablation of the cochlear duct has been reported (Farrior & Endicott 1971). The cochlear aqueduct is often wider in children and may account for the predominance of meningitis & spontaneous CSF otorrhoea in children (Palva 1970). In a review of 11 cases of nontraumatic CSF otorrhoea, nine were children and the majority were associated with major anomalies of the middle ear (Kramer & others 1971). More than 85 % of nontraumatic CSF otorrhoea, occur through the oval window. Less commonly the leak occurs through a fissure in the promontory or through a defect in the roof of the eustachian tube (Parisier & Birken 1976).

A syndrome of congenital deafness and otitic meningitis (Mondini's dysplasia) has been described (Stool & others 1967). The association of Mondini's dysplasia and non-traumatic CSF leakage through or around the stapes footplate has been documented (Skolnik & Ferrer 1959 and Barr & Wershall 1965). It has been suggested that in Mondini's dysplasia the CSF may reach the vestibule through a patent cochlear aqueduct or through the fundus of the internal auditory meatus (Clark & others 1978).

The foramen caecum near the crista galli in the floor of the anterior cranial fossa may remain patent and lead to a CSF fistula. This was the aetiology of one case encountered in the present study. A 3-year-old girl presented,to the Mersey Regional Department of Medical and Surgical Neurology, with CSF rhinorrhoea and few weeks later with meningitis. Iohexol-CT-cisternography demonstrated CSF leakage through a patent foramen caecum which was confirmed at surgery.

Congenital hydrocephalus also may lead to nontraumatic CSF fistulae as was demonstrated by Miller in 1828. CSF fistulae occurring in association with hydrocephalus often manifest as CSF rhinorrhoea because of the fragility of the cribriform plate and its juxtaposition to the subarachnoid space. The theory of erosion of the cribriform plate as a result of raised intracranial pressure has been demonstrated in experimental animals by injecting celloidin into the subarachnoid space in dogs under high pressure. It was found that the celloidin often escaped through the cribriform plate (Locke & Naffziger 1924).

Congenital nasal encephalocele may present with CSF rhinorrhoea spontaneously or after ill-advised biopsy of a suspected nasal polyp (Raskind & Doria 1966).

(b) Head Injuries and CSF Fistulae;

With the significant number of road traffic accidents and assaults, cranial trauma has become the most common cause of CSF fistulae. Though the majority of the literature considered traumatic CSF fistulae alone, the clinical series of CSF fistulae of mixed aetiology, reported over the years, have shown that trauma has increasingly become the most common aetiology in recent years (Table 1-1).

Table 1-2 ; The relative increase of traumatic CSF fistulae over the years :

Authors (Publication Year)	Total Number	Trauma leaks %
St Clair Thomson 1889	21	5
Ray & Bergland 1969	41	27
Brisman & Others 1970	35	26
Manelfe & others 1982	27	77
Westmore & Whittam 1982	100	81
Park & others 1983	42	69

Fractures involving the paranasal sinuses are the commonest cause of CSF leakage through the nose. In a survey of 128 cases of skull fractures involving the paranasal sinuses, 21 (16.5 %) patients developed CSF rhinorrhoea (Calvert 1942). In a series of 308 cases of non-missile head injuries involving the paranasal sinuses, 84 (27%) developed CSF rhinorrhoea and only 7.2 % of 1000 consecutive head injuries had fractures involving the paranasal sinuses (Lewin 1954). A further survey of 1,250 head injuries revealed an incidence of 24 % of basilar skull fractures, of which 11.5 % developed CSF leakage (Brawley and Kelly 1967) and similarly in a series of 1077 consecutive skull fractures, there were 168 basilar skull fractures (15.6 %), of which 40 (24 %) patients developed CSF leakage (Dagi & others 1983). Based on the data available from these large series, one can predict that the incidence of CSF rhinorrhoea following head injury would be 2.1 to 3.8 per cent.

The most frequent site of traumatic CSF fistulae is through the cribriform plate (Cairns 1937), because;

(1) The cribriform plate is intimately related to the subarachnoid space.
(2) The inner periosteum of the cribriform plate is the thinnest part of dura.
(3) The dura is firmly anchored by its extensions through the cribriform plate along the olfactory nerves.

Fractures involving the frontal, ethmoidal and sphenoidal air sinuses are the second most frequent source of CSF fistulae. These fractures are more likely to occur if the force was applied to the forehead such as a head-on blow. They also liable to occur when the face is moved backwards. In these situations the fracture often involves the cribriform plate leading to CSF rhinorrhoea (Cairns 1937). Fractures of the frontal bone alone are less likely to produce CSF leakage as the dura can be stripped easily without being torn at this site. Less commonly fractures involving the petrous bone may lead to CSF otorrhoea originating from the middle or posterior cranial fossa. Occasionally, petrous bone fractures lead to paradoxical CSF rhinorrhoea, if the tympanic membrane remains intact. In a survey of 279 basal skull fractures, 16 % were classified as temporal bone fractures, of which 8 % (4/45) were bilateral (Hicks & others 1980). Only four of 41 temporal bone fractures (10 %) developed CSF otorrhoea (Dedo and Sooy 1970). However, the reported incidence of CSF otorrhoea is much higher (33 %) following petrous bone fractures (Hicks & others 1980). This suggests that CSF otorrhoea is more likely to occur following fractures of the petrous bone compared with all temporal bone fractures. These data also suggest that the predicted incidence of CSF otorrhoea would be 6 % following basal skull fractures and 0.5 % of all head injuries, which is four times less common than that of CSF rhinorrhoea.

Although, the majority of temporal bone fractures are of mixed variety, they are conventionally classified into;

(1) Longitudinal temporal bone fractures, in which the fracture line passes parallel to the longitudinal axis of the temporal bone. Classically these fractures occur as a result of a blow to the frontal, temporal and parietal regions. The fracture line extends from the squamous temporal bone along the posterior part of the bony ear canal involving the tegmen tympani, which often damages the overlying dura.

(2) Transverse temporal bone fractures, which are fractures running at an angle to the longitudinal axis of the temporal bone and they often traverse the pyramidal process of the temporal bone containing the internal auditory canal. Less commonly transverse fractures pass through the vestibule or cochlea.

Longitudinal temporal bone fractures are 4 to 6 times more common than transverse fractures (Wright & Taylor 1972). In a series of 40 temporal bone fractures, 77 % were longitudinal and 33 % were transverse fractures (Hicks & others 1980). CSF otorrhoea and facial nerve injuries are more likely to occur in association with transverse temporal bone fractures. The reported incidence of CSF otorrhoea in association with longitudinal temporal skull fractures varies from 14 to 29 % (Griffin & others 1984 and Hicks & others 1980), while the incidence of CSF otorrhoea following transverse temporal bone fractures is 44 % (Hicks & others 1980). Facial nerve injuries occur in 10 to 18 % of longitudinal temporal bone fractures and develop in 38 to 50 % of transverse fractures (Kettel 1950, McCabe 1972, Miehlke 1973 & Fisch 1974).

The accumulated data from various series showed that more than 40 % of traumatic CSF leaks occur through the cribriform plate, one fifth through the sphenoid sinus, 16 % through the frontal sinus alone, 4 to 8 % through the petrous bone and 16 to 20 % through multiple defects. Fifty-two to seventy-nine per cent of post-traumatic CSF leaks occur acutely within 48 hours (Lewin 1954 [60 %], Robinson 1970 [52 %], Westmore & Whittam 1982 [57 %] and Park & others 1983 [79 %]). However, delayed traumatic CSF leakage can occur as long as 34 years after head trauma (Russel 1984). More than 60 % of post-traumatic CSF fistulae occur in patients below the age of 30 years (Robinson 1970 and Park & others 1983), but they are rare in children below the age of 2 years because of the elasticity of the skull base and the poor development of the paranasal sinuses in infants (Caldicott & others 1973). The reported adult to children ratio is 10 to 1 (Hendrick & others 1964, Hardwood-Nash 1970, Caldicott & others 1973 and Einhorn & Mizrali 1978), but there were more adults than children in the population. The incidence of basilar skull fractures is about 3.5 % and the CSF leakage rate is about 0.5 % in children below 15 years of age (Einhorn & Mizrali 1978).

The estimated incidence of post-traumatic aeroceles is between 0.5 and 1 per cent. The aerocele may enlarge over several days (Markham 1967). However, a higher incidence of 9.7% has been reported following head trauma requiring computed tomography and 82 % of the aeroceles were present 6 hours after the injury (Standel & Hacker 1986). This may merely be aconsequence of the increased sensitivity of computed tomography

as a method of investigation rather than a change in the mechanism or timing of the development of intracranial pneumocephalus.

(c) Post-Surgical CSF Fistulae;

CSF fistulae may complicate surgical treatment of paranasal, skull base and intracranial diseases. The most commonly implicated procedures are;

(1) Transsphenoidal pituitary surgery.

(2) Cranial surgery for tumours involving the floor of the cranial fossae.

(3) Cerebello-pontine angle (CPA) surgery.

(4) Nasal and aural surgery.

The CSF leakage often occurs immediately and it is often recognised by the surgeon at the time of operation . The majority of these fistulae are repaired at the time of the primary surgery, but many postsurgical CSF fistulae are recognised later and require further treatment. The relative incidence of postsurgical CSF fistulae is shown in table 1-2.

Table 1-2; The relative incidence of postsurgical CSF fistulae;

Authors (Publication Year)	Total Number	Iatrogenic leaks
Ray & Bergland 1969	41	47 %
Brisman & others 1970	35	29 %
Hicks & others 1980	43	23 %
Westmore & Whittam 1982	100	12 %
Park & others 1983	42	19 %

The apparent reduction in the relative incidence of postsurgical CSF fistulae (Table 1-2) is the result of anincreased incidence of CSF fistulae associated with head injuries (Table 1-1). The actual number of postsurgical CSF fistulae is certain to increase as more radical surgery, on both sides of the skull base, is being contemplated.

Transfrontal pituitary surgery carries about 0.5 % CSF-leakage-rate (Ray & Bergland 1969), while the risk of CSF leakage following trans-sphenoidal pituitary surgery varies from one to three per cent (Guiot 1973, Nicola 1975, Laws & Kern 1978, Wilson & Dempsey 1978, Faria & Tindall 1979, Derome & others 1980 and Hardy 1981).

The reported overall incidence of CSF rhinorrhoea & CSF otorrhoea following acoustic tumour surgery varied from 10 to 19% (House & others 1968 and Hicks & others 1980), while, translabrynthine surgery for cerebello-pontine-angle tumours is associated with 10 to 11% (Hicks & others 1980 and Thomsen & others 1989), of which 5 %, in Thomsen's series, required further surgery to close the CSF fistula. The average incidence of CSF leakage following cerebello-pontine-angle surgery is about 14 % (House & others 1968, Ojemann & others 1972, Bradly 1973, Glasscock & others 1975 & 1978, Hicks & others 1980 and Symon & others 1989). Symon & others (1989 & 1991) had also shown that the incidence of CSF leakage following acoustic tumour surgery has risen from 2.8 % in 1960's to 6.8 % in 1970's and to 18.4 % in 1980's, they had also shown that this rise in the incidence

of CSF leakage was related to the surgical approach.
A combination of retromastoid approach and dissection of the porus acousticus are more likely to cause CSF leakage (Symon & others 1989). In a collective series of 479 reported cases of CSF leaks following surgery, frontal craniotomy, transsphenoidal and nasal surgery were the most frequent causes of postoperative CSF leakage (Figure 1-6).

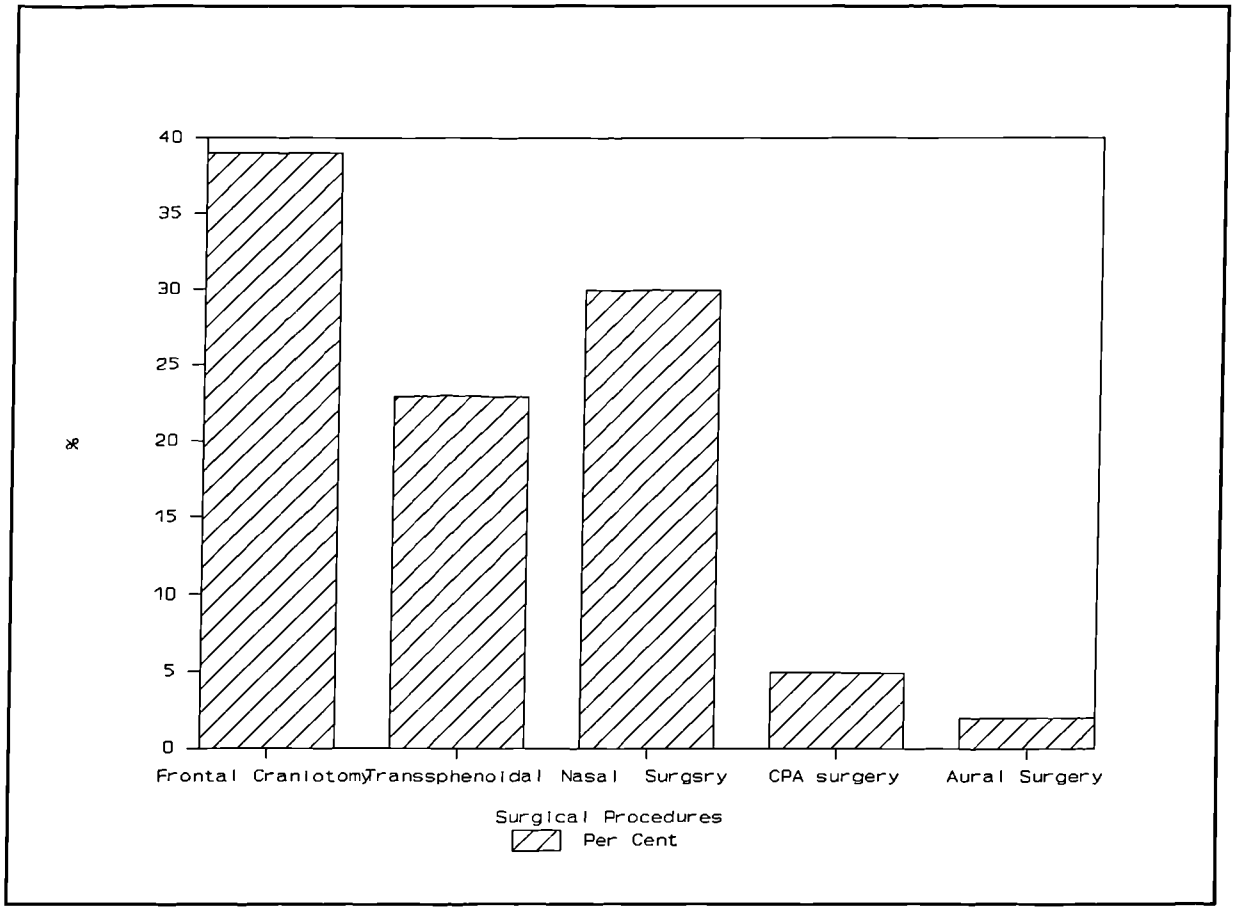


Figure 1-6; Relative incidence of CSF leaks after different surgical procedures :collected series of 479 cases of CSF leaks (Ray & Bergland 1969, Brisman & others 1970, Westmore & Whittam 1982, Park & others 1983 & Oberascher 1988.

(d) Raised Intracranial Pressure & Tumours;

Raised intracranial pressure, regardless of its underlying aetiology, may lead to CSF leakage. The fistula is more likely to occur through the cribriform plate as previously explained . Forty-five per cent of nontraumatic CSF fistulae were associated with raised intracranial pressure (Shugar & others 1981). Intracranial tumours may lead to CSF fistulae by direct invasion of the skull base or indirectly by raising the intracranial pressure. Pituitary tumours are the most frequent intracranial tumours associated with CSF fistulae, despite the fact that CSF leakage is a very rare presentation of pituitary tumours (Ommaya & others 1968). Pituitary tumours are more likely to produce CSF leakage following transsphenoidal surgery, subfrontal surgery, and radiotherapy (Baskin & Wilson 1982 and Landolt 1982). Rarely CSF leak may follow bromocriptine therapy of pituitary adenomas (Afshar 1982, Wilson & others 1983, Holness & others 1984, Kok & others 1985 and Bronstein & others 1989). There were only eight cases reported in the literature of CSF rhinorrhoea occurring secondary to bromocriptine treatment of prolactinomas without adjuvant surgery or radiotherapy (Afshar & Thomas 1982, Wilson & others 1983, Holness & others 1984, Kok & others 1985, Clayton & others 1985 & Bronstein & others 1989). The CSF leakage often starts within a month of treatment whatever the bromocriptine dosage. It has been postulated that the CSF fistula resulted from direct invasion of the dura by the adenoma. When the adenoma had shrunk because of the bromocriptine therapy, the CSF could flow past the residual tumour. One of the patients in this study has presented with an invasive prolactinoma

(55 years old woman with prolactin level 430,000 units/litre), which shrunk on bromocriptine but a month later, she developed CSF rhinorrhoea.

The second most common intracranial tumours causing CSF fistulae are meningiomas, particularly those occurring in the anterior cranial fossa. Tumours of the skull base also may lead to CSF fistulae especially those involving the paranasal sinuses. CSF fistulae, occurring in association with these tumours, are more likely to follow surgery and/or radiotherapy, but they rarely occur due to direct tumour invasion of the skull base or indirectly because of focal atrophy and raised intracranial pressure (ICP).

Hydrocephalus may lead to a CSF fistula because of raised intracranial pressure (ICP) and focal atrophy. The first reported case in the English literature, was due to hydrocephalus (Miller 1828).

Benign intracranial hypertension (BIH) was considered to be the cause of one case of nontraumatic CSF rhinorrhoea in the series reported by Brisman & others (1970), but this particular case had subtemporal decompression four years prior to the onset of CSF rhinorrhoea. In this study, there were two cases of untreated benign intracranial hypertension presented with non-traumatic CSF rhinorrhoea.

Frontal sinus osteomas have been implicated in the causation of nontraumatic aeroceles. The first case of a CSF fistula in association with bony dehiscence secondary to frontal osteoma was described by Dr Core from Montreal (Beauchamp & others 1951). More recently, two other cases of aeroceles complicating frontal sinus osteomas have been reported (Hardwidge & Varma 1985 and Huneidi & Afshar 1989).

(e) Focal Osteomyelitis and CSF Fistulae;

Focal osteomyelitis of the middle ear and paranasal sinuses may rarely lead to CSF leakage (Calcaterra 1980). CSF fistulae are more likely to complicate chronic middle ear infection and frontal osteomyelitis. However, a fatal CSF fistula secondary to sphenoidal sinus infection has been reported (Som & Kramer 1940) and in a series of 43 cases of nontraumatic CSF otorrhoea, 7 (16 %) CSF fistulae were secondary to chronic ear infection (Hicks & others 1980). Nevertheless, the mortality from otitic complications had been reduced from 30 % (39/129) to less than 4 % with the use of antibiotics (Hicks & others 1980).

(f) Idiopathic or True Spontaneous CSF Fistulae;

True spontaneous CSF fistulae (idiopathic) are exceptionally rare (Nussey 1966 and Ommaya & others 1968 & 1976). Most CSF fistulae, reported under " spontaneous " CSF leaks, were in fact associated with either congenital anomalies, focal atrophy or undetected underlying pathology.

1-4 CLASSIFICATIONS OF CSF FISTULAE:

The first classification, which was suggested by Cairns (1937) described four main categories of CSF fistulae ;

I - Acute traumatic CSF fistulae.

II - Delayed Traumatic CSF fistulae.

III- Iatrogenic CSF fistulae.

IV - Spontaneous CSF fistulae.

A further subgroup was added afterwards, to include CSF fistulae presenting with post-traumatic intracranial infection and/or aeroceles (Cairns 1937). This classification is not exclusive and uses the word spontaneous to include what is clearly CSF fistulae with known aetiology. True spontaneous CSF leakage is extremely rare .

A more popular classification was introduced by Ommaya in 1964, this was based on the aetiology of the CSF fistula (Ommaya 1964 and Ommaya & others 1968). Accordingly, the CSF fistulae were divided into traumatic and nontraumatic as follows ;

I - Traumatic (acute or delayed)

1- Accidental 2- Iatrogenic

II- Non-Traumatic

1- High CSF pressure 2- Normal pressure

a- Hydrocephalus..... a-Congenital

b- Tumours b-Focal atrophy

c-Osteomyelitis

This classification was modified by listing six causes under the non-traumatic type irrespective of the CSF pressure, which included ; space occupying lesions, hydrocephalus, empty sella syndrome, congenital anomalies and focal osteitis (Park & others 1983).

Both the original Ommaya's classification and its modified version are not entirely satisfactory as the subdivisions may often overlap. More complex classification has been suggested, in which all possible aetiological factors were listed as main divisions and each type was subdivided into high and normal pressure subtype (Spetzler & Wilson 1978).

Because of the complexity of CSF fistulae, no single classification can be exclusive and without overlapping of the subdivisions. However, from the management point of view, any classification to be practical should take account of;

(1) The site of the CSF fistula ,

(2) The aetiology of the fistula and

(3) The perpetuating factors .

It is important to differentiate between those fistulae involving the anterior, the middle and the posterior cranial fossae, as those involving the latter two often stop spontaneously. It is also important to differentiate between traumatic and non-traumatic CSF fistulae, as the non-traumatic type may be associated with an intra-cranial or extracranial disease, which may require surgical treatment. Similarly, the differentiation between CSF fistulae associated with perpetuating

factors and those which are not is important, as the CSF fistula is unlikely to heal unless the perpetuating factor is treated. The perpetuating factors are those forces which prevent natural healing of the fistula, these include :

(1) Poor tissue healing.

(2) Direct invasion by tumours.

(3) Osteomyelitis & Paranasal sinus infection.

(4) Presence of foreign bodies.

(5) Raised intracranial pressure (ICP).

Raised intracranial pressure (ICP) is by far the most significant factor in this context. It is implicated in both the aetiology and perpetuation of CSF fistulae. Causes of raised ICP include;

(1) Benign intracranial hypertension (BIH),

(2) Hydrocephalus.

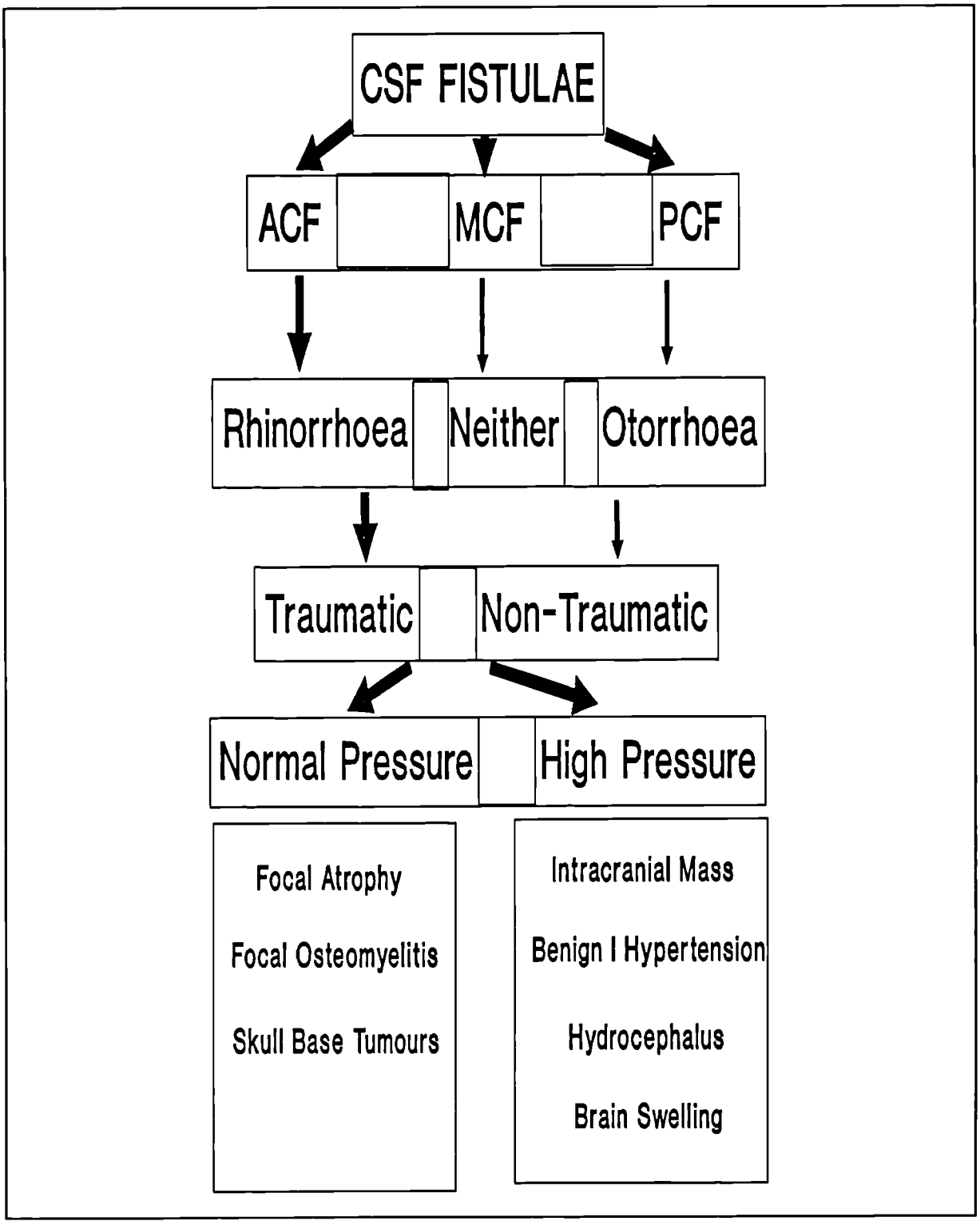
(3) Intracranial mass lesions.

(4) Brain swelling.

The pressure difference between the intracranial compartment and the CSF fistula forces a small brain hernia through the rent in the dura, which prevents natural healing and permanent fistula closure.

Throughout this thesis, a simple classification based on the previous points will be used, the advantages of which is that it forms the basis of management of these fistulae (Table 1-3).

Table 1-3 : The Practical Classification of CSF Fistulae



1-5 PRESENTATION OF CSF FISTULAE:

CSF fistulae can present in one of several ways;

(1) CSF Leak (Rhinorrhoea and/or Otorrhoea);

CSF rhinorrhoea occurs in 2.1 to 3.8 % of all closed head injuries and 7.2 to 11.5 % of all basilar skull fractures, while CSF otorrhoea occurs in 0.5 % of all closed head injuries and 10 to 33 % of temporal bone fractures. The CSF leakage begins within a week of the injury in 40 to 73 % of cases (Lewin 1954, Brisman & others 1970, Robinson 1970, Westmore & Whittam 1982 and Park & others 1983). The leaking CSF can be clear or bloody, meagre or profuse, but voluminous CSF leakage is uncommon except in fractures involving the middle fossa, particularly those involving the sphenoid air sinus (Lewin 1954). Straining, coughing, sudden movement or dropping the head particularly on waking up in the morning and putting the slippers on, or compression of the cervical jugular veins may increase or precipitate CSF flow through the fistula. Unlike nasal secretions, CSF contains very little protein and so it is not sticky and it does not "stiffen" a handkerchief. Sometimes the leaking CSF runs into the throat and causes a characteristic salty taste. If the CSF contains blood it forms a double ring stain on the pillow, linen, clothes or tissue paper, the inner ring is the dark blood and the outer ring is the halo caused by the CSF.

(2) Suspected (Occult) CSF fistulae ;

When there is no objective evidence of CSF leakage, CSF fistulae cannot be excluded and should be suspected in any patient having one or more of the following signs & symptoms;

(a) Bilateral back eyes (Panda's eyes - Figure 1-7), this is indicative of an anterior fossa fracture.

(b) Battle's sign, a bruise behind the ear, which is indicative of a middle fossa fracture.

(c) Haemotympanum, indicating middle ear involvement.

(d) A complaint of salty sensation at the back of the throat.

(e) Succussion splash on movement of the head indicating the presence of an aerocele.

(f) Unilateral or bilateral anosmia, indicating an anterior fossa fracture.

(g) Finding the double-ring sign on the patient's pillow or linen.

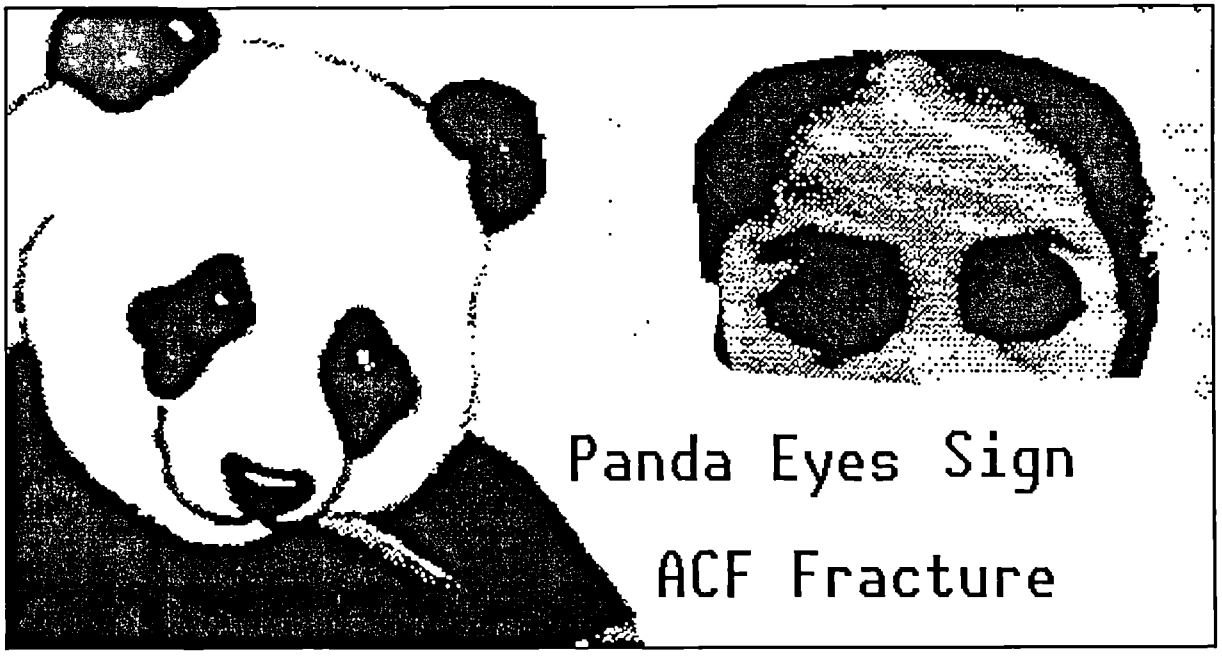


Figure 1-7: Panda's eyes or bilateral periorbital ecchymosis.

The relative incidence of these signs in basilar skull fractures are as follows;

Haemotympanum	80.9 %
Battle's sign	11.9 %
Panda's eyes	7.7 %
Anosmia	2.4 %

(3) Intracranial Aeroceles (Pneumocephalus):

The presence of intradural air is definitive evidence of a dural fistula unless air has been introduced during surgery and/or the investigation of the patient. The air can be any where in the cranial cavity and it is often asymptomatic, but it can produce mass effect, headache, focal neurological deficit and/or alteration in the level of consciousness. The air is detectable by computed tomography in 82 % within 6 hours of injury (Standel & Hacker 1986). These authors have also found an aerocele incidence of 9.7 % in head injuries requiring CT scanning. This figure is much smaller when conventional radiography is used. A lateral projection skull radiograph in the brow-up position of the head gives the best chances of demonstrating the intracranial air (North & Jennett 1972).

(4) Intracranial infection :

Meningitis can be the first presentation of CSF fistulae and this topic will be discussed in more detail in the next chapter.

Cross sectional surveys of CSF fistulae suggest that CSF rhinorrhoea is the commonest presentation (Figure 1-8).

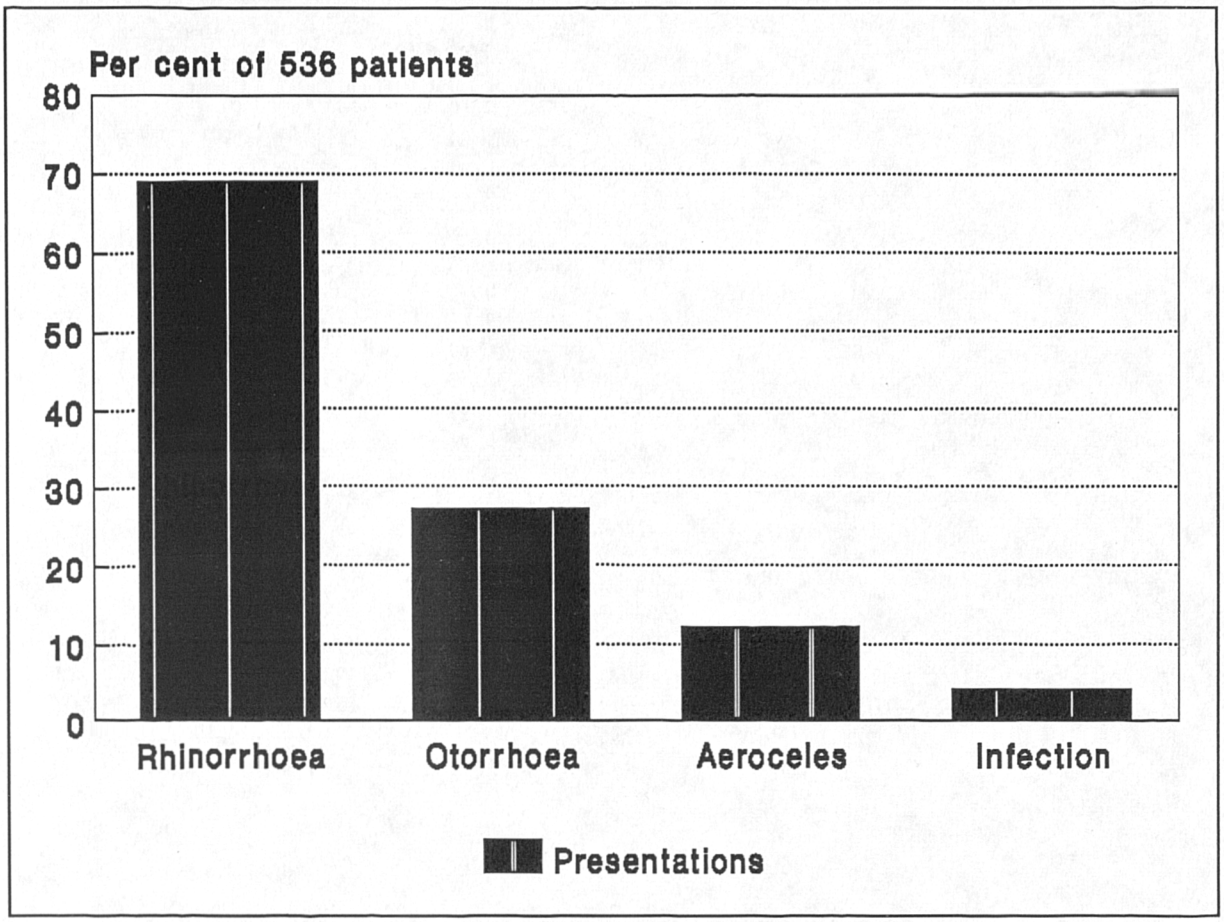


Figure 1-8: A histogram of the presentation of CSF fistulae :

Based on mixed series reported in the literature ; Lewin 1954 (84 cases), Robinson 1970 (59 patients), Leech & Paterson 1973 (155 cases), Ignelzi & others 1975 (43 cases), MacGee & others 1976 (58 cases), Klasterskey & others 1976 (52 cases), Dagi & others 1983 (33 cases) and Zrebeet & Huang 1986 (36 cases) The range of incidence of rhinorrhoea varied from 31 - 100 %, otorrhoea 20 - 69 % , aeroceles 29-36 % and meningitis from 4-15 % .

Laboratory and radiological methods have been used to confirm the diagnosis of CSF fistulae as follows;

(1) Biochemical tests :

(a) Glucose-Oxidase test papers:

These are not reliable and give false positive results in 45-75 % (Gadeholt 1964, Kirsch 1967, Healy 1969 & Kosoy & others 1972).

(b) Quantitative analysis of the fluid for glucose:

This is more reliable than the glucose-oxidase test papers and a glucose concentration of 30 mg % (1.7 mmol/l) is confirmatory of CSF (Gadeholt 1964).

In general testing the fistulous fluid for glucose is not satisfactory because false positive results can occur because of presence of glucose in nasal & lachrymal secretions and the leaking CSF is often mixed with blood which normally contains glucose. Furthermore, false negative results can happen as a result of a low glucose concentration in an infected CSF, particularly if the specimen for testing was collected in unfluorinated container.

(2) Immunological testing for $\underline{B_2}$-Transferrin :

Because $\underline{B_2}$-transferrin is present in the CSF only and it migrates slowly on electrophoresis, it can be detected in small amounts of CSF. The value of this technique will be discussed in chapter 6.

(3) Plain radiography :

Plain radiographs of the skull, particularly the lateral projection with the head in the brow-up position, may show intracranial air in 28 to 36 % of CSF fistulae (Lewin 1954, Robinson 1970 and MacGee & others 1976). Polytomography does not have any advantages over computed tomography (CT), but it can be of value if a CT-scanner is not available (Brandt & others 1983). Polytomography was reported to be positive in 67

to 88.8 % of basilar skull fractures, compared to 48.8 % when plain skull radiographs were used alone (Dagi & others 1983 and Menalfe & others 1982).

(4) Cisternography :

In this technique a traceable contrast or dye is injected into the subarachnoid space and traced along the CSF pathways and eventually through the CSF fistula. These techniques will be discussed in more detail in chapter 7. These techniques require an investment in a high degree of technology and expertise. The patient must be detained in hospital at least overnight and those who are severely ill are not suitable for cisternography. Furthermore, cisternography is contraindicated in patients with intracranial mass lesions because of the risk of brain herniation. Radioisotope cisternography (RIC) was reported to be successful in confirming the diagnosis of CSF fistulae in up to 85 % of cases
(Mamo & others 1982) and Metrizamide-CT-cisternography (MCTC) in 90 to 100 % of cases (Menalfe & others 1983 & Ozgen & others 1990). Fluorescein cisternography was reported to have a very high sensitivity in detecting CSF fistulae (Oberascher 1988). More recently digital subtraction cisternography (DSTC) was used to detect CSF fistulae (Byrne & others 1990). The value of these methods in the precise localization of CSF fistulae will be discussed in chapter 7.

Chapter 2

Bacterial Meningitis

Complicating

Unrepaired CSF Fistulae

2-1 Introduction:

Although, the rationale of treating CSF fistulae has long been based on the prevention of intracranial infection, the actual rate of morbidity and mortality from meningitis complicating dural fistulae is not well documented. In this chapter, the literature on the risk of meningitis & its sequelae in patients with CSF fistulae will be critically reviewed and a long-term follow up study of a large number of consecutive patients with CSF fistulae treated in the Mersey Region, will be presented to establish the actual risk of intracranial infection and its complications in these patients.

2-2 Epidemiology:

Bacterial meningitis continues to be the most serious complication of CSF fistulae despite the development of more and more powerful chemotherapeutic agents. It has the reputation of being treacherous and life threatening.

(1) Epidemiology of bacterial meningitis;

Descriptive epidemiological studies of bacterial meningitis, have identified that meningococci, streptococci and Haemophylus influenzae are the most commonly encountered pathogens (Frazer & others 1974, BMJ 1974, Hart 1990). The rate of Haemophylus influenzae meningitis was 40 per 100,000 population, Streptococcus pneumoniae meningitis 10 per 100,000 and Nisseria meningitides 5.4 per 100,000 (Frazer & others 1974). These three pathogens together accounted for 86 % (1,507 cases) of all reported cases of bacterial meningitis in 1973 (BMJ 1974).

Studies also have shown that the peak of incidence of Haemophylus influenzae & pneumococcal meningitis is in children of 1 to 4 years of age, the attack rate is slightly higher in males than females and the incidence is slightly higher during winter (Frazer & others 1974, Floyd & others 1974 & BMJ 1974). Geographical variation in the attack rate of meningitis has been shown in the United States (Frazer & others 1974) and the pathogens responsible vary in their frequency from country to another (Table 2-1).

Table 2-1: The relative incidence of bacterial meningitis in the United Kingdom compared to the United States and France ;

Country / State	U.S.A (New Mexico)	France (Paris)	All U.K.
Reference	Frazer & others	Aujard	B.M.J
Years	1964-1971	1986	1973
Streptococcus pneumoniae meningitis	16 %	12 %	15 %
Haemophylus influenzae	65 %	25 %	19 %
Nisseria meningitides	9 %	32 %	48 %

(2) Epidemiology of post-traumatic meningitis ;

The incidence of post-traumatic meningitis is often under-estimated because of the lack of adequate follow up. However, it is generally accepted that the average meningitis rate following closed head injury is about 1 % and the incidence of intracranial infection following basilar skull fractures varies from 2 to 9%. The risk of bacterial meningitis complicating CSF rhinorrhoea is about 28 %, sixty per cent of which occurs in the first month and more than 70 % occurs in the first year, but it can be delayed as long as 34 years (Table 2-2).

The meningitis risk following cranioaural CSF fistulae varies from 0 to 19 % , with a mean of 5.7 % (Table 2-3).

From table 2-2 and table 2-3 it can be seen clearly that long-term follow up data are lacking and the authors have mentioned the length of follow up in only three series; Leech's & Paterson (1973) series with an average follow up of 1.5 years, Ignelzi's & Vanderack (1975) series with a follow up range from 3 to 24 months and Zrebeet's & Huang (1986) series with a maximum follow up of 36 months. It is also clear that these authors have under-estimated the risk of bacterial meningitis in their patients with CSF fistulae because;

(1) Many of their patients were protected by early surgery.

(2) Follow up was for a short period.

(3) Many patients were lost to follow up.

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(3) Many patients were lost to follow up.

Table 2-2; The reported incidence of meningitis complicating CSF rhinorrhoea:

Authors (Year)	Total	MG%	MG%M1	MG%Y1	F.U
Calvert (1942)	11	36 %			N.A
Lewin (1954)	84	25 %	46 %	81 %	N.A
Mincy (1966)	54	22 %			N.A
Ray & Pergland (1969)	41	41 %			N.A
Grahne (1970)	13	46 %			N.A
Brisman & Others (1970)	35	49 %	22 %	33 %	N.A
Robinson (1970)	59	22 %	46 %	54 %	N.A
Leech & Paterson (1973)	118	9.9 %	83 %		18
Ignelzi & Vander-Arck (1975)	18	17 %			3-24
MacGee & Others (1976)	23	9 %			N.A
Westmore & Whittam (1982)	100	36 %	58 %	86 %	N.A
Menalfe & Others (1982)	27	37 %			N.A
Bjerre & Others (1982)	15	47 %			N.A
Dagi & Others (1983)	18	11 %			N.A
Zrebeet & Huang (1986)	11	27 %	100 %		36
Total & averages	**627**	**28 %**	**60 %**	**73 %**	

Total = total number of patients in series, MG%= The overall meningitis rate % of total, MG%M1= The percentage of meningitis in the first month, MG%Y1= % of meningitis in the first year after CSF leakage, F.U= the average follow up in months, N.A = Not available or was not reported .

Table 2-3; The meningitis rate following CSF otorrhoea:

Authors (Year)	Total	Meningitis	Follow up
Leech & Paterson (1973)	31	19 %	18
Ignelzi & Vander-Arck (1975)	25	0 %	3-24
MacGee & Others (1976)	35	3 %	N.A
Hicks & Others (1980)	43	12 %	N.A
Dagi & Others (1983)	15	0 %	N.A
Zrebeet & Huang (1986)	25	0%	N.A
Total & Averages	**174**	**5,7 %**	

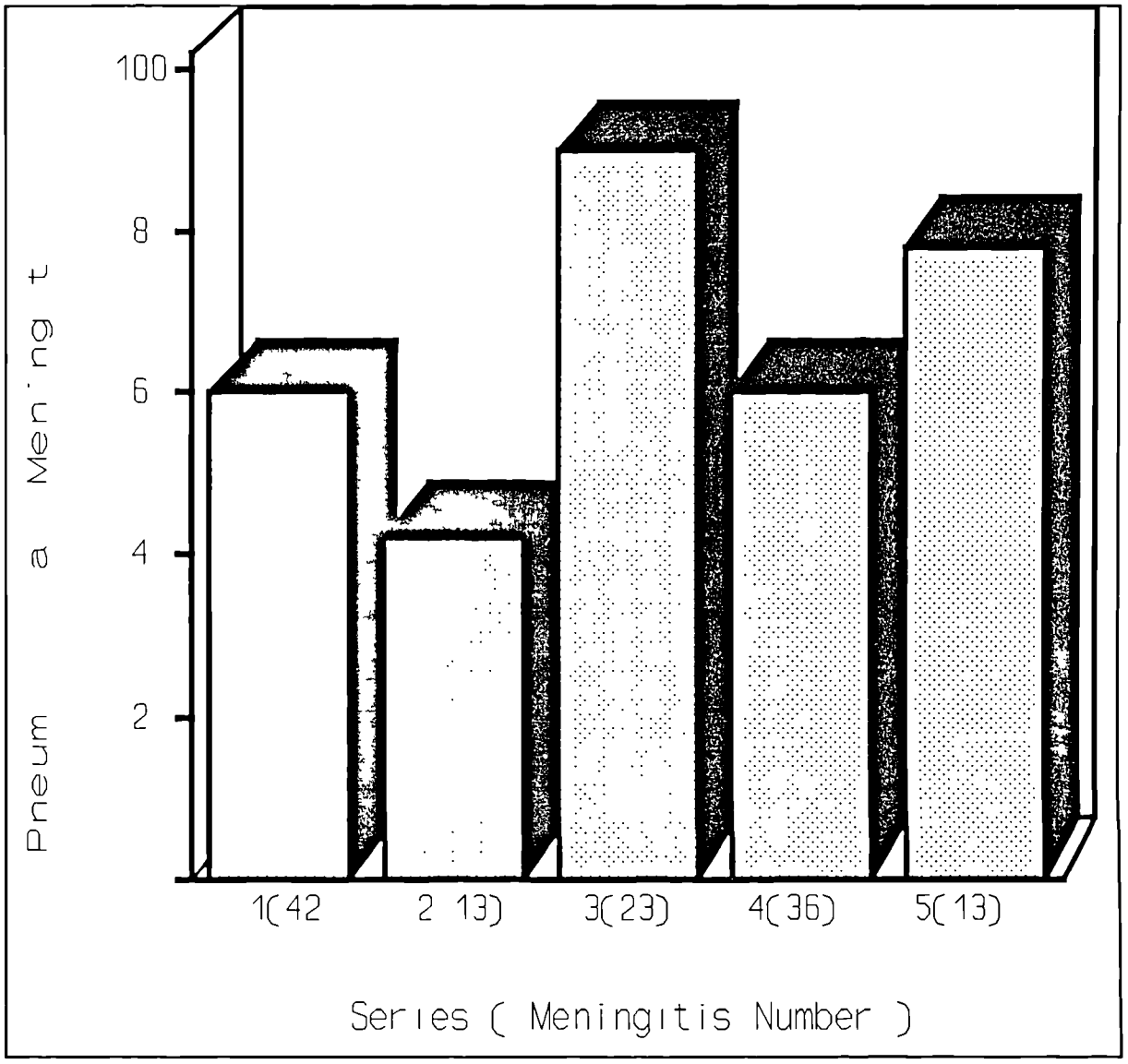
F.U= follow up in months, N.A= not available or was not reported.

2-3 Bacterial Aetiology of meningitis following dural fistulae:

Streptococcus pneumoniae is the most frequently cultured pathogen in meningitis complicating CSF fistulae. It was encountered in 43 to 78 % of positive CSF cultures (Figure 2-1), while Haemophylus influenzae, Streptococcus haemolyticus and Staphylococcus aureus accounted for the remainder. Klebsialla, Pseudomonas and enterobacteria were rarely encountered. In a Collection of 194 cases reported in various series of post-traumatic meningitis, where the causative organism was cultured from the CSF, 58 % of cases were due to Streptococcus pneumoniae, 12 % Streptococcus haemolyticus and 10% Haemophylus influenzae (Figure 2-2). In 21 to 57 % the organism was not positively identified either because the micro-organism

eluded the current laboratory culturing techniques or more likely the meningitis was previously treated with antibiotics.

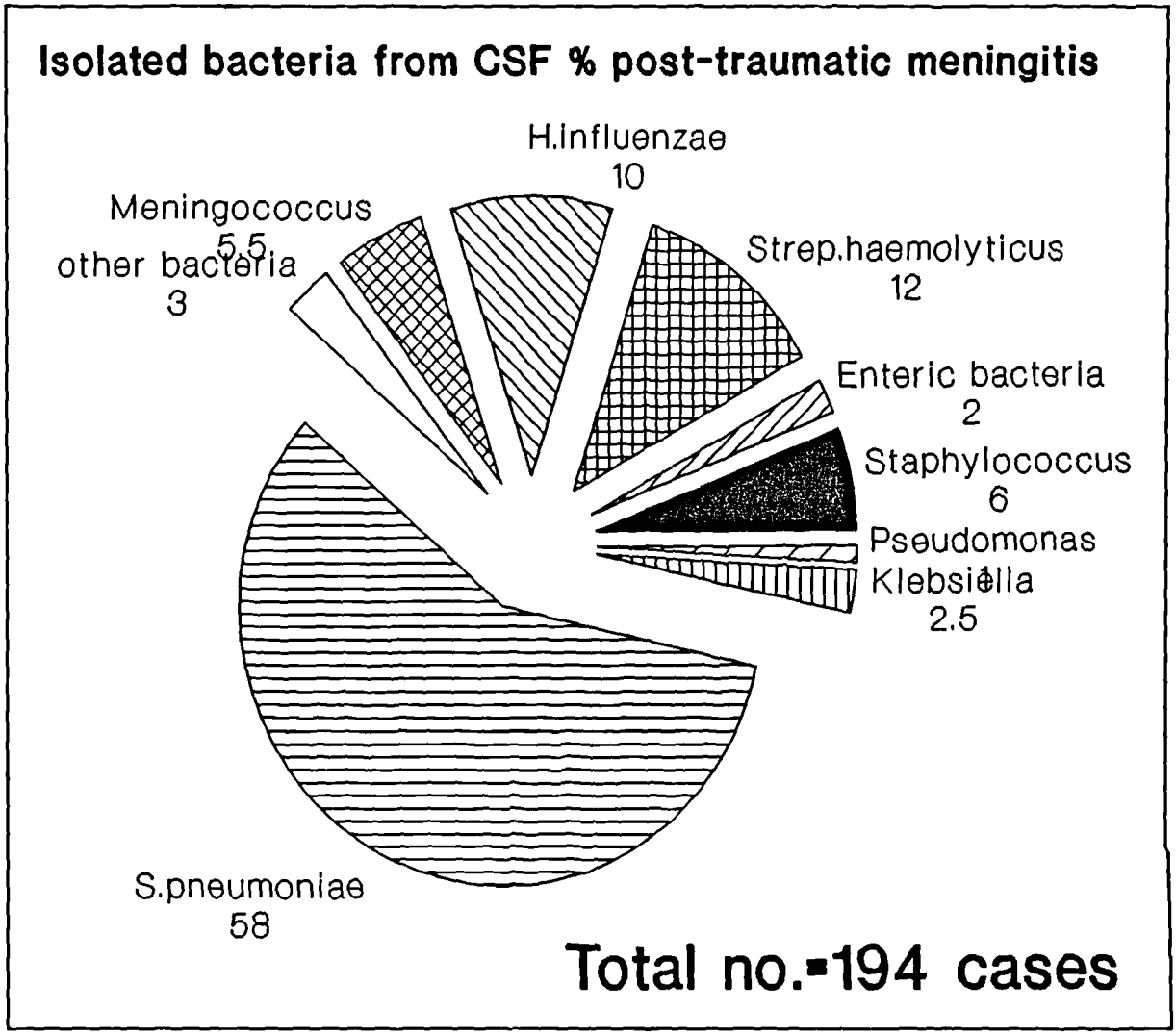
Figure 2-1: The per cent of Streptococcus pneumoniae isolated from CSF of patients with meningitis complicating dural fistulae ;



1=Lewin 1954, 2=brisman & others 1970, 3=Leech&Paterson 1973, 4=Westmore&Whittam 1982 & 5=Park &others 1983.

Figure 2-2: The relative incidence of different pathogens in a series of 194 reported cases of meningitis following CSF fistulae

(Collected from; Westmore & Whittam 1982, Leech & Paterson 1973, Lewin 1954, Klasterskey & others 1976, Dagi & others 1983, Zrebeet & Huang 1986, Ignelzi & Vanderack 1975, Norman 1947, Beachamp & Benjamin 1951, Scheneider & Thompson 1956, Samuel & others 1981, Bryan & Ternigan 1979, Brisman & others 1970, Gissane & Rank 1940 and Linell & Robinson 1940)



2-4 Pathogenesis of post-traumatic meningitis;

Meningitis following CSF fistulae is thought to progress according to two steps;

(a) Acquisition of the pathogenic bacteria.

(b) Meningeal seeding and invasion.

(a) Acquisition of pathogens:

Twenty to sixty per cent of the population are carriers of Streptococcus pneumoniae at any given time, which explains the rapid development of pneumococcal meningitis in some patients. Eight of Appelbaum's cases (1960) developed florid meningitis within 24 hours after head trauma. On the other hand nearly all children acquire Haemophylus influenzae by the age of 3 months. However, only 5 % of children below the age of 6 years carry Haemophylus influenzae, which explains the fact that Haemophylus influenzae meningitis is uncommon in adults. Furthermore, nearly a quarter of the population acquire a new serotype of Streptococcus pneumoniae every year (Gwaltney & others 1975) and despite the fact that the period of colonization is variable between individuals, the attack rate of meningitis is more common in those who are recently colonized. The most virulent serotypes of Streptococcus pneumoniae are types; 1, 2, 3, 4, 7, 8, 12 & 14 and of Haemophylus influenzae is type b.

(b) Meningeal seeding and invasion;

Once the upper respiratory tract is colonized, the bacteria can reach the central nervous system through the dural fistula

and an inflammatory reaction will ensue, the severity of which depends on;

(1) The host defence mechanisms.

(2) The virulence of the invading organisms.

(1) Host Defence Mechanisms:

(i) The skull & Dura as a barrier;

These are the first line of defence against the development of meningitis. The dura in particular, because of its tough texture and high vascularity, provides a considerable barrier against micro-organism invasion (Rowbotham & Little 1985). However, in the presence of a CSF fistula both the bone and dura are breached and this important defence factor no longer exists.

(ii) Antibodies;

The regional immunoglobulin concentration in the CSF is very low and the blood-to-CSF ratio of IgG is more than 800 to 1. This suggests that antibodies do not cross an intact blood brain barrier (BBB) and they are unlikely to be involved in the early stages of meningitis. Experimental models of meningitis have been developed in rabbits by inoculation of pneumococci and in these animals the cisternal injection of monoclonal antibodies has slowed the initial rate of growth of the pneumococci and has rapidly decreased the CSF pneumococcal concentration (Scheld & Kealy 1983).

(iii) Complement-mediated responses;

Normal CSF contains no or insignificant complement activity (Simberkoff & others 1980), but meningeal inflammation leads to variable complement concentration in the CSF.

The complement deficiency in the CSF in the presence of meningitis results in poor opsonization and inefficient phagocytosis. Absent or barely detectable opsonic activity has been shown in 18 patients with meningitis of different aetiologies (Simberkoff & others 1980). These results have been amplified in a recent study using experimental meningitis in rabbits (Bernbardt & others 1981). It has been suggested that the variable CSF complement concentration may be the result of complement leaking through an inflamed blood brain barrier and/or rapid complement degradation by leukocyte proteases (Greenwood & Whittle 1977).

(iv) Phagocytosis;

Although the exact mechanism by which leukocytes traverse the blood brain barrier is unknown, leukocytes are abundant in purulent CSF. This process is perpetuated by chemotaxis mediated by chemotactic agents such as C5a (Nolan & others 1975). Despite the abundance of polymorphonuclear leukocytes in the infected CSF, phagocytosis is insufficient because of the lack of opsonization. The arachnoid lining cells possess some phagocytic activity, but this activity is of little value in purulent CSF (Morse & Low 1972). However, human clinical data and meningitis in experimental models have shown that purulent meningitis with a low CSF leukocyte count is associated with grave prognosis (Quaade & Kirstensen 1962, Baird & Whittle 1975, Hodges & Perkins 1975 and Chow & others 1980). However, other workers did not find any significant difference between leukopenoeic and normal experimental animals inoculated with pneumococci (Petersdorf & others 1962 and Emst & others 1983).

However, the evidence, from human clinical studies and experimental-animal studies, suggests that there is a regional deficiency of both cell-mediated and humoral immunity against meningitis in the CSF.

(2) The Virulence of the micro-organisms;

(i) The capsular polysaccharides;

Both Streptococcus pneumoniae and Haemophylus influenzae, which are the most common organisms encountered in meningitis complicating dural fistulae, possess capsular polysacchrides, which are important virulence determinants. All capsule-deficient mutants of Haemophylus influenzae were found to be incapable of producing systemic infection (Moxon & Vaughn 1981).

(ii) Pilia;

Piliated strains of Haemophylus influenzae are more likely to adhere to the respiratory mucosa, but the value of pilia as virulent factors remains to be determined.

(iii) The lipopolysaccharides;

The lipopolysacchrides (LPPs) of Haemophylus influenzae are implicated in the virulence of these organisms, the Lipopolysaccharides possess endotoxin activity and may lead to complement resistance (Shaw & others 1976).

(iv) Multiplicity of serotypes;

The presence of multiple serotypes,(e.g Streptococcus pneumoniae has 84 serotypes), makes these organisms elude the immune system and renders the development of effective vaccine difficult if not impossible.

(v) Extracapsular enzymes;

The expression of extra-capsular enzymes, such as Β-lactamase and IgA-1-protease, leads to degradation of Β-lactam antibiotics and IgA. IgA is the main immunoglobulin involved in the mucosal defence mechanism against bacterial invasion.

Pathophysiology of bacterial meningitis;

The bacterial invasion and multiplication in the nervous system and the ingress of leukocytes in the CSF through the choroid plexus produces an inflammatory response. The activated neutrophils take in large amounts of oxygen and glucose in order to kill bacteria. In this process, some neutrophils secrete superoxides, singlet oxygen, hydrogen peroxide and lysosomal enzymes. This, together with bacterial breakdown products, will potentiate the inflammatory response. Some bacterial breakdown products, such as pneumococcal teichoic acid and lipopolysaccharides may have direct toxic effects or may activate the alternative complement cascade with the resultant C3a and C5a. The latter factors act as anaphylotoxins, chemotactic agents and opsonins. Other bacterial breakdown products such as peptidoglycans cause the release of Interleukin 1 from

macrophages and monocytes. The Interleukin 1 affects the blood brain barrier either directly or via prostaglandins or leukotriens. All these factors act co-operatively to produce neurological damage (Hart 1990) by:

(1) Increasing the intracranial pressure.

(2) Depriving the neurones of oxygen and glucose.

(3) Altering the cerebral perfusion.

(4) Leading to anaerobic glycolysis producing lactate.

The inflammatory cells are flushed over the cerebral cortex and become entrapped in fibrin forming plugs, which block the arachnoid granulations (Scheld & others 1979). CSF absorption becomes insufficient and the capillary permeability increases. The CSF pressure increases, which may lead to increased cerebral perfusion pressure and some cerebral hypoperfusion may follow (Reivich & others 1969). However, the CSF pressure may not rise sufficiently to produce hypoperfusion in the presence of an active CSF leakage.

2-5 Mortality & Morbidity of Bacterial Meningitis:

Mortality;

Pneumococcal meningitis carries a mortality rate of 17 to 59 %, with a mean of 28 %. In the past, it has caused the greatest number of deaths from meningitis in the United Kingdom (BMJ 1974). However, there is no doubt that the introduction and development of antimicrobial agents have reduced the meningitis mortality. Appelbaum (1960) has reported a series of 91 cases of post-traumatic meningitis, of which 100 % died in

the pre-antibiotic era, 72 % died on sulphonamides alone and 7% died on antibiotics with and without sulphonamides. Nevertheless, the mean mortality rate from pneumococcal meningitis is still about 28 %, despite modern antimicrobial agents and intensive therapy (MacKenzie & others 1967 and Hook & others 1983). The mortality rate from meningitis following CSF fistulae is slightly less than that associated with other risk factors. This relatively benign course of post-traumatic meningitis may be a reflection of the youth and fitness of most of the affected individuals with dural fistulae. It has been postulated that drainage of the infected CSF through the fistula might be responsible of the reduced mortality in recurrent meningitis (Dandy 1944). However, an equal incidence of bacteraemia has been reported in association with meningitis, in those with and those without CSF fistulae (Levin & others 1972). Whitecar & others (1966) suggested that the reduced mortality from pneumococcal meningitis complicating trauma, is the result of infection with less virulent strains of pneumococci. However, it is more likely that the main factor responsible for the reduced mortality from meningitis complicating CSF fistulae is the fact that the majority of these patients are young, fit and under medical surveillance because of the underlying dural fistula.

The average mortality rate from meningitis complicating CSF fistulae is 20 % (Table 2-4).

Table 2-4: The mortality rate % from meningitis complicating CSF fistulae :

Authors (Year)	No.of meningitis	Mortality %
Calvert (1942)	11	55
Lewin (1954)	16	25
Appelbaum (1960) *	42	88
Appelbaum (1960) @	20	10
Brisman & Others (1970)	17	6
Levin & Others (1972)	138	19
Westmore & Whittam (1982)	36	3

* Pre-antibiotic series, @ Post-antibiotic series .

Furthermore, mortality from meningitis may result because of unsuccessful treatment or because of the delay in the diagnosis. It has been stated that up to 18 % of patients with meningitis were partially treated (Tettenborn 1986) and a failure rate of 3 % when ceftazdime was used and 9 % when ampicillin & chloramphenicol were used has been reported (Tettenborn 1986).

Morbidity:

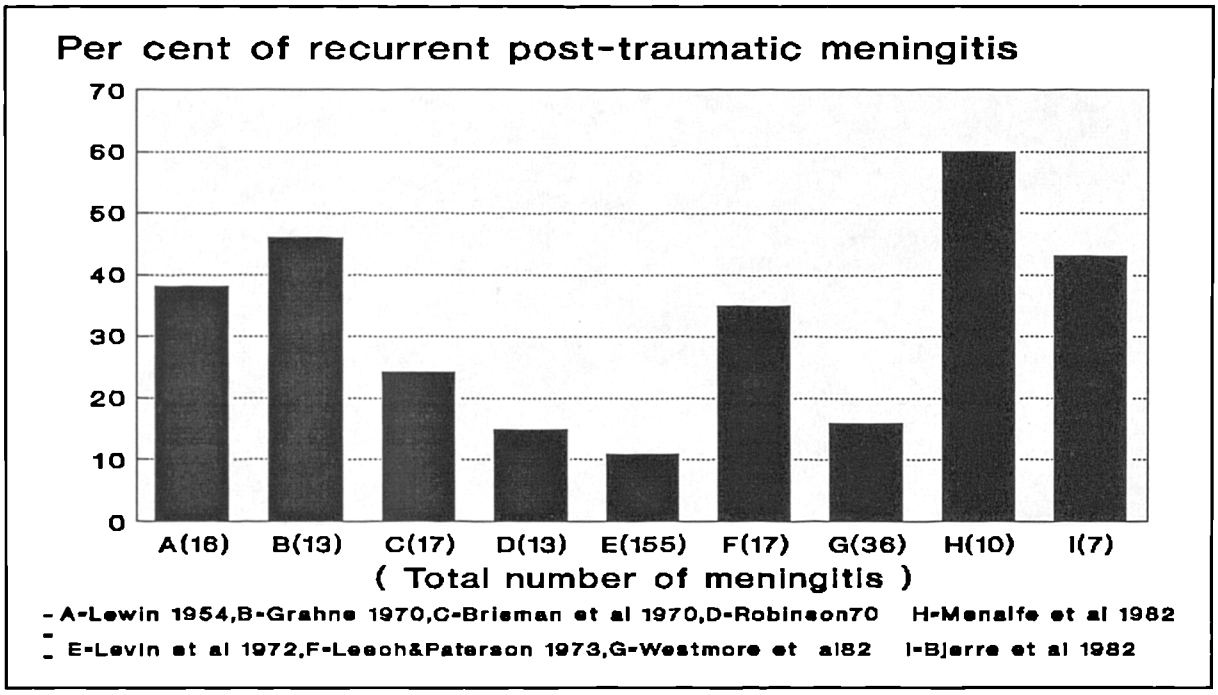
Bacterial meningitis not only has the reputation of being life-threatening, but it also carries considerable morbidity.

(i) Recurrent meningitis;

Recurrence of intracranial infection is the major complication of meningitis complicating dural fistulae (Norman

1949, Beauchamp & others 1951, Levin & others 1972). This is different from relapses of meningitis occurring as a result of inadequate or prematurely stopped therapy (Norman 1949).
True recurrence of meningitis is an index of the presence of dural fistula and is encountered in 11 to 60 % of cases, with an average incidence of 30 % (Figure 2-3).

Figure 2-3: The incidence of recurrent meningitis (%) in dural fistulae ;



(ii) Neurological damage;

The second most common complication of meningitis, following dural fistulae, is the development of neurological deficit (Levin & others 1972). The neurological complication rate following non-recurrent meningitis is 13 % and reaches 29 % following recurrent episodes of meningitis. MacKenzie & others (1967) reported a 20%

neurological damage rate, in the survivors of meningitis and Adams & Petersdorf (1980) stated that up to 30 % of patients with pneumococcal meningitis develop permanent residua, including; dementia, epilepsy, deafness & hemiplegia. While, Smith & others (1985) stated that approximately 10 % of all children, surviving Haemophylus influenzae meningitis, have gross neurological disability and an additional 40% have other neurological deficits compromising their normal function. These deficits included; 10-40 % hearing loss, 15 % language delay, decreased cognitive ability and changes in behaviour.

(iii) Hydrocephalus;

Hydrocephalus can develop acutely following meningitis or it can occur at a later date. In the acute stage of meningitis, the inflammatory exudate delays the passage of CSF through the foramina of the forth ventricle, leading to obstructive hydrocephalus or it can slow the absorption of CSF by obstructing the arachnoid villi, causing communicating hydrocephalus. Subsequent fibrosis may partially or totally occlude the foramina of the forth ventricle and the basal cisterns, leading to obstructive hydrocephalus at a later date following recovery from meningitis. Streptococcus pneumoniae & Haemophylus influenzae are among the common causes of hydrocephalus complicating bacterial meningitis (Milhorat 1972). The reported incidence of hydrocephalus complicating meningitis, in patients with dural fistulae is 10 to 20% (Eljamel & Foy 1990, MacKenzie & others 1967).

2-6 Vaccinations against meningitis;

The development of a polyvalent effective vaccine against all pathogens responsible for the development of meningitis, is a formidable task because of the following factors;

(1) Almost all known bacteria pathogenic to man have been isolated from patients with meningitis complicating dural fistulae.

(2) Many of these pathogens are multivalent, for example; Streptococcus pneumoniae has 84 serotypes and a vaccine against one serotype does not prevent infection with another.

(3) Many of these bacteria are protected from the immune system by capsular polysaccharides, which are poor immunising antigens especially in children below 2 years of age.

No trials have been carried out to determine the effectiveness of the existing pneumococcal vaccine against meningitis. However, the pneumococcal vaccine was effective in preventing pneumococcal pneumonia in up to 80 % of healthy young adult South African miners (Austrian & others 1976 and Smit & others 1977). On the contrary, there was no difference in the incidence of radiologically-confirmed pneumonia in the elderly patients with and without the use of the pneumococcal vaccine (Austrian & others 1981). An overall 50 per cent reduction in the incidence of pneumococcal otitis media in infants, using the

polyvalent pneumococcal vaccine, was reported (Teeles & others 1981, Makela & others 1981 and Sloyer & others 1981), but the protection was short lived (less than 6 months).

At present, the effectiveness of the licensed pneumococcal vaccine in preventing meningitis in patients with CSF fistulae, is undetermined.

2-7 A study of the long-term risk of meningitis in Unrepaired Dural Fistulae

2-7,1 Introduction;

Much has been written about post-traumatic meningitis in the last 40 years or so, but none of the published studies has addressed the meningitis-free survival of patients with CSF fistulae. The follow up data are either lacking, insufficient or for short period usually less than a year. Observations over a long period of time are essential, for in many cases the first attack of meningitis is delayed for as long as 14 to 34 years (Kraus 1962, Linell & Robinson 1941 and Russel & Cummins 1984). Most of the quoted figures for the risk of meningitis complicating dural fistulae are related to a short term follow up. Actuarial probabilities, derived from life-table-analysis are more meaningful in defining the risk of meningitis in these patients on a weekly, monthly and annual basis.

2-7,2 Objectives ;

(1) To determine the actuarial risk of developing meningitis in patients with CSF fistulae.

(2) To determine the adverse prognostic factors for meningitis in patients with dural fistulae.

(3) To determine the complications of meningitis in patients with CSF fistulae.

2-7,3 Patients and Methods:

The study was based on two hundred and fifty-seven consecutive patients with definite CSF fistulae, who were treated in the Mersey Region in the antibiotic era. This included all patients with CSF fistulae who survived the original cause of the CSF fistula between 1944 and 1990 (Figure 2-5).

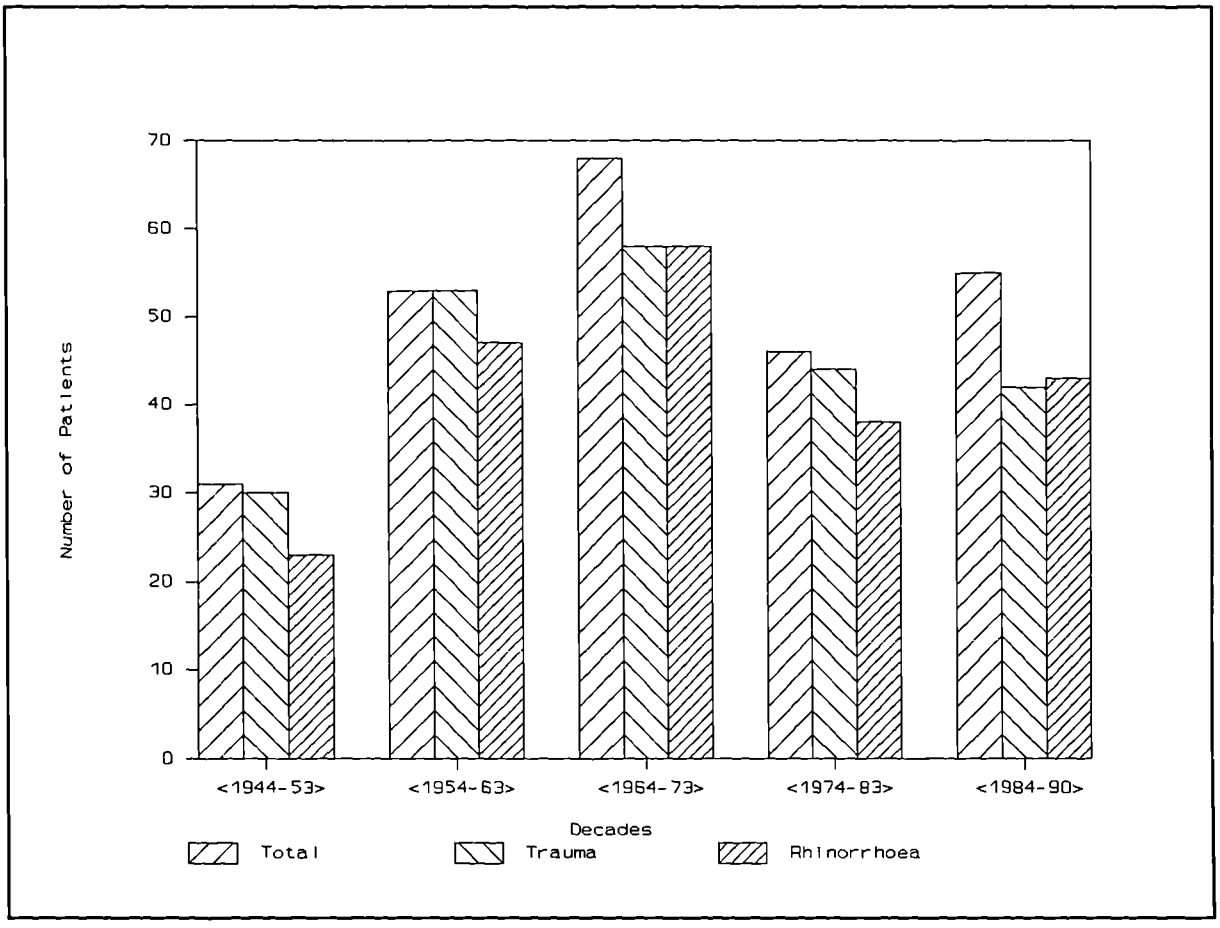


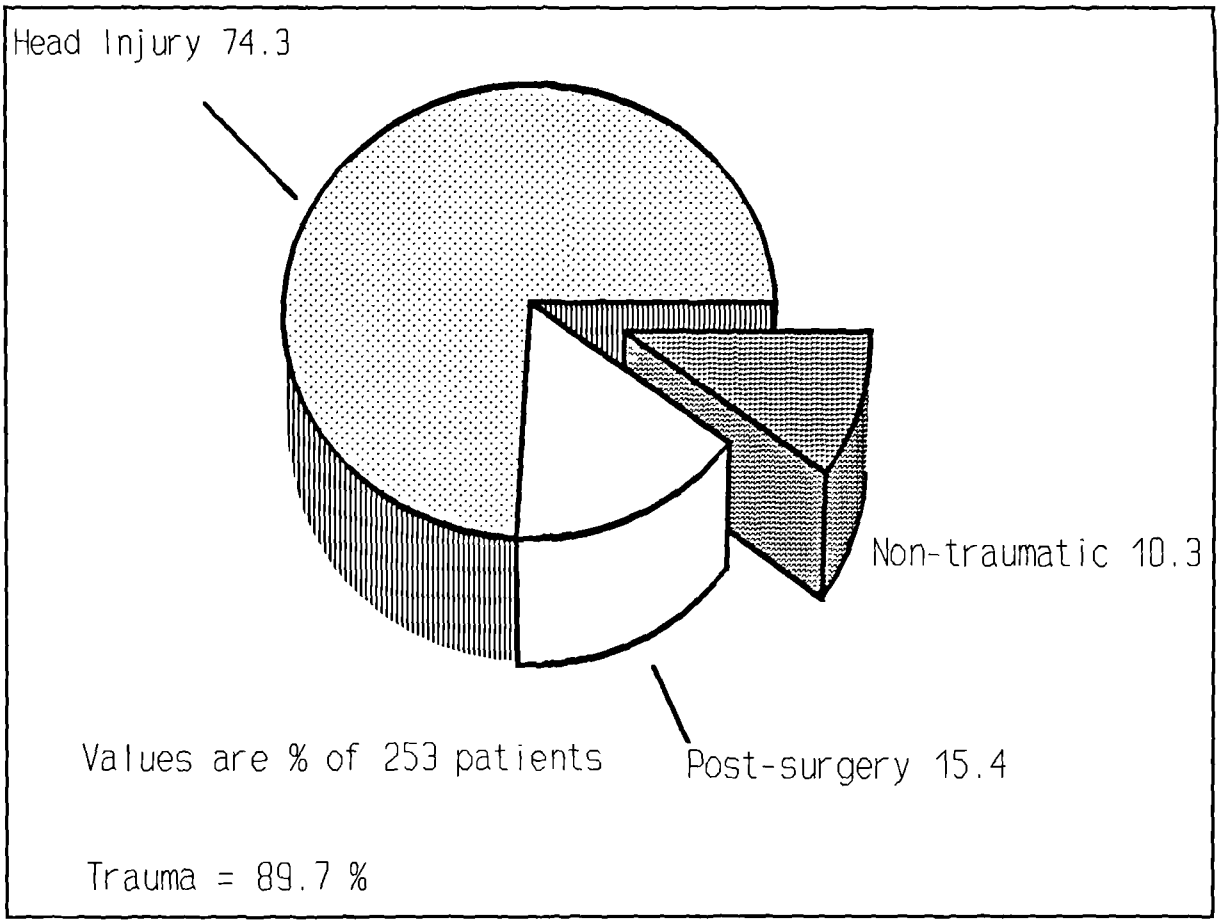
Figure 2-5; A histogram showing the relative incidence of CSF fistulae in The Mersey Region 1944 - 1990 .

These patients were traced by using the regional computer data-base, the neuroradiology data-base, the neurotheatre records and the medical records of the Mersey Regional Department of Medical and Surgical Neurology. Detailed follow up data was obtained from the clinical records and up to date information was obtained through questionnaires send to the Family Health Services Authorities (FHSAs) and the general practitioners.

Adequate follow up data was obtained on all patients except four, who were not traceable, two had traumatic CSF rhinorrhoea in 1954 and another two developed post-traumatic meningitis in 1962. The rest of the population study (253 patients) were followed up until the patient's death, surgical dural repair or the end of 1990 . The mean follow up period was 2.5 years (Range one week to 20 years, Standard Deviation 2 years).
The data collection form is shown in Appendix A.

2-7,4 Aetiology of 253 CSF fistulae;

The study comprised 188 (74.3 %) patients, who developed a CSF fistula in association with a closed head injury, 39 (15.4%) post-surgical and 26 (10.3 %) non-traumatic CSF fistulae (Figure 2-6).



Trauma = Head injury + Post-surgical = 89.7 %.

Figure 2-6: The aetiology of 253 cases of CSF fistulae .

Road traffic accidents were responsible for more than 60 % of CSF fistulae associated with closed head injuries, while nasal and paranasal sinuses' surgery was the cause of more than 60 % of the post-surgical CSF fistulae and more than 70 % of the non-traumatic CSF fistulae were associated with normal CSF pressure (Table 2-4).

Table 2-4: The causes of 253 cases of CSF fistulae:

Causes of CSF fistula	Total No	Percentage
A: **Head Injuries;**	188	
Road Traffic Accidents	113	60.1
Falls	42	22.3
Assaults	12	6.4
Push Bicycle Related	4	2.1
Motorcycle accidents	5	2.7
Others	12	6.4
B: **Post-surgical;**	39	
Anterior Fossa Craniotomy	12	30.8
Nasal Surgery	11	28.2
Cerebello-Pontine Angle	8	20.5
Trans-sphenoidal	4	10.25
Aural and Mastoid	4	10.25
C: **Non-traumatic *;**	26	
Congenital fistulae #	5	19.2
High CSF pressure @	4	15.4
Focal atrophy	15	57.7
Pituitary lesions <>	2	7.7

* Two were associated with deafness and one with osteoscelorosis. # Including: two petrous bone, one patent foramen caecum. @ Including two benign intracranial hypertension. <> One empty sella and one prolactinoma treated with bromocriptine.

2-7,5 Statistical Methods;

The data were analyzed in two steps. Firstly, the Kaplan-Meier product-limit method was used to calculate the survival curves free from meningitis (Kaplan & Meier 1958). Actuarial estimation of the probability of an event (q_t), such as meningitis, among patients with CSF fistulae is a method of assessing the occurrence of only that event. Those patients, who died of a cause other than meningitis or had the CSF fistula repaired were removed from the denominator for the observed interval. This denominator then represented only those patients at continuing risk of meningitis (n_t). The survival free from meningitis at time interval (t);

$$I_t = \prod q_t = \prod (n_t - p_t)/n_t$$

$$\prod = \text{Pie}$$

where p_t is the number of patients who developed meningitis during the observation period. Suppose that at time t there were Mt patients developed who meningitis and that just before these cases of meningitis occurred there were Nt subjects at risk. Then, the estimated probability of meningitis at time t (Pt); Pt= Mt/Nt and the probability of survival free from meningitis at time t (Qt) = 1-Pt. The 95 % confidence intervals were calculated for the value of the survival proportion at particular times during the follow up using a modified Greenwood's formula $I_t^{\exp(+/-1.96s)}$, where I_t is the survival proportion at time (t);

$s = SE(I_t)/(-I_t \ln I_t)$ and $SE(I_t)$ is the standard error = $I_t\{(1-I_t)/Nt\}^{0.5}$ (Greenwood 1926).

The average meningitis-rate in a follow up period (M%) was calculated using the follow up period (T) meningitis-rate (Y) as follows; $M\% = 100(1-(1-Y/100)^{1/T})$ %. For example, if the meningitis rate at the end of 10 years of follow up was equal 58 %, then the average meningitis-rate (1-10 years) equal

$$100 (1 - (1 - 58/100)^{0.1}) \% \text{ per year}$$

Simple division of Y by the follow up period may be used to obtain M%, but this is only accurate if Y is very small.

Secondly, the influence of potential prognostic factors (all those shown in Table 2-6) on the meningitis-rate was determined by analyzing the survival data with a computerised biomedical data program statistical package based on the Cox's proportional hazards regression model (Cox 1972). Stepwise proportional hazards analysis provides estimates of regression parameters (the B coefficient) for each independent (prognostic) variable with an associated standard error and p value. If the ratio of the B coefficient to the standard error (SE) exceeds 1.96 the p value is less than 0.05. Except for pneumocephalus and the onset of CSF leakage, univariate factors, which were significant at the 0.05 level were included in the model, and a forward stepwise procedure was used, beginning with the most significant variable and then the other univariate factors, in order of significance. Variables were excluded if the p value exceeded 0.05 except pneumocephalus and the onset of CSF leakage, which were forced into the model because of medical commonsense and previous reports of apparent significance of these variables.

The hazard ratio is the ratio of the rate of the outcome event (such as meningitis), occurring at some point in time (conditional on survival until that time) in the follow up of a group of patients with a given (prognostic) factor to the rate of the outcome event occurring in a group of patients without that factor. This was derived by calculating the exponential of the B coefficient. For example, if h(t;x) is the hazard rate for a subject with a prognostic factor x, then the proportional hazard model is given by; $h(t;x)=h0(t)\exp(bx)$, where b is a vector of an unknown regression coefficient and h0(t) is an unknown hazard function for an individual with a prognostic factor x=0. The 95% confidence interval of the hazard ratio was calculated by;

exponential (B coefficient +/- 1.96 x Standard Error).

2-7,6 Results and Discussion

The study sample:

Only those patients who developed a definite CSF fistula are presented in this analysis. Consequently, patients who died without confirmation of the CSF fistula or in whom the fistula was not objectively diagnosed, were excluded. The relative incidence of CSF fistula and its complication, meningitis, did not change over the last four decades (Chi^2-with Yates' correction = 1.62, d.f =4 , p value > 0.05).

Diagnosis:

In all these patients a clear demonstration of CSF leakage or pneumocephalus was documented and subsequently the CSF fistula was confirmed by cisternography, surgically or at post-mortem. Meningitis was diagnosed clinically and confirmed by isolating the pathogen from CSF (67 %) or by the presence of a pyogenic picture in the CSF without growing the actual pathogen (33 %).

Baseline Characteristics:

Table 2-5 summarises the baseline features of the study population, the value represents the total number of patients out of the 253 patients with CSF fistulae unless otherwise specified.

Age and Sex;

The mean age of the study population was 34.4 years (range 2 to 78 years) and there was no significant difference between the age distribution in the traumatic (head injury), post-surgical or the nontraumatic subgroups of patients ($p > 0.05$). However, the female to male ratio was different in the three groups (Table 2-6). Figure 2-6 shows the age and sex distribution of 253 patients with CSF fistulae. Fifty per cent of patients were below the age of 30 years, which is similar to previous reports (Table 2-7), the youngest child in this study population was 2 years old and the child to adult ratio was 1:6, less than the 1:10 ratio reported in the literature (Hindrick & others 1964, Hardwood-Nash 1970, Caldicott & others 1973 and Einhorn & Mizrali 1978).

Table 2-5 : Baseline characteristics in 253 patients with CSF fistulae, value=number of patients unless otherwise stated;

Characteristics ;	Value
Aetiology:	
Traumatic:	227
Closed head injury	188
Post surgical	39
Nontraumatic:	26
Normal pressure	22
High pressure	4
CSF leakage:	
Rhinorrhoea	209
Otorrhoea	17
Fractures;	
Paranasal sinus	174
Temporal bone	8
Facial	89
Pneumocephalus	44
Mean (SD) Age (Years)	34.4 (18.9)
Males (Females)	189 (64)
Antibiotics Prophylaxis	
Used in some form	145
Adequately used	109
Not used at all	106
Duration of CSF leakage:	
< 48 hours	35 (15%)
3 to 7 days	60 (27%)
8 to 14 days	46 (20%)
15 to 30 days	37 (16%)
> 30 days	48 (21%)
Onset of CSF leakage;	
Immediate	135
1 to 7 days	29
> 7 days	36
Meningitis	86
Recurrent meningitis	29

Table 2-6: The Sex distribution in 253 patients with CSF leaks:

Subgroups	Males	Female	Male:Female ratio
Head injury	153	55	3 :1
Postsurgical	23	16	1.4:1
Nontraumatic	13	13	1 :1

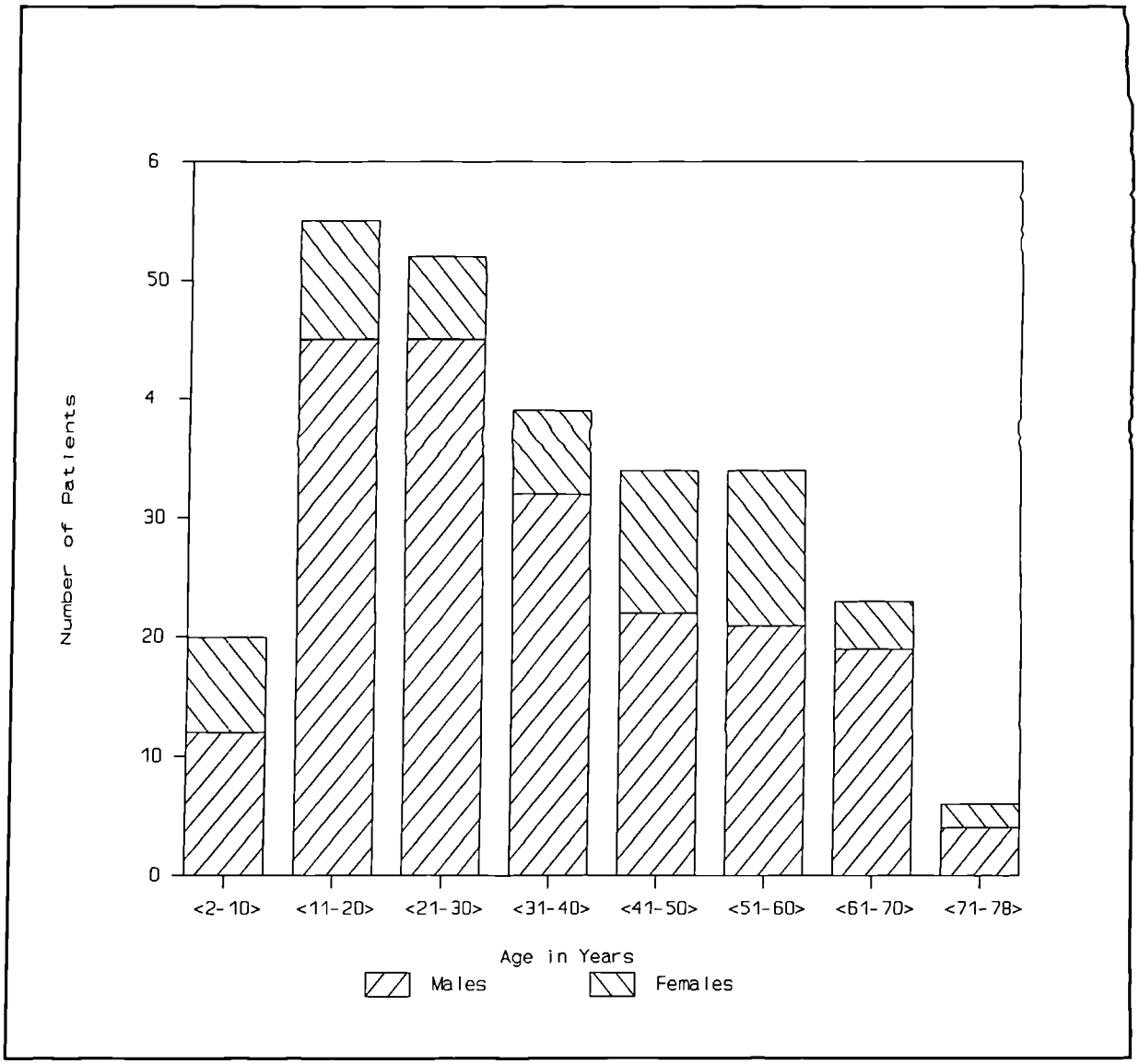


Figure 2-6: A histogram showing the age and sex distribution in 253 patients with CSF fistulae. The top figures represent females.

CSF Leakage;

226 (89 %) patients presented with CSF leakage, of which 92 % (209/226) had CSF rhinorrhoea and 8 % (17/226) had CSF otorrhoea. The CSF leakage started immediately following trauma in 67.5 % (135/200), within the first week of trauma in 14.5% and later than a week in 18 % , which is similar to previously reported series (Table 2-7).

Table 2-7: The percentage of patients < 30 years of age and early onset of CSF leakage in four major reported series:

Authors (Year)	% of patients early onset *	% of young patients @
Lewin (1954)	68	
Robinson (1970)	58	64
Westmore & Whittam (1982)	52	59
Park & others (1983)	79	60

* Onset within 7 days from trauma and @ patients below 30 years of age.

Forty-two per cent of those who leaked CSF, stopped leaking CSF within a week, 28 % persisted for more than a week but less than 3 weeks and 30 % persisted for more than 3 weeks (Figure 2-8).

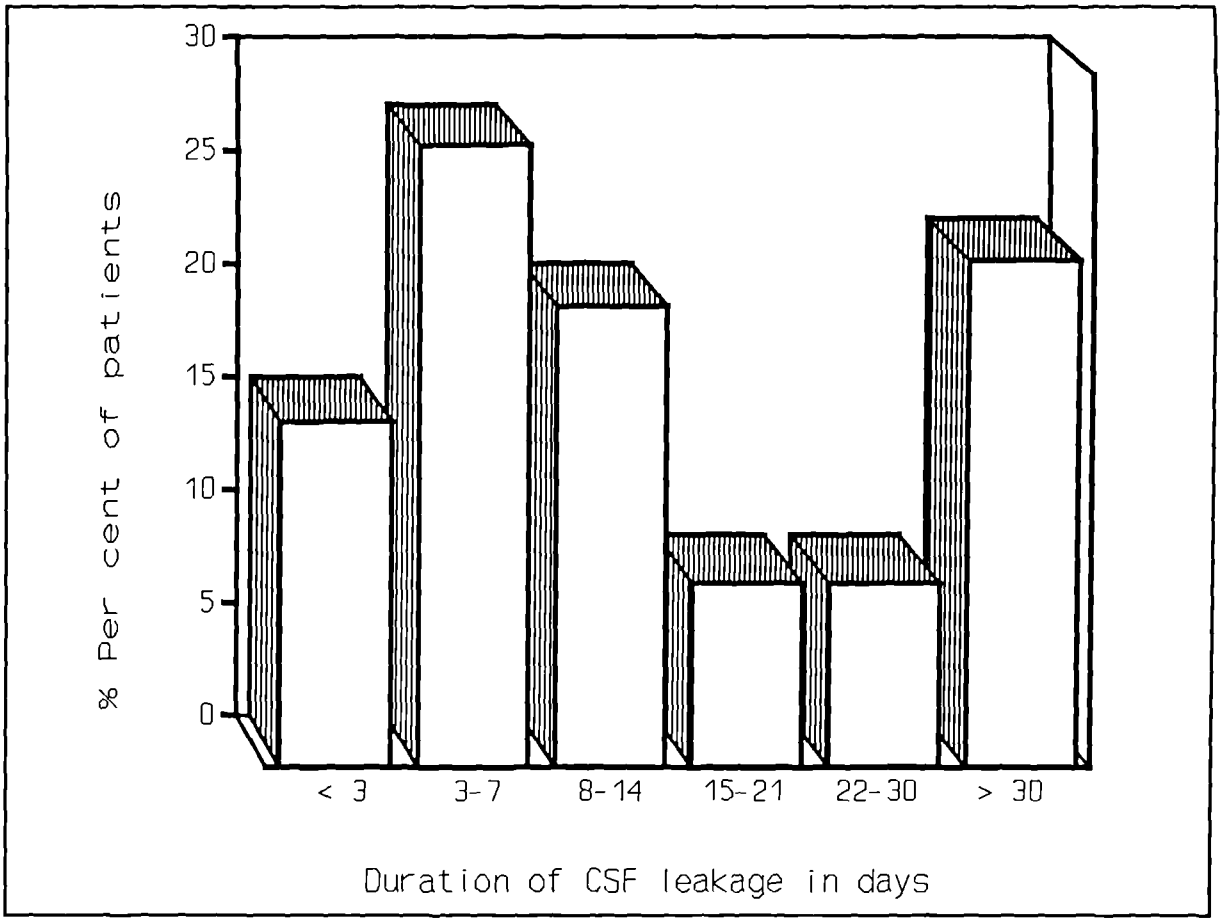


Figure 2-8: The duration of CSF leakage in 253 patients with CSF fistulae .

Abnormal radiological findings :

Pneumocephalus was noted in 44 patients (17 %) and fractures involving the paranasal sinuses were noted in 174 patients (93% of the traumatic cases associated with head injuries). However, there were only 8 (3.2 %) temporal bone fractures and 89 (47 % of traumatic CSF fistulae) facial fractures, the details of which will be discussed in chapter 5.

The survival curves of survival free from meningitis and the actuarial risk of meningitis in patients with CSF fistulae :

Eighty-six patients developed bacterial meningitis at some stage during the follow up period prior to fistular repair. To avoid heterogeneity, patients who developed recurrent CSF leakage following dural repair were excluded from the survival analysis and they will be discussed at a later stage.

The Kaplan-Meier product-limit estimate of survival free from meningitis (excluding patients who died of a cause other than meningitis or who had the CSF fistula repaired) showed that by the end of four weeks from the onset of CSF leakage 91.9 % survived free from meningitis and the average risk of meningitis during the first four weeks was 2.4 % per week.
69.1 % of patients survived free from meningitis for a year and the average meningitis rate (first year from CSF leakage) was 3 % per month. However by the end of 10 years follow up only 41.5% were free from meningitis and the average annual risk of meningitis was 9.8 % per year (Table 2-8 and Figure 2-9).

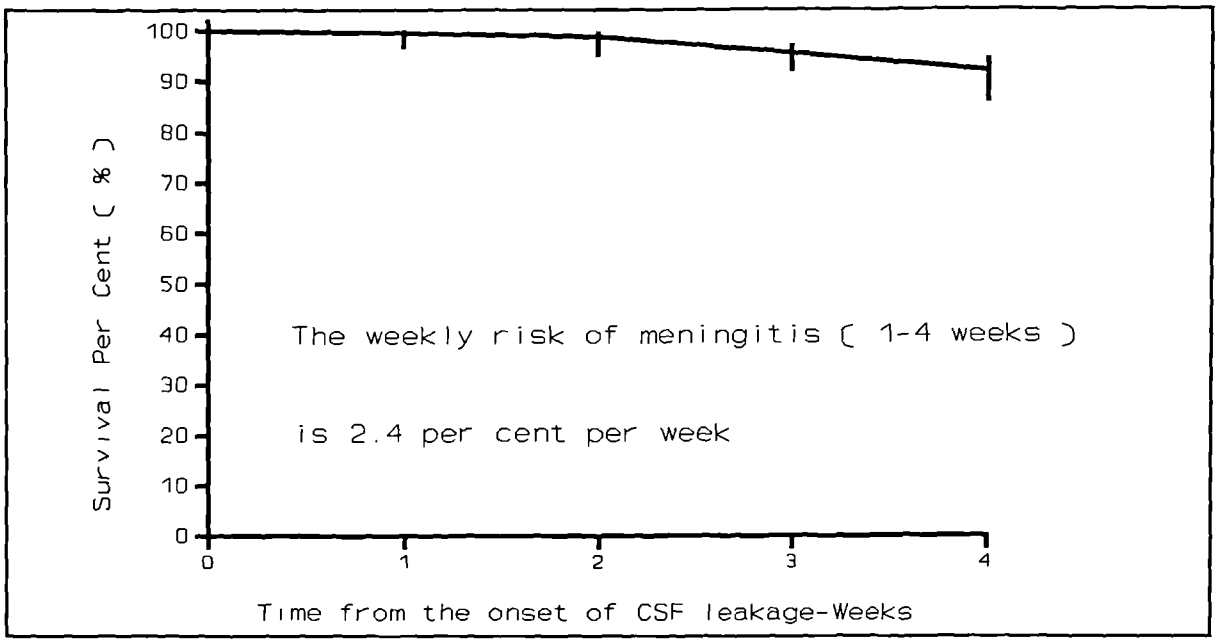
There was no significant difference in the survival free from meningitis of patients who presented with CSF otorrhoea alone and those who presented with rhinorrhoea (Logrank test X^1-square 0.0053 & $p < 0.05$). However, the number of patients who developed CSF otorrhoea alone was very small (17 patients).

Table 2-8: The Kaplan-Meier product-limit of survival free from meningitis in 253 patients with CSF fistulae:

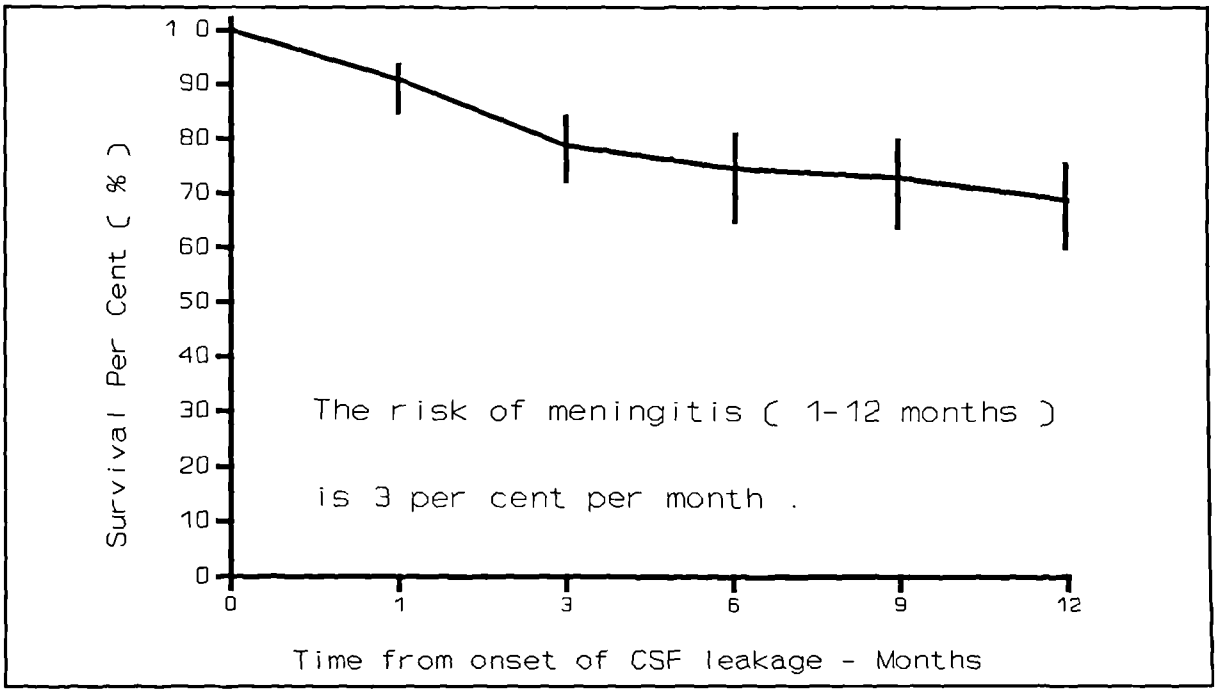
Time Interval t Wks=weeks Mns=months Yrs=years	No. patients meningitis Mt	Total No. at Risk Nt	Survival proportion free from meningitis Qt	Survival free from meningitis percent It	The 95 % confidence intervals for It
0	-	253	1.000	100.0	-
1 Wks	1	252	0.996	99.6	97.2 to 99.9
2 Wks	2	250	0.988	98.8	96.4 to 99.6
3 Wks	7	210	0.955	95.5	91.8 to 97.6
4 Wks	7	185	0.919	91.9	87.2 to 94.9
1 Mns	2	163	0.908	90.8	85.5 to 94.2
3 Mns	19	145	0.789	78.9	72.3 to 84.1
6 Mns	5	94	0.747	74.7	66.1 to 81.4
9 Mns	2	92	0.731	73.1	64.4 to 80.0
12 Mns	5	91	0.691	69.1	60.4 to 76.2
2 Yrs	8	88	0.628	62.8	54.3 to 70.2
4 Yrs	5	55	0.571	57.1	46.6 to 66.3
6 Yrs	2	40	0.542	54.2	42.2 to 64.8
8 Yrs	6	34	0.446	44.6	33.3 to 55.3
10 Yrs	2	29	0.415	41.5	29.9 to 52.7
12 Yrs	2	21	0.375	37.5	25.1 to 50.0
16 Yrs	6	16	0.234	23.4	14.2 to 34.0
20 Yrs	5	11	0.128	12.8	6.8 to 20.7

Figure 2-9; The Kaplan-Meier Survival Curves of Survival free from meningitis in 253 patients with CSF fistulae; The Vertical lines represent the 95% confidence intervals

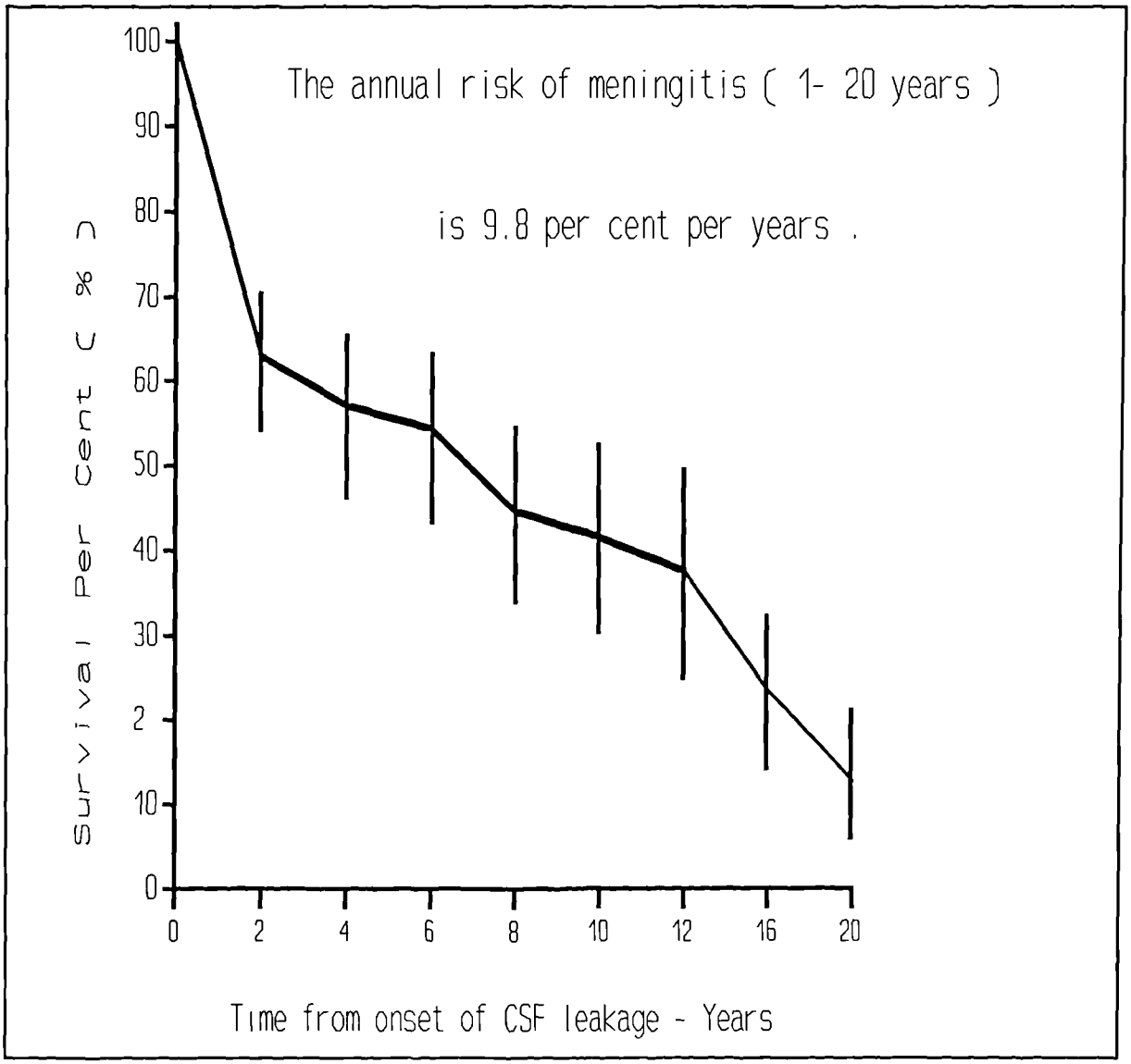
2-9 a: survival curve in the first 4 weeks



2-9 b: survival curve in the first Year



2-9 c: survival curve in the first 20 years



Prognostic factors;

The only significant adverse prognostic factor for developing meningitis in patients with CSF fistulae was CSF rhinorrhoea (Table 2-9 & Figure 2-10). For example, a patient presenting with CSF rhinorrhoea (hazard ratio = 2.34), is 2.34 times more likely to develop meningitis than another patient with CSF otorrhoea.

Pneumocephalus and onset of CSF leakage were forced into the model because of previously reported increased risk of meningitis in those with intracranial air and those with late onset CSF leakage. Age, sex, skull fractures, facial fractures and the aetiology of the CSF fistula did not have any significant adverse effect. The possible role of antibiotic prophylaxis will be discussed in more detail in the next chapter.

Table 2-9: Proportional hazards analysis in 253 patients with CSF fistulae, for the outcome event, MENINGITIS.

Prognostic factors	B-coefficient	B/SE***	Hazard Ratio	95 % confidence interval for hazard ratio
Rhinorrhoea*	0.85	10.3	2.34	2.00 , 2.7
Duration of CSF Leak @	0.05	1.6	1.05	1.00 , 1.1
Late onset#	0.09	1.2	1.09	0.95 , 1.3
Intracranial air	0.01	0.4	1.01	0.95 , 1.1

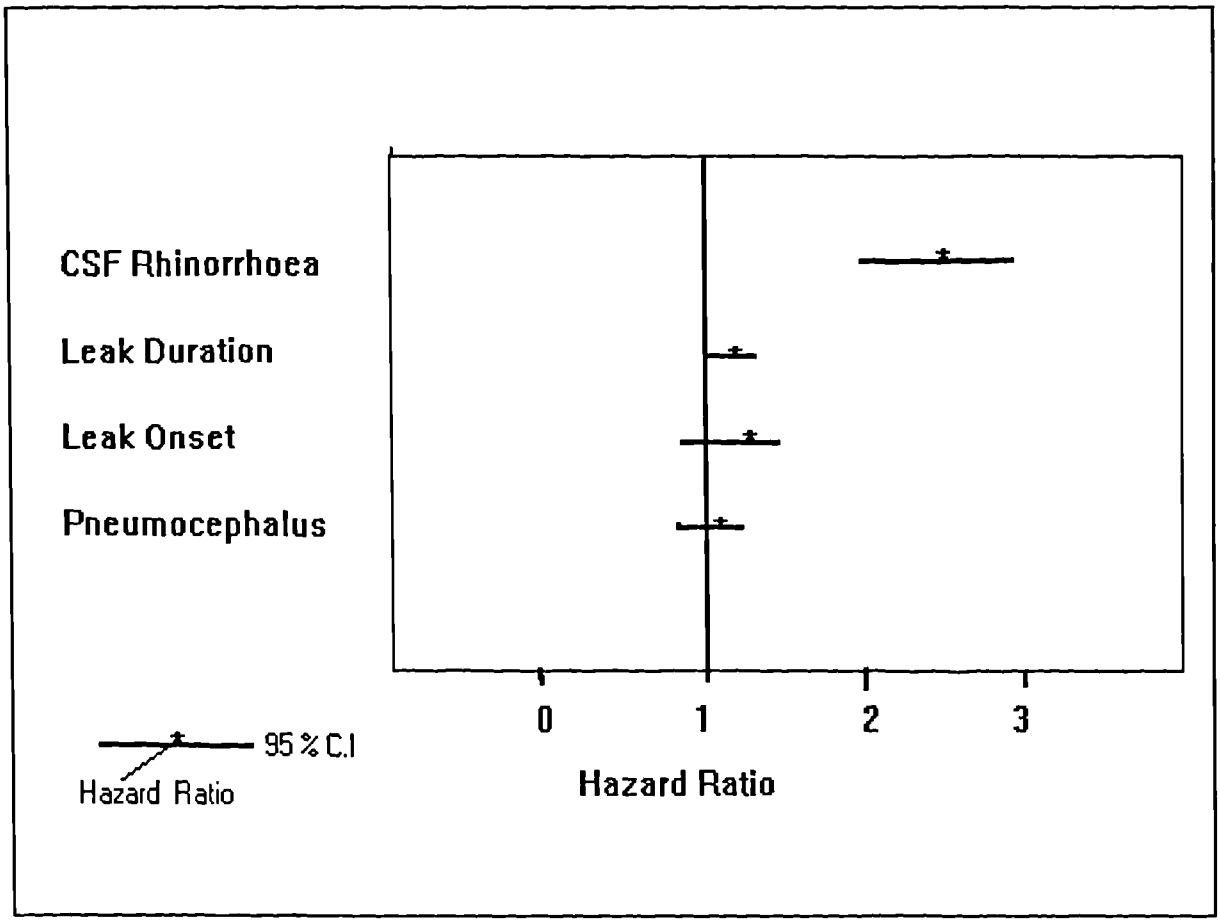
*** An B/SE value of < 1.96 is not significant at 0.05 level

* CSF rhinorrhoea,

@ duration > 7 days.

onset within 7 days from trauma.

Figure 2-10; The proportional hazards analysis of 253 patients with unrepaired CSF fistulae; A ratio of one means no increased risk;



Bacterial aetiology of 86 cases of meningitis complicating dural fistulae;

Fifty-seven per cent of positive CSF cultures, had grown Streptococcus pneumoniae, 35 % of CSF cultures were negative and 12 % of CSF isolates were Haemophylus influenzae (Table 2-10). These results are similar to those reported in the literature (Lewin 1954, Brisman & others 1970, Leech & Paterson 1973, Westmore & Whittam 1982 and Park & others 1983), Figures 2-1 & 2-2.

Table 2-10: CSF isolates in 58 patients with meningitis complicating CSF fistulae. 35 % (30/86) showed no growth:

Pathogens	Number	%
Streptococcus pneumoniae	33	57
Haemophylus influenzae	7	12.1
Staphylococcus aureus	3	5.2
Strept. haemolyticus	1	1.7
Nisseria meningitides	1	1.7
Diphtheroids	1	1.7
Coliforms	2	3.4
Pseudomonas aeroginosa	1	1.7
Unknown	9	15.8
Total (% of 86)	58	(67)

The outcome of the first attack of meningitis;

The outcome of the first attack of meningitis was looked at in terms of death, recurrence of meningitis, abscess formation, epilepsy and permanent neurological damage.

Mortality:

Four (4.7 %) patients died as a result of intracranial infection despite antibiotic treatment. All the deaths occurred in patients, who manifested traumatic CSF rhinorrhoea.

Two patients were receiving antibiotic prophylaxis (Table 2-11). The relatively low mortality in this study reflects the fact that the majority of these patients were young and received intensive therapy. However, if these patients suffered meningitis abroad or without vigilant medical care, it might have been a different story as the accepted mortality rate from meningitis world wide is about 20 %.

Table 2-11: Details of patients with CSF fistulae, who died as a result of meningitis:

Patient No.	P1	P2	P3	P4
Age (Years)	46	15	18	43
Sex	Female	Male	Male	Male
CSF leakage	CSFR	CSFR	CSFR	CSFR
Onset of CSFR	Im.	Early	late	Im.
Duration of CSFR (days)	3	30	21	4
Antibiotic prophylaxis	NO	NO	Yes	Yes
Onset of meningitis from CSF leakage	7 days	3 months	4 years	3 months

CSFR = CSF Rhinorrhoea & Im.=immediate .

Recurrent meningitis:

Twenty-nine (33.7 %) patients had more than one attack of meningitis, of which 59 % (17/29) had two attacks, 28 % had three, 10 % had four and 3 % had six attacks of meningitis during

the follow up period. Seventy-six per cent of the recurrent attacks of meningitis occurred after two years of follow up and the longer patients with CSF fistulae were followed up, the more they developed recurrent attacks of meningitis (Chi^2 with Yates' correction = 17.3, d.f.3, p value < 0.01, Table 2-12). The duration of CSF leakage was less than two weeks in 69 % of those who had more than one attack of meningitis, but the duration of CSF leakage had no significant effect on the incidence of recurrent meningitis (Chi^2 with Yates' correction = 0.202, d.f.3, p value = 0.918, Table 2-12).

Table 2-12: Summary of recurrent meningitis in 253 patients with CSF fistulae:

Time Period	Menin No	2 attks	3 attks	4 attks	6 attks	Re.MG Total	Re. MG %
Follow up 0-1 Mnts	23	2	2			4	17*
2-12 Mnts	26	3				3	12*
2-10 Yrs	25	8	5	2		15	60*
11-21 Yrs	12	4	1	1	1	7	58*
Duration of CSF Leakage < 3days	26	3	3	2	1	9	35@
3-14days	34	7				11	32@
15-30days	10	3	4			3	30@
> 30days	16	4	1	1		6	38@
Total	86	17	8	3	1	29	33.7

Mnts=months, Yrs=years, Menin=meningitis, attks=attacks, Re.MG=recurrent meningitis, * Statistical analysis of period of follow up and incidence of recurrent meningitis Ch^2 (Yates' corrected) = 17.3, Two tailed p=0.000011, d.f 3, Standard error of difference=0.095. @ Statistical analysis of duration of CSF leakage was not significant, Ch^2=0.202, p=0.918, d.f 3, Standard error of difference=0.11 and 95% confidence interval -0.23 to 0.21 .

Intra-cerebral abscess:

Five (6 %) patients developed intra-cerebral abscesses, all of which were of traumatic origin. Full details of these five patients is shown in table 2-13. Two of these patients were receiving antibiotic prophylaxis.

Neurological damage;

Four patients developed permanent focal neurological deficit (2 hemiparesis , 1 visual field defect and 1 bilateral deafness) and twelve (14 %) developed seizures.

Table 2-13: Details of those who developed cerebral abscess:

Patient No.	P1	P2	P3	P4	P5
Age (Years)	15	15	30	18	21
Sex	Male	Male	Male	Male	Male
CSF leakage	CSFR	CSFR	CSFR	CSFR	CSFO
Onset (Leak)	Im.	early	Im.	early	Im.
Duration of leak	4 days	30 days	3 days	21 days	10 days
Antibiotic prophylaxis	NO	NO	NO	Yes	Yes

CSFR=CSF Rhinorrhoea, CSFO=CSF otorrhoea, Im.=immediate .

2-8 Summary and Conclusions:

In this chapter, the literature concerning the risk of intra-cranial infection in patients with CSF fistulae was reviewed and a long-term follow up analysis of 253 patients with CSF fistulae was presented.

Trauma was the main aetiology (89.7 %), CSF rhinorrhoea was the main symptom (82.6 %), the CSF leakage stopped within a week in 42 % of cases and began within a week of trauma in 82%, the mean age was 34.4 (+/- 18.9) years and 74.7 % were males.

During the follow up period 86 patients developed meningitis with a mortality rate of 4.7 % and a total morbidity of 58.4 %. CSF culture was positive in 65 % and the pathogen was Streptococcus pneumoniae in 57 % and Haemophylus influenzae in 12 % of CSF isolates. The morbidity included; 33.7 % who developed recurrent attacks of meningitis, 14 % seizures, 4.7 % permanent neurological deficit and 6 % intra-cranial abscesses. Over the first four weeks following CSF leakage, the actuarial average risk of meningitis was 2.4 % per week, over the next 11 months it was 3 % per month and over the next ten years it was 9.8 % per year. The most significant adverse prognostic factor associated with increased risk of meningitis was CSF rhinorrhoea (Hazard ratio = 2.34). Though delayed onset and persistence of the CSF leakage for more than seven days were also associated with an increased risk they did not reach statistical significance.

Therefore, patients with CSF fistulae irrespective of the fistula's aetiology, duration and onset are at continuing risk of meningitis which carries a substantial morbidity and potentially fatal. The vast majority of these patients are young and the economical and social consequences of meningitis and its sequelae should be considered. Although, the mortality from meningitis is reduced by antibiotic therapy, clinical and experimental studies have shown regional deficiency of both humoral and cell-mediated immunity in the central nervous system and thus meningitis can be rapidly fatal in these patients. Therefore, prevention of meningitis in these patients is desirable at an early stage.

Chapter 3

The Possible Value of Antibiotic Prophylaxis in the management of patients with unrepaired dural fistulae

3-1, Introduction:

The controversy surrounding the use of prophylactic antibiotic treatment, in patients with CSF fistulae, becomes obvious from reading the recommendations advocated by authors and editors of the most recent general and neurosurgical textbooks (Brown 1990, Editorial, Br J Neurosurg). The following authors have advocated antibiotic prophylaxis in patients with dural fistulae;

(1) Hoff (1980). Neurosurgery & Surgery of the Pituitary. In; Way LW ed. Current Surgical Diagnosis and Treatment.

(2) Crockard (1988). Intracranial Emergencies. In; Cuschieri, Giles & Moossa eds. Essential Surgical Practice.

(3) Teasdale & Galbraite (1989). Head Injuries. In; Symon, Thomas & Clark eds. Rob & Smith's Operative Surgery; Neurosurgery.

(4) Mendelow (1990). Management of Head Injuries. In; Hospital Update.

(5) Bullock & Teasdale (1990). Head Injuries I. In; ABC of Major Trauma. BMJ.

While, the following authors disavowed the use of antibiotic prophylaxis in patients with CSF fistulae;

(1) Dagi & George (1988). The management of CSF Leaks. In; Schemideck & Sweet eds. Operative Neurosurgical Techniques.

(2) Spetzler & Zabramski (1990). Cerebrospinal Fluid Fistulae. In; Youmans JR eds. Youmans Neurological Surgery.

This unsatisfactory situation has arisen from the lack of adequate follow up data on treated and untreated patients with CSF fistulae. Previous cross sectional surveys have been reported with inconclusive results because of the following reasons;

(1) Lack of data on the long term survival free form meningitis,

(2) The majority of patients included in these series were protected by surgery at an early stage.

(3) Many patients were lost to follow up.

Therefore, there is a need for further documentation of the long term survival of patients who have or have not received prophylactic antibiotics.

3-2. Objective;

To determine the possible effects of prophylactic antibiotic treatment in patients with unrepaired CSF fistulae.

3-3. Design & Setting;

Retrospective analysis of patients with unrepaired dural fistulae, who were treated or untreated with prophylactic antibiotics. Antibiotic prophylaxis was considered to be adequate if it was started within three days of the onset of CSF leakage and continued for at least a week after the CSF leakage stopped.

The study was carried out in the Mersey Regional Department of Medical and Surgical Neurology and these patients were

followed up until the patient's death, surgical intervention, or the end of 1990. The mean follow up period was 2.5 years.

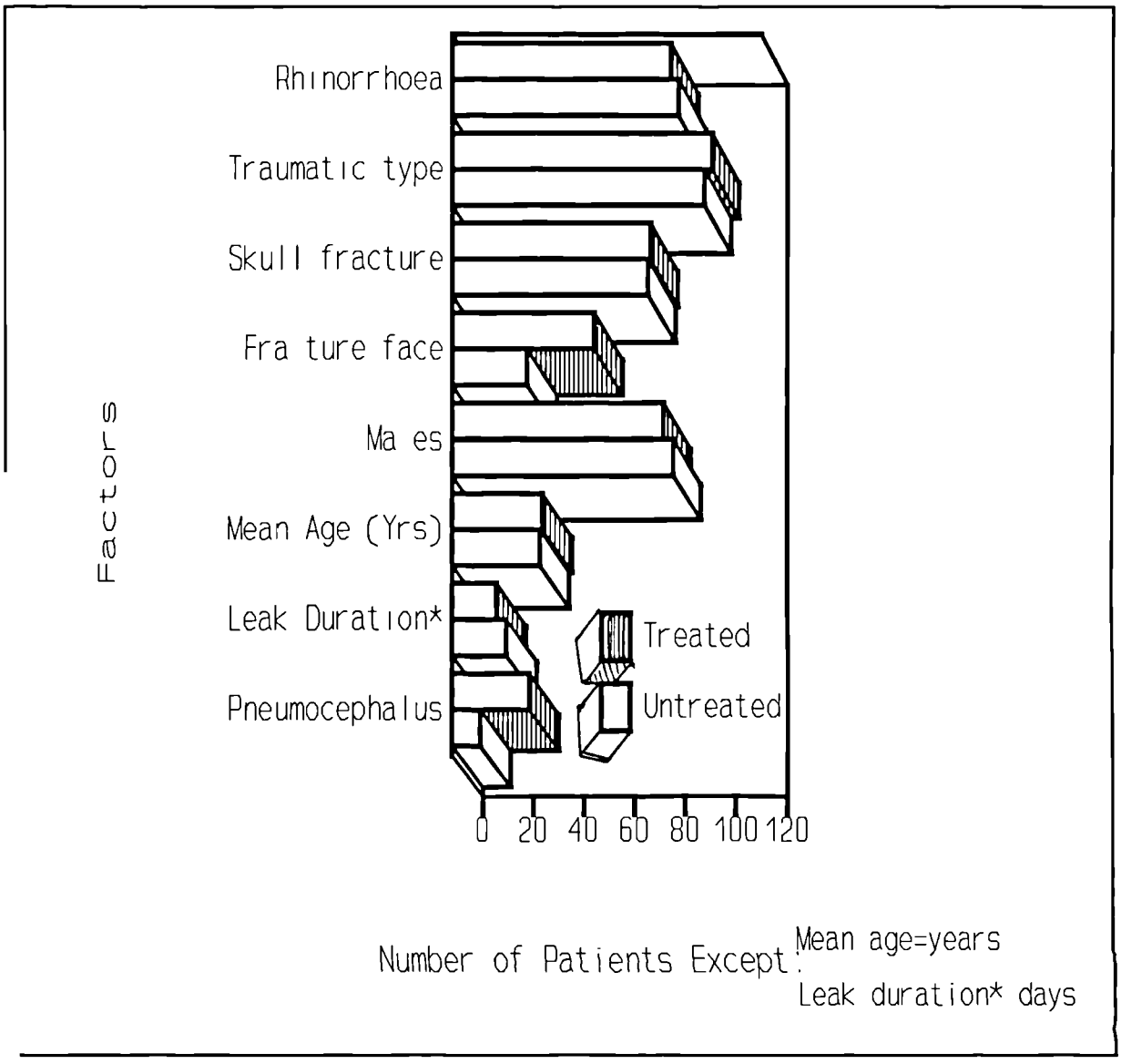
3-4, Patients & Methods ;

The study population comprised 106 patients with CSF fistulae, who were treated with antibiotic prophylaxis (Group A), and 109 patients, who were not treated with antibiotics (Group B). The baseline characteristics of the two groups are summarised in figure 3-1. The two groups of patients were closely matched for age, sex, incidence of CSF rhinorrhoea, duration of CSF leakage, type of CSF fistula and presence of paranasal skull fractures (Chi^2- p values > 0.05). There were more patients with facial fractures and pneumocephalus in the group who received antibiotic prophylaxis (Chi^2- P values < 0.05), but, these two particular factors were not adverse prognostic factors for meningitis (Chapter 2). Therefore, pneumocephalus and facial fractures are unlikely to have affected the survival free from meningitis in the two groups of patients.

The Kaplan-Meier product-limit technique was used to estimate the survival curves of survival free from meningitis of the two groups (A&B) (Kaplan & Meier 1958 & Chapter 2). The annual meningitis risk was calculated from the survival data as follows; Annual Meningitis Risk (1-6 years after CSF leakage) = $100\ (1-(1-Y/100)^{1/6})$, where Y= the meningitis rate at 6 years.

The survival data were compared using the logrank test (Mantel 1966) and were further analyzed using the standard biomedical programs data package (Dixon 1985). All the listed Chi^2 values were with Yates' correction and p values were two tailed.

Figure 3-1; The baseline characteristics of patients with CSF fistulae, who were treated (Group A) and untreated (Group B) with antibiotic prophylaxis :



3-4, Results :

(A) Early risk of meningitis:

The meningitis rate during the first week of CSF leakage was 6.6 % in the treated (group A) and 9.17 % in the untreated group (B), which is not statistically significant difference at the 0.05 level (Chi^2 (Yates' correction) = 0.0963, d.f.1, p value > 0.05). The incidence of meningitis during the first four weeks of CSF leakage is summarised in table 3-1. The difference in the meningitis rate during the first four weeks of CSF leakage, was not statistically significant among the two groups (Chi^2 = 1.92, d.f 3, p > 0.05).

Table 3-1: The meningitis rate during the first four weeks of CSF leakage, Group A = treated with prophylactic antibiotics & Group B = untreated patients.

Interval	Group A (%)	Group B (%)
1 week	7/106 (6.6)	10/109 (9.17)
2 weeks	4/78 (5.13)	8/90 (8.89)
3 weeks	4/64 (6.25)	3/85 (3.53)
4 weeks	1/53 (1.89)	2/71 (2.82)

(B) Late meningitis and the annual risk of meningitis :

The meningitis rate during the first six years following CSF leakage in the treated group (A) was 7.63 % per year. While the incidence of meningitis in the untreated group (B) during the same period was 11.9 % per year. Although antibiotic prophylaxis has reduced the risk of meningitis in those who were treated, the

difference was not statistically significant at the 0.05 level (Chi^2 = 0.94, d.f 5, p > 0.05) Table 3-2.

Table 3-2: The cumulative risk of meningitis during the first 6 years following CSF leakage in treated (group A) and untreated (group B) with prophylactic antibiotics .

Interval	Group A	Group B
1 Year	23.6	42,4
2 Years	27.6	44,3
3 Years	27.6	44.3
4 Years	27.6	46.8
5 Years	27.6	51.0
6 Years	37.9	53.3

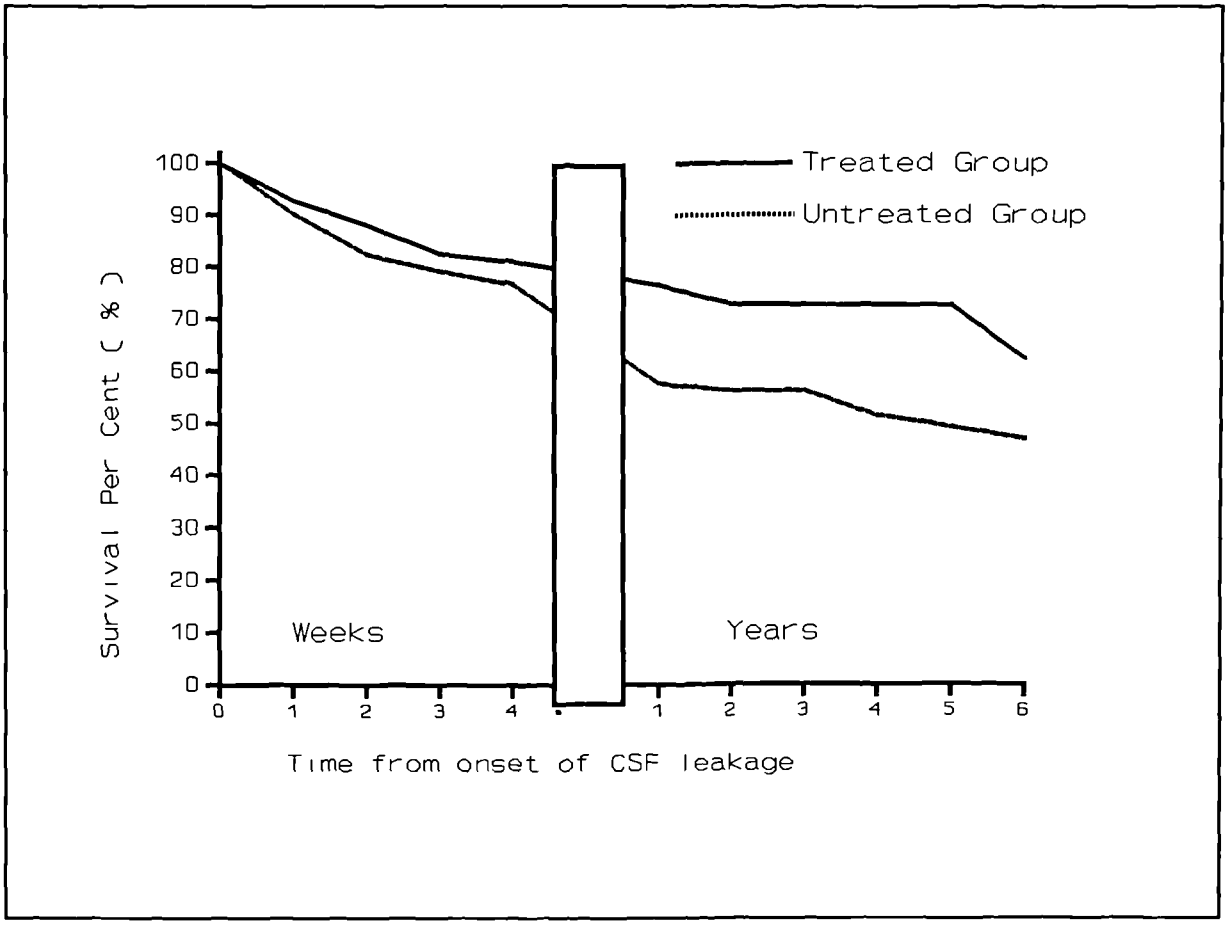
Survival Free from Meningitis :

81 % of patients in the treated group (A) and 76.7 % of the untreated patients (Group B) survived free from meningitis for four weeks. Although more patients survived free from meningitis longer in the treated group (A), the overall survival free from meningitis was not statistically different in the two groups (The logrank test; Chi_1-Squared= 3.092 and Chi_2-Squared= 2.80 , p value > 0.05) Table 3-4 and Figure 3-2.

Table 3-4: The survival data of survival free from meningitis, Group A= treated and Group B= untreated with antibiotics ; FFM & SFFM= survival free from meningitis :

Time interval t	No. menin-gitis	No. at risk	Sur-vival FFM	SFFM %	95% confidence intervals
0					
Group A	-	106	1.000	100.0	-
Group B	-	109	1.000	100.0	-
1 week					
Group A	7	97	0.928	92.8	85.8 to 96.4
Group B	10	103	0.903	90.3	83.2 to 94.5
2 weeks					
Group A	4	78	0.880	88.0	79.2 to 93.3
Group B	8	90	0.823	82.3	73.7 to 88.2
3 weeks					
Group A	4	64	0.825	82.5	72.1 to 89.3
Group B	3	78	0.791	79.1	69.7 to 85.9
4 weeks					
Group A	1	53	0.810	81.0	69.2 to 88.6
Group B	2	66	0.767	76.7	66.3 to 84.3
1 year					
Group A	2	36	0.765	76.5	61.6 to 86.2
Group B	12	48	0.575	57.5	46.2 to 67.3
2 years					
Group A	1	19	0.724	72.4	51.1 to 85.6
Group B	1	31	0.557	55.7	41.7 to 67.5
3 years					
Group A	0	12	0.724	72.4	44.5 to 88.0
Group B	0	26	0.557	55.7	40.4 to 68.5
4 years					
Group A	0	10	0.724	72.4	41.3 to 88.9
Group B	2	24	0.512	51.2	36.3 to 64.2
5 years					
Group A	0	9	0.724	72.4	40.3 to 89.2
Group B	1	23	0.490	49.0	34.3 to 62.2
6 years					
Group A	1	7	0.621	62.1	28.9 to 83.3
Group B	1	21	0.467	46.7	31.9 to 60.2

Figure 3-2: The survival curves of survival free from meningitis, Group A = 106 treated patients with prophylactic antibiotics & Group B = 109 untreated patients:



Regression analysis of the survival data of group A & B, showed no significant difference between the survival free from meningitis of those who were treated and those who were not treated with prophylactic antibiotics (Table 3-4).

Table 3-4: Summary of the regression analysis of the survival data , Group A treated & Group B untreated:

Factor\Group	Group A	Group B
B-coefficient	0.177	-0.019
Standard Error	0.148	0.124
t statistic	1.198	-0.155
p value	0.265	0.881
95 % confidence interval of B	-0.16 0.52	-0.31 0.27

Isolated pathogens from CSF:

Antibiotic prophylaxis was associated with a significant increase in the number of gram negative meningitis and failure to isolate the micro-organisms (Chi^2 = 5.7, d.f 1, p value 0.01) Table 3-5.

Table 3-5: The incidence of Gram negative meningitis and the number of negative cultures in: Group A (treated) and Group B (untreated with prophylactic antibiotics):

CSF cultures	Group A	Group B
Total number of meningitis	20	36
Gram negative meningitis	3 (16%)	0
No growth	11 (55%)	14 (39%)

3-6, Discussion:

Are prophylactic antibiotics of any value in preventing meningitis in patients with unrepaired CSF fistulae ?

The literature on this subject was reviewed in 1970 (MacGee & others 1970). These authors found that 5 % (4/77) of the reported cases of CSF fistulae developed meningitis despite antibiotic prophylaxis. While, 14 % (46/325) of the untreated patients developed meningitis. However, the meningitis-rate in the treated and untreated patients with prophylactic antibiotics was not statistically significant ($p > 0.05$).

In the following 20 years, six more studies, addressing the same question, were published (Leech & Paterson 1973, Ignelzi & VanderArk 1975, Klaterskey & others 1976, Einhorn & Mizali 1978, Dagi & others 1983 & Zrebeet & Huang 1986). Except for Leech & Paterson's series, none of the other authors found any statistically significant difference in the incidence of meningitis among those who received and those who did not receive antibiotic prophylaxis (Table 3-6).

Leech & Paterson (1973) found that 16.6 % of those who were treated adequately and 0 % of those who were treated inadequately with prophylactic antibiotics developed meningitis in the first week after trauma. Although their figures have reached statistical significance at 0.05 level, these results should be interpreted with caution because:

(1) Most of their patients in the two compared groups received antibiotic treatment of some form. One group was selected because the antibiotic prophylaxis was considered adequate,

while the control group consisted of those who received inadequate antibiotic prophylaxis and those who were not treated.

(2) They defined " adequate " antibiotic prophylaxis as 500 mg of penicillin & 500 mg of sulphonamide given 6 hourly during the CSF leakage and continued for at least seven days after the CSF leakage ceased, which is very difficult to ascertain in a retrospective analysis.

(3) The difference was only statistically significant in the first week post-trauma.

(4) The majority of the patients were protected by early surgery and many were lost for follow up.

(5) The actual number of patients who were not given antibiotics at all in that series was unclear.

Table 3-6: Summary of the up-to-date literature on prophylactic antibiotics in CSF fistulae: Group A = treated, Group B = untreated with antibiotics , the figures represent patients with meningitis/ Total :

Authors	Group A	Group B	p value
MacGee & others 1970	46/325	4/77	N.S
Leech & Paterson 1973	7/42	0/76	Sig.
Ignelzi & VanderArk 1975	0/79	2/57	N.S
Klaterskey & others 1976 *	1/26	0/26	N.S
Einhorn & Mizali 1978	0/14	0/32	N.S
Dagi & others 1983	0/63	2/65	N.S
Zrebeet & Huang 1986	2/28	1/14	N.S

* Prospective controlled trial
N.S = not significant and Sig = significant at 0.05 level..

In the present study, the survival free from meningitis and the annual risk of meningitis in the first six years following the onset of CSF leakage were not statistically different in those who were treated and those who were not treated with prophylactic antibiotics.

In conclusion, there is no scientific evidence to support the routine use of prophylactic antibiotics in patients with CSF fistulae. Therefore, it is ethically justifiable to withhold prophylactic antibiotics and keep a constant vigil for early symptoms & signs of intra-cranial infection in these patients, introducing appropriate therapy should meningitis develop.

Can prophylactic antibiotics be harmful to these patients ?

As a result of the indiscriminate use of antibiotics, multi-resistant bacteria have emerged. A multi-resistant Streptococcus pneumoniae strain was recently reported in south London (Tettenborn 1986) and the estimated incidence of penicillin-resistant Streptococcus pneumoniae is about 1.5 % (Broome & others 1980). Two cases of post-traumatic meningitis due to ampicillin-resistant Haemophylus influenzae have been reported (Bryan & Serringan 1979) and the reported incidence of ampicillin-resistant Haemophylus influenzae varied from 14 to 21% (Spiroponlou & others 1978, Ward & others 1978, Jacoson & others 1981 and Tettenborn 1986). There were at least two case reports of chloramphenicol-resistant haemophylus influenzae (Kimmonth & others 1978 and Lerman & others 1980). The incidence of sulphonamide- resistant Nisseria meningiditis is about 30 % (Simasthien & others 1980).

Furthermore, antibiotic prophylaxis has been shown to change the naso-pharyngeal micro-flora towards more invasive virulent Gram negative bacteria. Four out of five patients on prophylactic antibiotics have shown this change by the fifth day of antibiotic treatment (Ignelzi & VanderArk 1975). An epidemic of Klebsiella aerogenes infections affecting a neurosurgical intensive therapy unit as a result of the indiscriminate use of antibiotics has been reported in 1970 and the epidemic was not possible to control except by stopping all antibiotic treatment (Price & Sleigh 1970). In the present study the number of cases of Gram negative meningitis and the number of negative CSF cultures were significantly higher in those who were treated prophylactically with antibiotics.

In conclusion, the weight of evidence suggests that the indiscriminate use of antibiotics may result in an increased number of resistant and more invasive micro-organisms. It may lead to partial treatment of meningitis, obscuring the signs of intracranial infection and leading to failure of isolating the responsible pathogens.

3-7, Summary & Conclusions:

This analysis comprised 106 patients, who received adequate antibiotic prophylaxis and 109 patients who were not treated with antibiotics. The two samples were closely matched for age, sex, type of CSF fistula, site and duration of CSF leakage and presence of skull fractures. There were more patients with facial fractures and pneumocephalus in those who were treated with antibiotics, but these two factors were not adverse prognostic factors for meningitis.

The first week meningitis rate was 6.6 % and 9.17 % in the treated and untreated groups respectively, while the annual risk of meningitis was 7.6 % in the treated and 11.9 % in the untreated groups. However, these differences did not reach statistical significance ($p > 0.05$). The survival curves of survival free from meningitis was similar in the two groups in the first four weeks and although patients survived longer free from meningitis in the treated group this was not statistically significant ($p > 0.05$). There were more Gram negative and partially treated cases of meningitis and negative CSF cultures in the treated group.

Therefore, there is no scientific evidence to support the routine use of antibiotic prophylaxis in patients with CSF fistulae. Routine use of antibiotic prophylaxis may result in perpetuating resistant and more virulent strains of bacteria and may result in failure to grow the pathogens because of partially treated meningitis. It is ethically justifiable to withhold antibiotic prophylaxis in patients with CSF fistulae and keep a constant vigil for early signs of intra-cranial infection,introducing appropriate treatment should meningitis develop.

Chapter 4

The Role of Surgical Dural Repair in the Management of CSF Fistulae

4,1 Introduction

The principle of closing CSF fistulae was first introduced by Grant in 1923 and the first successful repair of a dural fistula was reported in 1926 (Dandy 1926). Since then, there has been a growing awareness of its importance in the management of patients with CSF leaks. Surgical repair of persistent CSF fistulae gained support and it was mandated by the associated risk of intracranial infection despite the use of modern antibiotics. It has been recommended to all patients with dural fistulae by many authors (Calvert 1942, Lewin 1954 & 1966 and Morley & Hetherington 1957). However, proponents (Lawson 1934, Adson & Uihlein 1949, Browder 1960, Dawson 1962, Brawley & Kelly 1967, O'Connell 1968, Schineider 1969 and Leech & Paterson 1973) of conservative treatment have disputed the high success of dural repair and recommended waiting for sometime before choosing surgery. The waiting period varied from 1 to 8 weeks. This conservative approach is the result of;

(1) Lack of long-term survival data of patients who were treated conservatively.

(2) High operative mortality, morbidity and negative exploration rates that have been reported in the sixties.

Modern surgical dural repair remains the same as the original Grant-Dandy technique. Nevertheless, in recent years, several improvements in the diagnostic and surgical techniques have been achieved. The introduction of microsurgery and computed tomography in the early seventies have revolutionised neurosurgery. These advances in imaging techniques, cisternography and microsurgery were paralleled by improved neuroaneasthesia and intensive therapy. This progress in the medical sciences has changed the ways these patients are managed. However, no published comparison,

between the results of surgery before and after the introduction of microsurgery and computed tomography, could be found.

4.2 Objectives

(1) To determine the prognosis and adverse prognostic factors in patients who underwent surgical dural repair.

(2) To compare the results of surgical dural repair before and after the introduction of microsurgery and CT scanning.

4.3 Patients and Methods

The clinical records of all patients who underwent surgical dural repair in the Mersey Regional Department of Medical and Surgical Neurology between 1944 and 1990 were critically reviewed. The patient population was identified using the neurotheatres' records and was traced through the Family Health Services Authorities and the family practitioners. The follow up data was obtained by questionnaires sent to the family practitioners.

The study population comprised 203 patients, in which 183 CSF fistulae were of traumatic origin (158 head injuries & 25 post-surgical) and 20 were non-traumatic. 232 operations were performed, of which 203 were primary and 29 were secondary repairs. Follow up details were obtained until either the patient's death or until the end of 1990. The mean follow up was 5 years (Range one to 32 years, SD = 3.5 years).

Statistical methods:

For surgery-associated mortality, negative exploration rate, failure of dural repair and immediate surgical complications, simple analysis of proportions was performed

using a Biomedical Statistical Package Software (Dixon 1983). For long-term results of surgery life-table methods (Kaplan and Meier 1958) and the logrank tests (Mantel 1963 & 1966) were used for analyses of time from surgery to the first subsequent event, such as meningitis. Those who had negative surgical exploration or died of other cause than meningitis were excluded from the denominator.

The 95 % confidence intervals for survival were calculated from;

$$95\ \%\ \text{confidence Interval of } Ix = Ix^{EXP(+/-1.96s)},$$

Ix=the survival proportion and s=Standard Error of Ix divided by (Ix ln Ix).

The average annual risk of an outcome event (such as meningitis) was calculated from the survival data as follows;

$$\text{Annual Risk} = 100(1-(1-Y/100)^{1/x})\%,$$

where x= the time interval in years and Y=the incidence of the outcome event by the end of x years of follow up.

The influence of potential prognostic factors on the rate of an outcome event (such as meningitis) was determined by analyzing the survival data with a biomedical software based on the Cox's proportional hazards regression model, which provides estimates of regression parameters (*B*-coefficient) for each independent variable (Cox 1972). The hazard ratio was calculated from the; exponential (*B*-coefficient) and the 95 % confidence interval of the hazard ratio was calculated from the;

exponential(*B*-coefficient+/- 1.96 x Standard Error).

4,4 Outcome Measures

Surgery-associated events:

(1) Death within 30 days of surgery.

(2) Negative surgical exploration rate.

(3) Failure of surgical repair, in which CSF leakage continued postoperatively.

(4) Immediate post-operative complications, including intracranial haematomas, neurological deficit, thromboembolic complications and extra-cranial sepsis.

Long-term outcome measures:

(1) Meningitis.

(2) Recurrent CSF leakage following initial stoppage by surgical repair.

(3) Epilepsy.

4,5 Results:

4,5-1 Baseline Characteristics:

Age & Sex;

The mean (Standard Deviation) age was 33.5 (18) years (Range from 2-76 years) and the female to male ratio was 1 to 3.2.

CSF Leakage;

More than 90 % were traumatic (78 % associated with head injuries and 12 % post-surgical) and less than 10 % were non-traumatic in origin. 82.3 % presented with CSF rhinorrhoea and the mean (Standard Deviation) duration of CSF leakage was 9 (3) days. 74.4 % of CSF leaks started and about a third of them stopped within a week. 67 % of the CSF leaks persisted more than a week.

Indications for Surgery;

The main indication for surgical repair was intracranial infections in 69 patients, persistent CSF leakage for more than one week in 76 patients (including 9 patients reoperated because of failed primary repair) and recurrent CSF leakage in 45 patients (including 20 patients reoperated because of CSF leak recurrence). The remaining 42 patients underwent surgical repair prophylactically. Table 4-1 summarizes the baseline characteristics of these patients.

Table 4-1; The baseline characteristics of 203 patients with CSF fistulae, who underwent surgical repair, Group A included patients who underwent surgery before microsurgery & CT scan and Group B included those who were repaired after microsurgery and CT scanning were introduced, SD=Standard Deviation.

Factors	Group A	Group B	Total
Total Number	116	87	203
Age Mean (SD) Range years	31.2(16.7) 2-76	35.7(19.4) 3-72	33.5(18) 2-76
Males	96	57	153
Aetiology: Head injuries Post-surgical Non-traumatic	 97 12 7	 61 13 13	 158 25 20
CSF rhinorrhoea otorrhoea	97 1	70 8	167 9
CSF Leakage: Mean duration(SD) Onset in a week Stopped in a week Persisted >1 week	 8(3) days 81 40 76	 10(3) days 70 26 61	 9(3) days 151 66 137
Fractures;Skull Facial	95 32	52 18	147 50
Antibiotic prophylaxis	49	58	97
Meningitis	40	29	69

4,5-2 Surgery-associated events:

Six patients died within 30 days of surgery (2.6 %), two underwent surgery and no repair was undertaken (0.9 %), 13 of the primary repairs failed to stop the CSF leakage (6.4 %) and 24 patients suffered post-operative complications (10.3 %).

Mortality;

The mortality rate before and after the introduction of microsurgery and CT scan was 3.4 % and 2.5 % respectively (Chi-square = 3.57, df=1, $p > 0.05$). The cause of death was thromboembolism in two, postoperative sepsis in two and neurological complications in another two patients. Seven other patients died sometime during the follow up because of unrelated causes. Three after six months, two within 3 and another two within 27 years.

The adverse prognostic factors for death were;

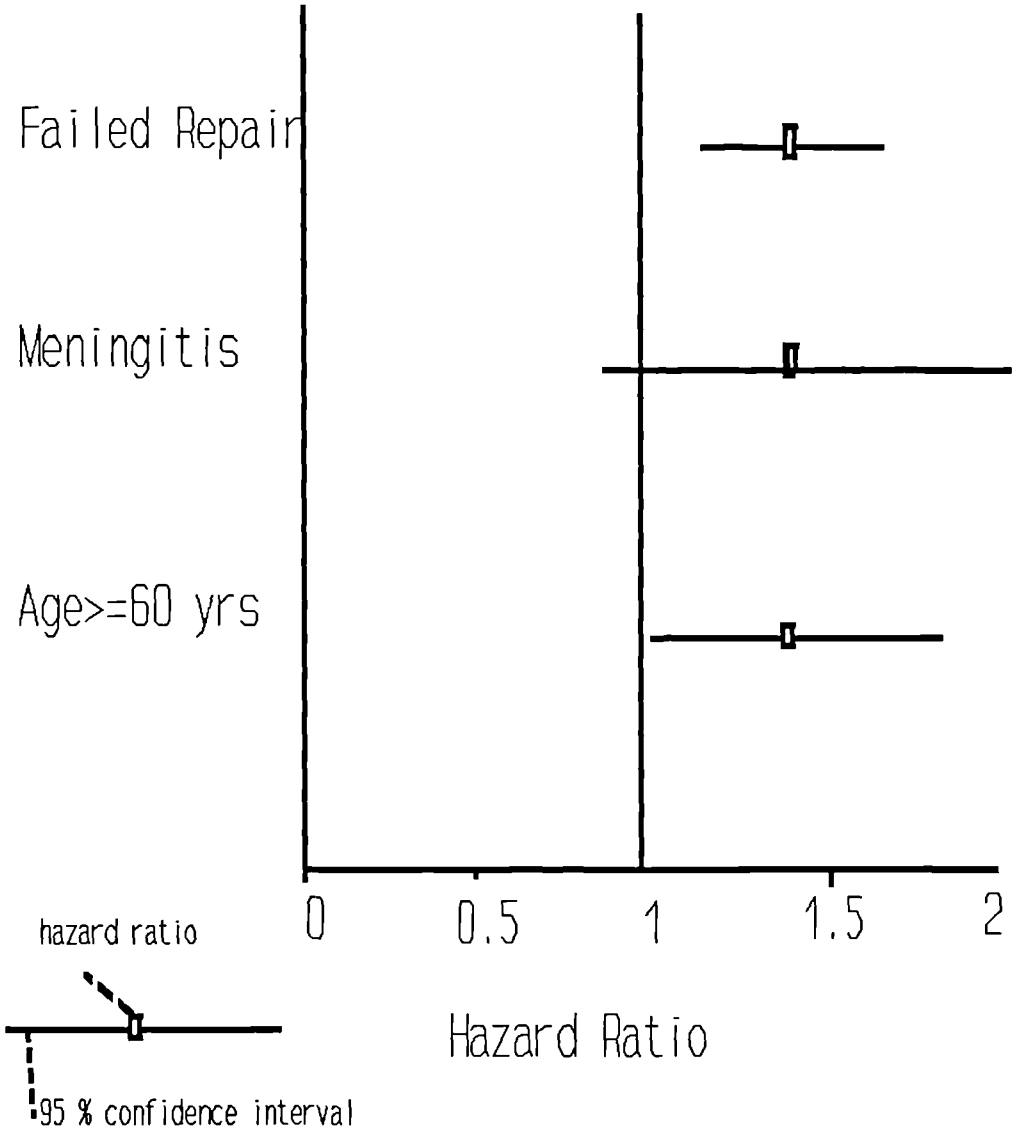
(1) Age of 60 years or above (hazard ratio = 1.37).

(2) Failure of dural repair (hazard ratio = 1.39).

(3) Meningitis (hazard ratio = 1.39).

Therefore, a 60-year-old patient, who continues to leak CSF leak following surgical repair and develops meningitis is 6 times more likely to die than a younger patient who had uneventful successful repair (Table 4-2 and Figure 4-1). Sex, surgical approach, type of CSF fistula, onset and duration of CSF leakage and the use of prophylactic antibiotics did not have a significant effect on the mortality rate.

Figure 4-1: Adverse prognostic Factors for Death



Meningitis was forced in the model because of medical common sense as the reported mortality from meningitis is still up to 20 % .

Table 4-2; Proportional hazards analyses in 203 patients with repaired CSF fistulae;

Outcome events	Prognostic factors	*B*-coeff.	*B*/SE **	Hazard Ratio	95 % C.I.***
Death	Failed Repair	0.331	4.11	1.39	1.19 to 1.63
	Meningitis @	0.332	1.5	1.39	0.9 to 2.15
	Age > =60 yrs	0.318	2.22	1.37	1.04 to 1.82
Immediate morbidity	Repair during third week	0.414	4.64	1.51	1.27 to 1.8
	Skull #	0.15	5.24	1.16	1.1 to 1.23
	Age > =60yrs@	0.181	1.21	1.2	0.89 to 1.61
Meningitis	Recurrent leak	0.739	13.85	2.09	1.89 to 2.32
	Failed Repair	0.062	2.33	1.06	1.01 to 1.12
	Preoperative meningitis@	0.136	1.34	1.15	0.94 to 1.4
Recurrent CSF leak	Non-traumatic aetiology	0.954	8.13	2.6	2.1 to 3.3
Epilepsy	Skull #	0.236	2.08	1.27	1.02 to 1.58
	B.F.C @	0.034	0.33	1.04	0.54 to 1.96
	Postoperative complication	0.629	2.08	1.88	1.04 to 3.39

= fracture, ** if the value is > 1.96 the p value < 0.05, *** 95 % confidence intervals of the hazard ratios, coeff. = coefficient and @ factors which were forced in the model because of their significance in previous reports and medical common sense .

Negative exploration;

Two patients underwent bifrontal exploration and no repair was undertaken because the CSF fistula could not be found (0.9 % negative exploration rate). In another three patients, although the surgeon was not absolutely sure about the site of the

CSF fistula, surgical dural repair of the anterior cranial fossa was undertaken. In all the later three patients, the CSF leakage stopped immediately after the surgery. None of these five patients had adequate pre-operative localisation of the CSF fistula. The negative exploration rate was not statistically different before (1.7 %) and after (0 %) the introduction of microsurgery and CT scanning (Chi-square with Yates' correction = 0.26, df=1, $p > 0.05$).

Failure of Dural Repair;

Thirteen patients continued to leak CSF following dural repair (6.4%). There was no statistically significant difference in the failure rate before and after the introduction of microsurgery and computed tomography (Chi-square 0.054, df=1, $p > 0.05$). There were no significant adverse prognostic factors.

Immediate Post-operative complications;

Twenty-four (10.3 %) developed immediate post-operative complications (Table 4-3). The prognostic factors that were associated with a significant risk of developing postoperative complications included;

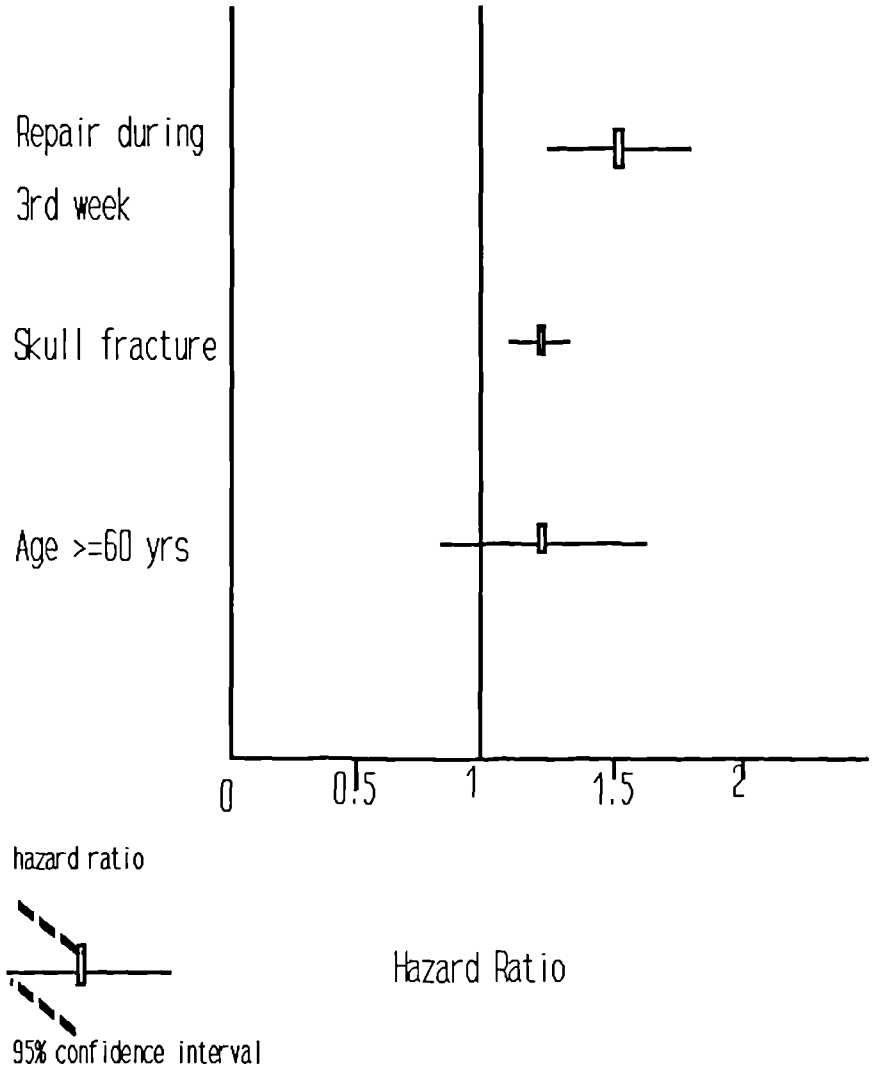
(1) Surgery during the third week of CSF leakage (hazard ratio 1.51).

(2) Head injury with skull fractures (hazard ratio 1.16).

(3) Age >= 60 years (hazard ratio 1.2).

Therefore, a 60-year-old patient, who had a traumatic CSF fistula repaired during the third week of the onset of CSF leakage, is twice as likely to develop post-operative complications as a younger patient with non-traumatic CSF fistula repaired one week after the onset of the CSF leakage (Table 4-2 and Figure 4-2).

Figure 4-2; Adverse Prognostic Factors for immediate Morbidity



Although, microsurgery and CT scanning had reduced the overall post-operative complication rate, there was no significant difference in the complication rate among those who were repaired before and after the introduction of microsurgery and computed tomography (Table 4-3).

Table 4-3; The postoperative complications in 24 patients; Group A and Group B indicate those who were repaired before and after the introduction of microsurgery and CT scan:

Immediate complication	Total	Group A	Group B	p
Intracranial haematoma	0.4 %	0	1.1 %	NS
Visual disturbances	2.6 %	3.4 %	2.3 %	NS
Limb weakness	4.3 %	5.2 %	4.6 %	NS
Behaviour changes	2.6 %	4.3 %	1.1 %	NS
Wound & Bone infection	3.5 %	4.3 %	3.4 %	NS
Thromboembolism	0.9 %	0	2.3 %	NS
Chest infections	0.9 %	0.9 %	1.1 %	NS

NS=Not significant.

4,5-3 Long-term outcome measures:

Meningitis;

Five patients developed meningitis sometime during the follow up following successful dural repair (2.2 %). Those who developed meningitis in association with recurrent CSF leakage or failure of repair were excluded from this analysis.

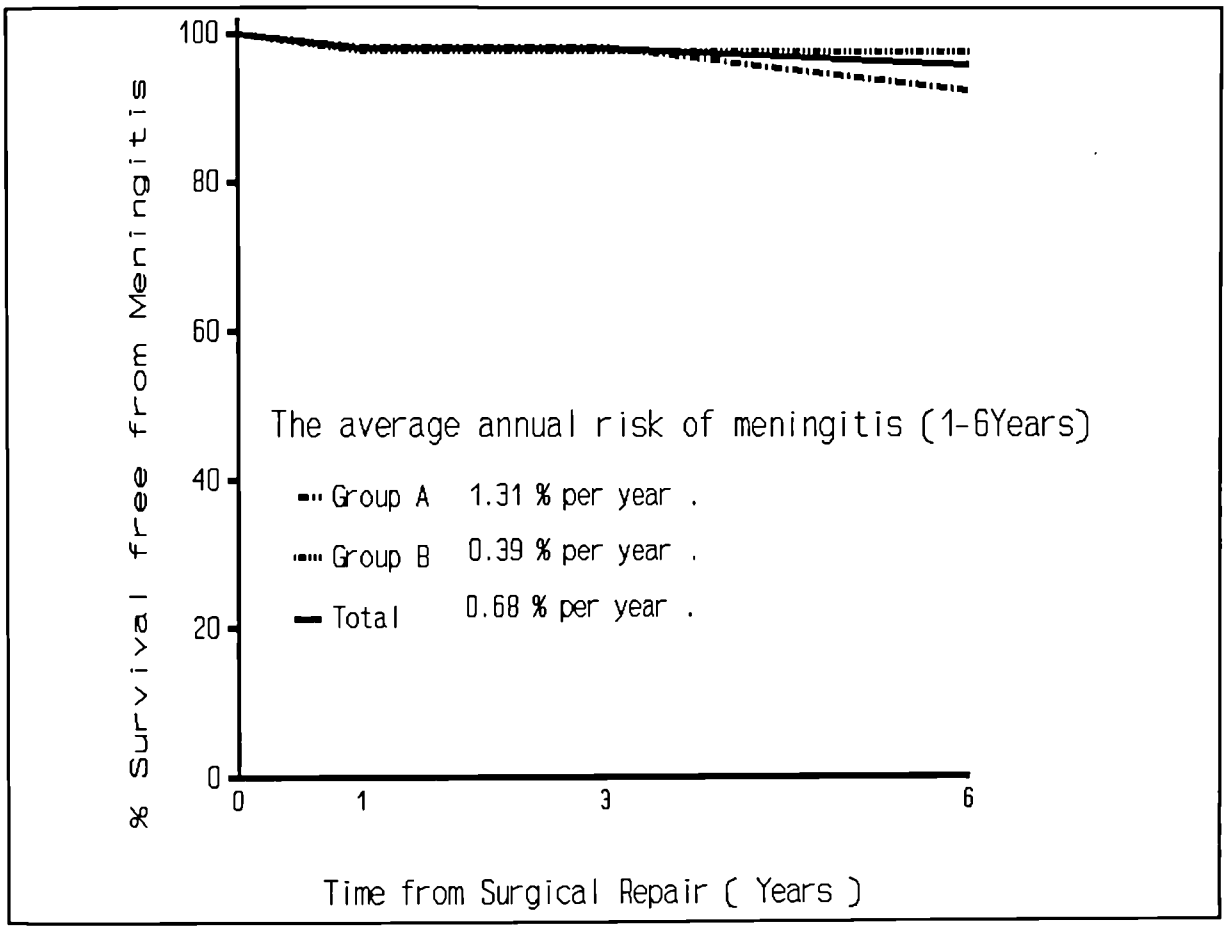
Ninety-six per cent of the patients survived 6 years free from meningitis following dural repair. The corresponding figure before and after the introduction of microsurgery and computed tomography were 92.4 % & 99.8% respectively, but this difference was not statistically significant (logrank test Chi_1-square 0.12, Chi_2-square 0.115, 1p & 2p were > 0.05). The life-tables are summarized in Table 4-4 and Figure 4-3.

The average annual risk of meningitis (1-6 years following dural repair) = 0.68 % per year. It has been reduced by the introduction of microsurgery and computed tomography from 1.31 % per year to 0.39 % per year.

Table 4-4; Life-tables of survival free from meningitis of 203 patients following surgical dural repair; Groups A & B designate those who underwent repair before and after the introduction of microsurgery & CT scanning;

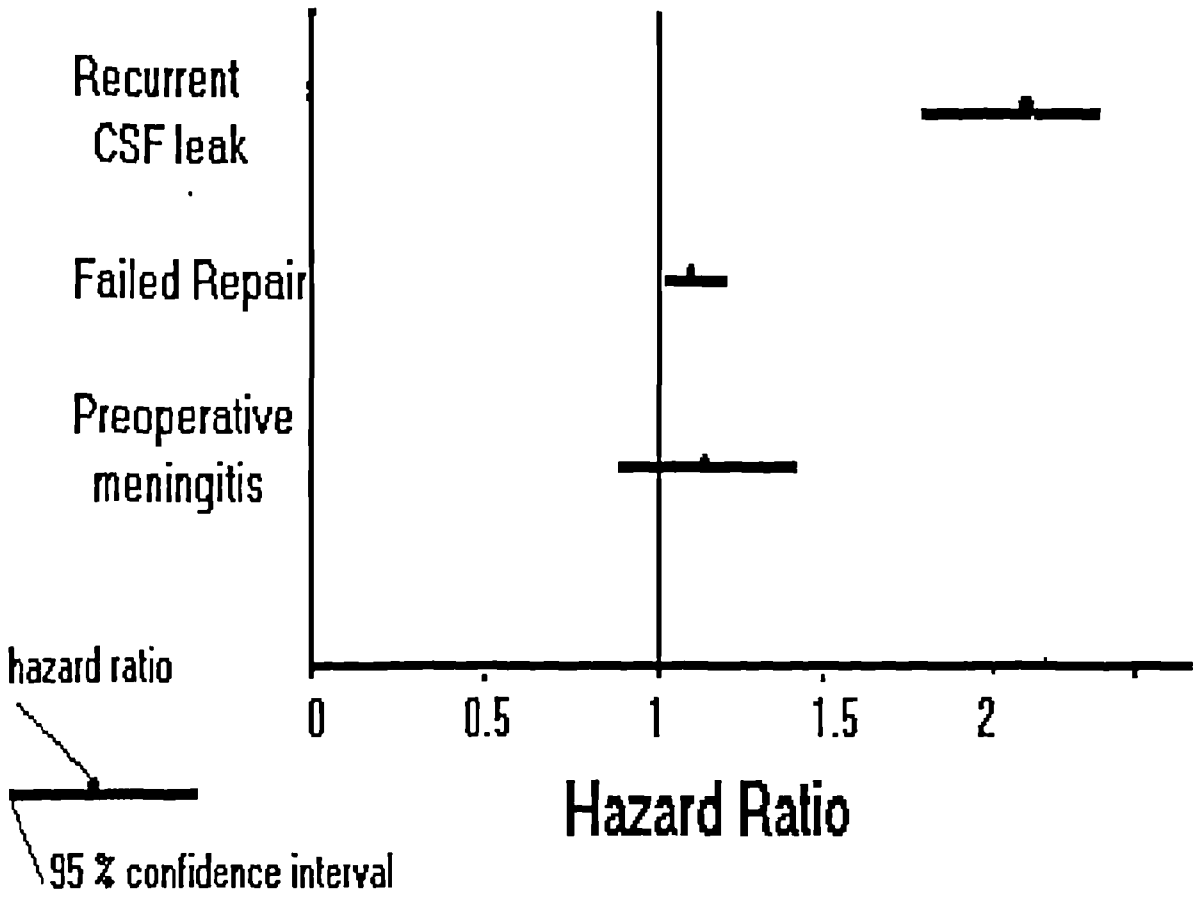
Time (Years)	Group	No.Men - ingitis M	No. at Risk N	Menin- gitis p %	Estimate Survival Ix %	95 % confidence intervals
0	A	-	116	-	100.0	-
	B	-	87	-	100.0	-
	Total	-	203	-	100.0	-
1	A	2	112	0.018	98.2	93.1*99.5
	B	2	85	0.024	97.6	91.1*99.4
	Total	4	197	0.02	98.0	94.7*99.2
3	A	0	24	0	98.2	70.6*99.9
	B	0	43	0	97.6	84.9*99.7
	Total	0	67	0	98.0	89.8*99.6
6	A	1	17	0.059	92.4	66.1*98.5
	B	0	32	0	97.6	80.0*99.8
	Total	1	49	0.02	96.0	85.1*99.0

Figure 4-3; The survival curves of survival free from meningitis following dural repair in 203 patients with CSF fistulae; Groups A & B represent those who had surgery before and after the introduction of microsurgery and CT scanning;



The significant adverse prognostic factors for developing meningitis after surgical dural repair were recurrent CSF leakage (hazard ratio 1.78) and failed surgical repair (hazard ratio 1.08). Age, sex, duration & onset of CSF leakage, site of CSF fistula, surgical approach, type of dural graft and skull fractures did not have any significant adverse effect on the subsequent development of post-repair meningitis (Table 4-2 and Figure 4-4).

Figure 4-4: Prognostic Factors for Meningitis



Recurrent CSF leakage;

CSF leakage recurred in 22 patients sometime during the follow up period, of which 59 % occurred during the first year following surgical repair. However, 66.6 % remained free from recurrent CSF leakage for 12 years following surgery. Thirteen of the

recurrent CSF leaks occurred among those who underwent surgical repair before the introduction of microsurgery and computed tomography, but there was no significant difference in the survival free from recurrent CSF leakage among those who were repaired before or after microsurgery and CT scanning (Logrank test; Chi_1-square 0.988, Chi_2-square 0.851 and 1p & 2P > 0.05). Table 4-5 and Figure 4-4 summarize the survival free from recurrent CSF leakage.

Table 4-5; The life-table of survival free from recurrent CSF leakage in 203 patients with repaired CSF fistulae; Groups A & B represent those who were repaired before and after the introduction of microsurgery & CT scanning;

Time (years)	Group	No. of recurrent leaks	No.at Risk N	Recurr-ent rate %	Estimate Survival Ix %*	95 % # confidence interval
0	A	-	103	-	100.0	-
	B	-	77	-	100.0	-
	Total	-	180	-	100.0	-
1	A	8	103	0.078	92.2	85.4*95.9
	B	5	77	0.065	93.5	85.5*97.2
	Total	13	180	0.072	92.8	88.1*95.7
3	A	2	24	0.083	84.5	65.1*93.6
	B	1	42	0.024	91.3	78.4*96.6
	Total	3	66	0.046	88.6	78.9*94.0
6	A	2	17	0.118	74.6	51.5*87.8
	B	2	30	0.067	85.2	68.5*93.5
	Total	4	47	0.085	81.1	68.4*89.0
9	A	1	17	0.059	70.2	47.1*84.4
	B	0	26	0	85.2	67.8*94.5
	Total	1	43	0.023	79.2	65.8*87.8
12	A	0	15	0	70.2	46.2*85.0
	B	1	15	0.067	79.5	53.7*91.9
	Total	1	30	0.033	76.6	60.0*87.0

* Ix = the survival free from recurrent CSF leakage # 95 % confidence intervals of Ix.

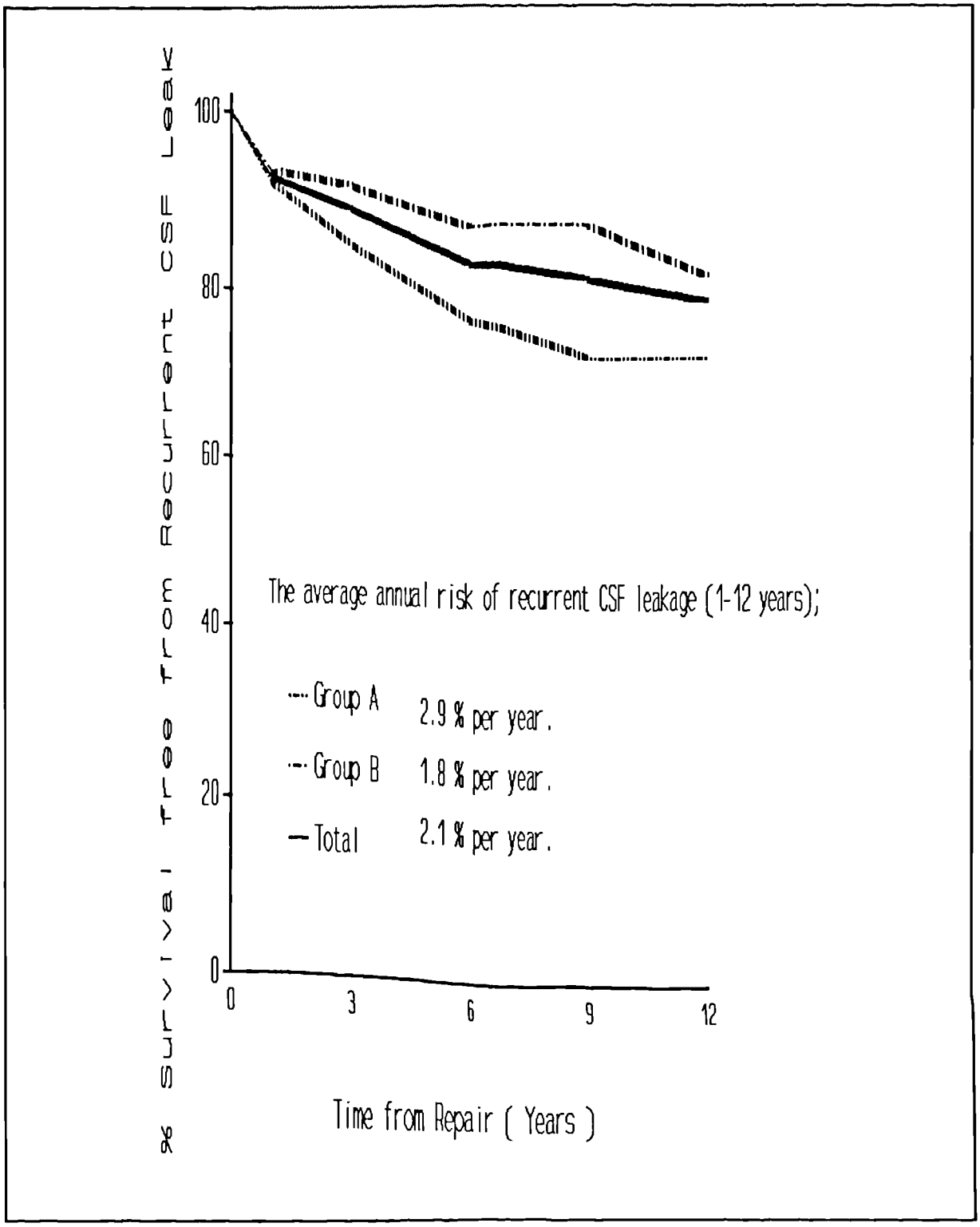


Figure 4-5; Survival Curves of survival free from recurrent CSF leak ; Groups A & B represent those who were repaired before and after the introduction of microsurgery & computed tomography.

The average annual risk of developing recurrent CSF leakage (1-12 years following surgical repair) was 2.1 % per year . The average annual risk of recurrent CSF leakage was reduced from 2.9 % per year to 1.8 % per year by introducing microsurgery & computed tomography (Figure 4-5).

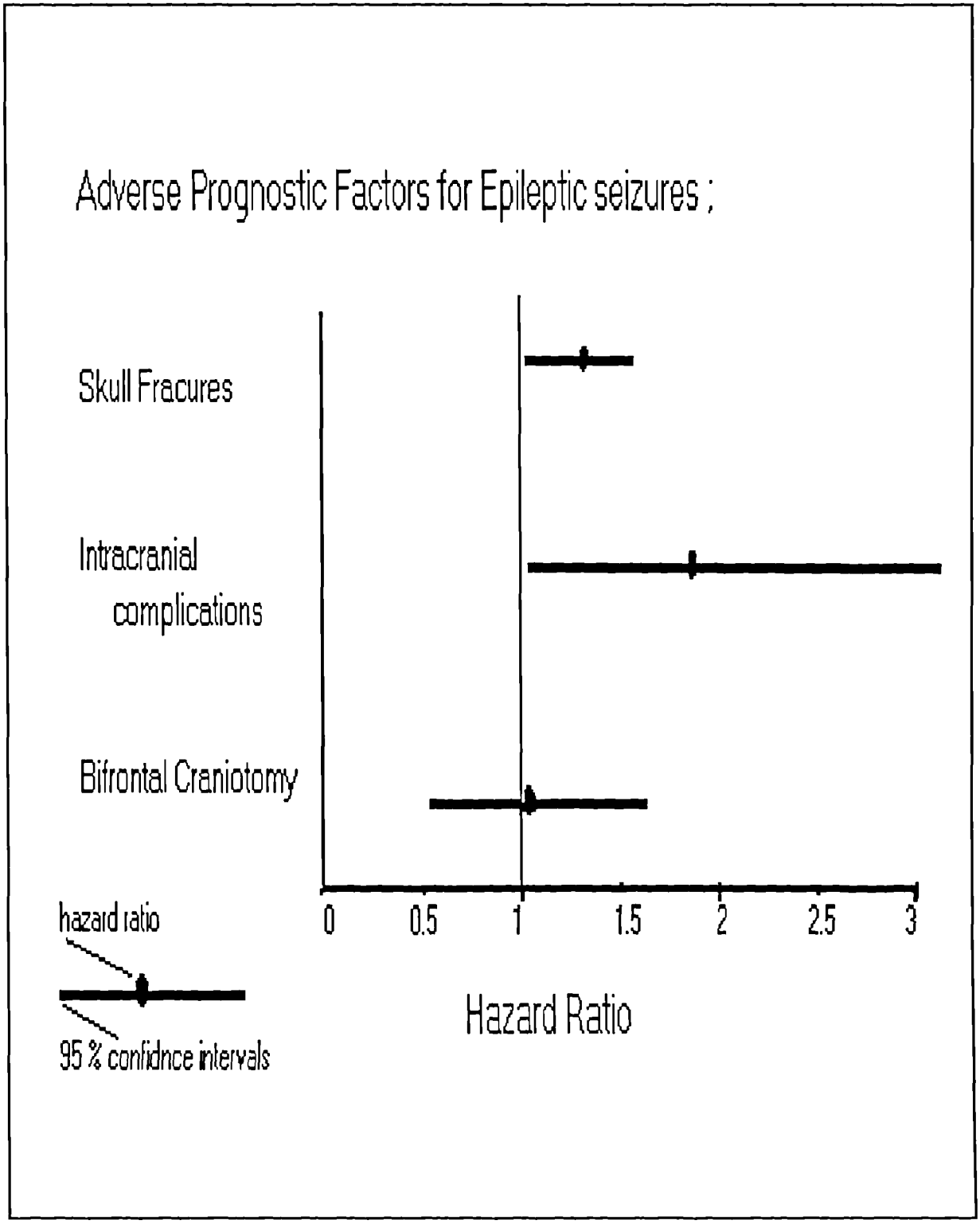
The only significant adverse prognostic factor for CSF-leak recurrence was the aetiology of the CSF fistula. Following surgical repair patients with non-traumatic CSF fistulae (hazard ratio 2.6) are at risk of developing CSF-leak recurrence 2.6 times that of patients with traumatic CSF fistulae (Table 4-2).

Epileptic Seizures ;

Twenty-six (12.8 %) patients developed epileptic seizures following surgical repair. More than 50 % of the seizures occurred immediately after surgery. There was no significant difference in the incidence of seizures between those who underwent surgical repair before or after the introduction of microsurgery & computed tomography (Chi-square 0.0119, df = 1, $p > 0.05$).

Perhaps, it is not surprising to find that the most significant adverse prognostic factors for seizures were presence of skull fractures (hazard ratio 1.27) and post-operative intracranial complications (hazard ratio 1.88). For example, a patient with an anterior fossa fracture, who develop an intracranial haematoma post-operatively is 2.6 times at risk of developing seizures than a patient with uneventful repair of non-traumatic CSF fistula. Although the surgical approach was not a *significant adverse factor* for seizures, it was forced into the model because of medical common sense (Figure 4-6).

Figure 4-6; Proportional hazards for post-operative seizures in 203 patients with repaired CSF fistulae;



4,6 Discussion:

4,6-1 The case for surgical dural repair of CSF fistulae:

Although, CSF leakage stops spontaneously in many patients, this is not a reliable sign of natural healing. Stoppage of CSF leakage can be the result of blood clot, brain hernia through the fistula, over-drainage of CSF or natural healing. Natural healing is often an ineffective barrier against infection because it may consist only of few strands of fibrous tissue or nasal mucosa (Lewin 1954 & Okada and others 1991). Furthermore, cases of meningitis can be delayed for as long as 34 years in those who had unrepaired CSF fistulae (Russel & Cummuns 1984 and Okada & others 1991).

There are no published randomised controlled trials comparing the results of conservative and operative management of CSF fistulae. However, the results of cross sectional surveys, that have been published over the years, suggested that the risk of meningitis in those who were treated conservatively far outweighed the acute risks of surgery. Except for Grahne's, Calvert's and Leech & Paterson's series, all the series listed in Table 4-7 supports surgical intervention. Grahne's (1970) & Calvert's (1942) series did not show significant difference between conservative and operative treatment because the numbers were very small (Total 26 & 21 patients respectively). Leech & Paterson (1973) showed no significant difference between conservative and operative treatment. However, in their series the mean follow up was very short (1.5 years), the vast majority of those who were treated conservatively stopped leaking CSF within a week and the overall incidence of meningitis was very small (9 %) compared with other series. Despite these facts, the risk of meningitis in those who were treated conservatively in that series was 8 % (4/53) compared to 1.5 % (1/65) in the operated patients (Surgery reduced the meningitis rate 5 times).

Table 4-6; Published series of patients with CSF fistulae who were treated conservatively and surgically ;

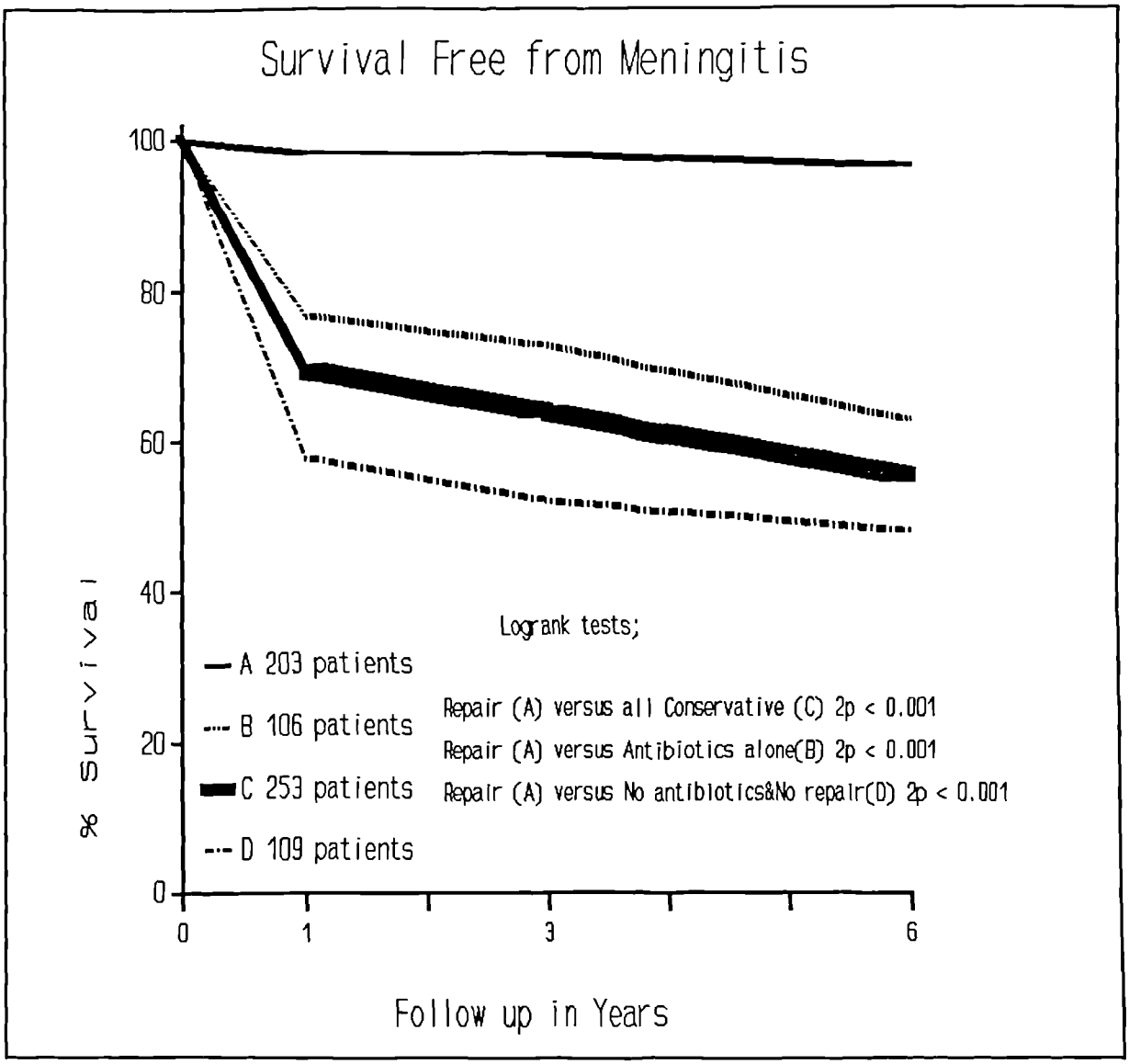
Authors (Year)	Factors	Conservative (%)	Surgery (%)	Chi-square*	p-value
Calvert (1942)	Total Mening. Deaths	11 4 (36) 2 (17)	10 1 (10) 0	 0.82 0.45	# > 0.05 > 0.05
Lewin (1954)	Total Mening. Deaths Morbid.	84 16 (25) 4 (5.1) 2 (2.6)	52 2 (4) 1 (1.9) 5 (10)	 6.50 0.15 2.12	 < 0.05 > 0.05 > 0.05
Grahne (1970)	Total Mening.	13 6 (46)	13 1 (7.7)	 3.13	# > 0.05
Robinson (1970)	Total Mening. Deaths Morbid.	59 13 (22) 0 2 (3.4)	78 0 1 (1.3) 10 (13)	 16.51 0.76 2.65	 < 0.01 > 0.05 > 0.05
Leech & Paterson (1973)	Total Mening. Deaths Morbid.	118 11 (9.3)	65 1 (1.4) 2 (2.8) 12 (17)	 2.97	 > 0.05
Westmore& Whittam (1982)	Total Mening. Deaths Morbid.	100 36 (36) 1 (1) 28 (28)	43 1 (2.3) 1 (2.3)	 16.07 0.38	 < 0.01 > 0.05
Park & others (1983)	Total Mening.	32 13 (31)	31 0	 13.49	 < 0.01
All series combined	Total Mening. Deaths Morbid.	417 99 (23.7) 6 (1.4) 34 (8.2)	292 6 (2.1) 5 (1.7) 27 (9.2)	 62.31 0.41 0.14	 < 0.01 > 0.05 > 0.05

small numbers, Mening.=meningitis & Morbid.=morbidity.

No long-term follow up analyses have been published yet. However, the survival data presented in this chapter and chapters 1 & 2 shows that the long-term prognosis of

patients with unrepaired CSF fistulae is not so good. Only 42.1 % of the untreated and 62.4 % of those who were treated with antibiotics survived free from meningitis for 10 years. In comparison, the prognosis of those who were treated surgically is very good with up to 99.8% survived free from meningitis for 10 years (The logrank tests; Chi_1-square 81.8 , Chi_2-square 75.7 and 1p & 2p < 0.001) Figure 4-7.

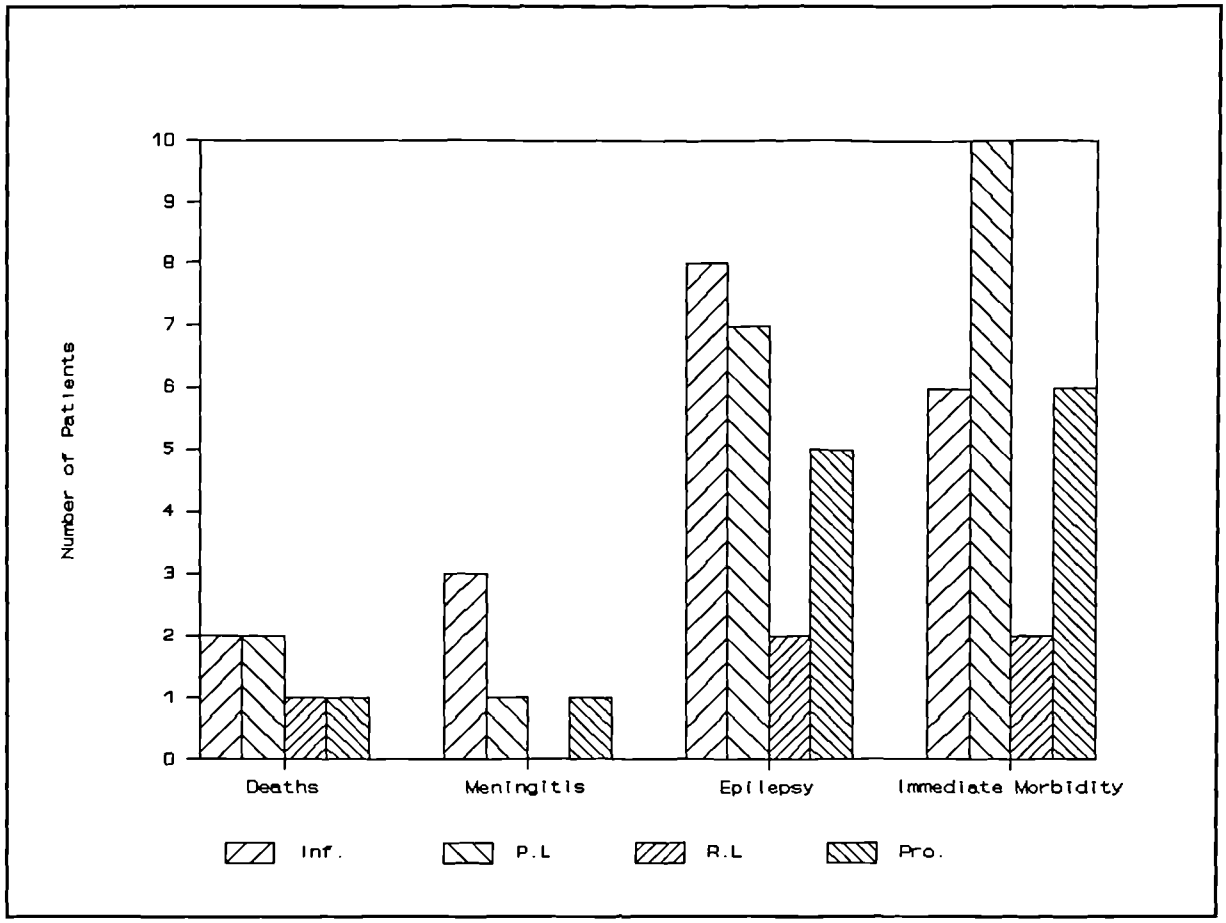
Figure 4-7; Survival curves of survival free from meningitis of 253 patients with CSF fistulae treated conservatively (C) and 203 patients treated surgically (A) ;



The average annual risk of meningitis in those who were treated conservatively was 9.8 % per year and in the surgically treated patients the annual risk of meningitis was 0.2% per year (Logrank test $2p < 0.001$). Furthermore, the operative mortality has been reduced in recent years to less than 2.5 %, compared to the meningitis mortality rate of at least 4.7%. The mortality from meningitis associated with dural fistulae is likely to be under-estimated because the onset of meningitis is often delayed and the CSF fistula may have been forgotten.

There were no significant differences in the surgery-associated events among those who were operated on prophylactically (42) and those who were operated on because of intracranial infection (69) or persistent (76) or recurrent (45) CSF leakage (Figure 4-8). The indication for surgery was not a significant adverse factor for post-operative meningitis or recurrent CSF leakage (Table 4-2).

Figure 4-8; The influence of indication of dural repair on the outcome measures; Inf. = 69 were repaired because of infection, P.L. =76 were repaired because of persistent CSF leak, R.L. =45 repaired because of recurrent leaks and Pro. =42 were repaired prophylactically;



This study has produced clear evidence that surgical repair provides an excellent long-term protection against meningitis in patients with dural CSF fistulae. It also shown that the short-term complications of surgery are not significantly greater than those associated with meningitis. Thus, it is ethically justifiable to recommend surgical dural repair to every patient with a proven CSF fistula irrespective of CSF leakage onset and duration.

4,6-2 Timing of Surgical Repair:

The life-tables of survival free from meningitis have shown that the longer CSF fistulae were not repaired, the more that these patients developed meningitis. Clearly, if the object of surgical repair is to prevent intracranial infection, then the sooner it is done the better. Nevertheless, surgical repair is a major undertaking and extra-risks are run if the patient is operated on while recovering from the immediate effects of acute trauma. Brain swelling limits the surgical exposure making the surgical repair a formidable task and increases the chances of missing the dural perforation. In such circumstances, it is wise to wait until the brain swelling subsides and the patient is in a better general condition before surgery is undertaken.

There is a general agreement that patients who are unlikely to survive the underlying disease (such as severe head injury or end stage cancer of the skull base) for a long period should not be repaired. However, those who are likely to survive the original aetiology, should be repaired when they are fit for surgery. By waiting in these patients, no gain can be achieved, but more patients will develop meningitis. The average risk of meningitis is 2.4% per week (1-4 weeks from the onset of CSF leakage), 3 % per month (1-12 months) and 9.8 % per year (1-20 years). Excepting the third week of CSF leakage, the post-operative complications were not significantly affected by the timing of surgery. Surgery during the third week of CSF leakage was a significant adverse factor for postoperative complications (Table 4-2). Furthermore, the failure rate was significantly increased in those who were repaired after 3 months of CSF leakage (Chi-square 16.4, d.f 6, $p < 0.05$). The recurrent rate of CSF leakage was generally increased in those who were repaired after one month of CSF leakage, but this was not statistically

significant (Table 4-7). The incidence of postoperative meningitis among those who were repaired during the third week of CSF leakage was 1.5 to 2 times that among those who were repaired during the first two weeks, but this was not statistically significant.

Table 4-7; 203 patients who underwent surgical repair of CSF fistulae divided into 7 groups according to the timing of surgery from the onset of CSF leakage ;

Time of Repair*	1 week	2 weeks	3 weeks	4 weeks	1-3 months	4-18 months	> 18 months
Total No.	33	29	27	21	43	24	26
Mean age#	30.2	31.7	36.9	32.8	30.7	41.3	31.2
Mean leak duration	3 days	10 days	11 days	17 days	3 weeks	7 months	1 year
Follow up#	7	2	5	4	4	5	8
Meningitis pre-repair	2 **	5 **	8 **	6 **	14 **	13 **	23 **
Operative mortality	1 @	1 @	1 @	1 @	1 @	1 @	0 @
Failure of repair	1	2	1	1	1	6 ***	1
Recurrent leak @@	1	1	1	2	7	3	6
Postrepair meningitis	1	1	2 @@@	0	0	0	1
Surgical morbidity	3	2	9 ****	1	5	3	1
Epilepsy<x	4	5	3	4	4	3	1

* timing of surgical repair from the onset of CSF leakage. # in years. ** highly significant, Chi-square 53, d.f.6, $p < 0.0001$. *** Chi-square 16.4, d.f.6, $p < 0.05$. @ Not significant, Chi-square 1.3, d.f.6, $p > 0.05$. **** Chi-square 15.5, d.f.6, $p < 0.05$. @@ Not significant, Chi-square 10.8,d.f.6, $p > 0.05$. <x Not significant, Chi-square 3.7, d.f.6, $p > 0.05$. @@@ Not significant, Chi-square 5.3, d.f.6, $p > 0.05$.

Clearly, early surgical repair did not adversely affect the operative mortality and morbidity. Furthermore, surgical repair within the first two weeks of CSF leakage carried the least recurrence and meningitis rates.

4,5-3 Surgical approach:

The major advantages of intradural repair include;

(1) Direct visualization of dural perforation and the overlying brain cortex.

(2) The brain and intracranial pressure will tamponade an intradural placed graft.

The disadvantages of frontal craniotomy are the development of intracranial haematomas, seizures and anosmia. The major advantage of an extradural approach is minimizing operative brain trauma and its major disadvantages include;

(1) The difficulty to visualize the dural defect, its extent and the associated cortical damage.

(2) The difficulty to plug a defect from the outside against a brain hernia and the in tracranial pressure.

Out of the 232 surgical repairs undertaken in 203 patients; 27 were extradural, 66 were unifrontal intradural and 139 bifrontal intradural explorations (Table 4-8). Among those who underwent extradural repair, the rates of recurrence (2/27), failure (1/27), postoperative meningitis (1/27) and mortality (0/27) were not significantly different from those associated with intradural repair. The neurological complication rate was reduced by 50% (Not significant) and the incidence of epilepsy was reduced by 60 % (Chi-square 2.6, d.f.2, $p > 0.05$). However, we are dealing with only 27 highly selected patients, who underwent extradural repair either because the CSF fistula was situated in

the sphenoid sinus or because of failed intradural repair. Although, bifrontal craniotomy had reduced the recurrence rate by 30 % and the meningitis rate by 80 % without increasing the operative mortality and morbidity, the differences between uni- and bi-frontal exploration were not statistically significant (Table 4-8).

Table 4-8; Comparison of the surgical approach in 232 surgical repairs (203 patients); 27 extradural (EDR), 66 unifrontal (UFC)& 139 bifrontal (BFC):

Approach (No.)	EDR (27)	UFC (66)	BFC (139)	Chi^2	p (df2)
Mortality	0/27	3/66	3/139	1.8	> 0.05
Failure rate	1/27	3/66	9/139	0.5	> 0.05
Recurrent rate	2/27	8/66	12/139	0.8	> 0.05
Meningitis	1/27	3/66	1/139	3.5	> 0.05
Epilepsy	1/27	10/66	15/139	2.6	> 0.05
Complications	1/27	7/66	16/139	1.5	> 0.05

It is reasonable that cribriform plate and middle cranial fossa dural defects should be explored intradurally using a unilateral approach. Unilateral frontal craniotomy can be extended to the contralateral side or middle fossa without undue increase in the

operative mortality & morbidity. Extradural transnasl dural repair is sufficient in selected patients particularly those with CSF fistulae through the tuberculum sellae.

4,5-4 Dural Graft:

The dural graft, which has stood the test of time, is the autologous fascia lata graft. However, the pericranium and the temporalis muscle and fascia are also autologous patch materials, which have been used by many authors. A pericranial or temporal muscle or fascial patch avoids a second surgical procedure on the thigh to obtain the graft. Other patch materials (such as Xenoderm, Lyodura, Gelatin sponge & Fibrin mesh) have been advocated, but their use has been reduced because of the fear of introducing infection (such as HIV infection) and foreign body reactions. The dural graft can be fixed in place either by sutures or by an adhesive glue (Tisseel glue or fibrin glue prepared from the patient's fresh blood). However, the most important factor in maintaining the graft in place is the tamponade effect of the brain.

In this study, 139 fascia lata and 80 pericranium or temporalis fascia grafts have been used. The results of dural repair were not significantly different in those who had fascia lata graft (n=139) and in those who had pericranial or temporalis fascia graft (n=80).

Clearly, a pericranial graft or temporalis fascia and muscle is as effective as fascia lata graft in preventing meningitis and CSF leak recurrence without the added thigh procedure (Fifure 4-9).

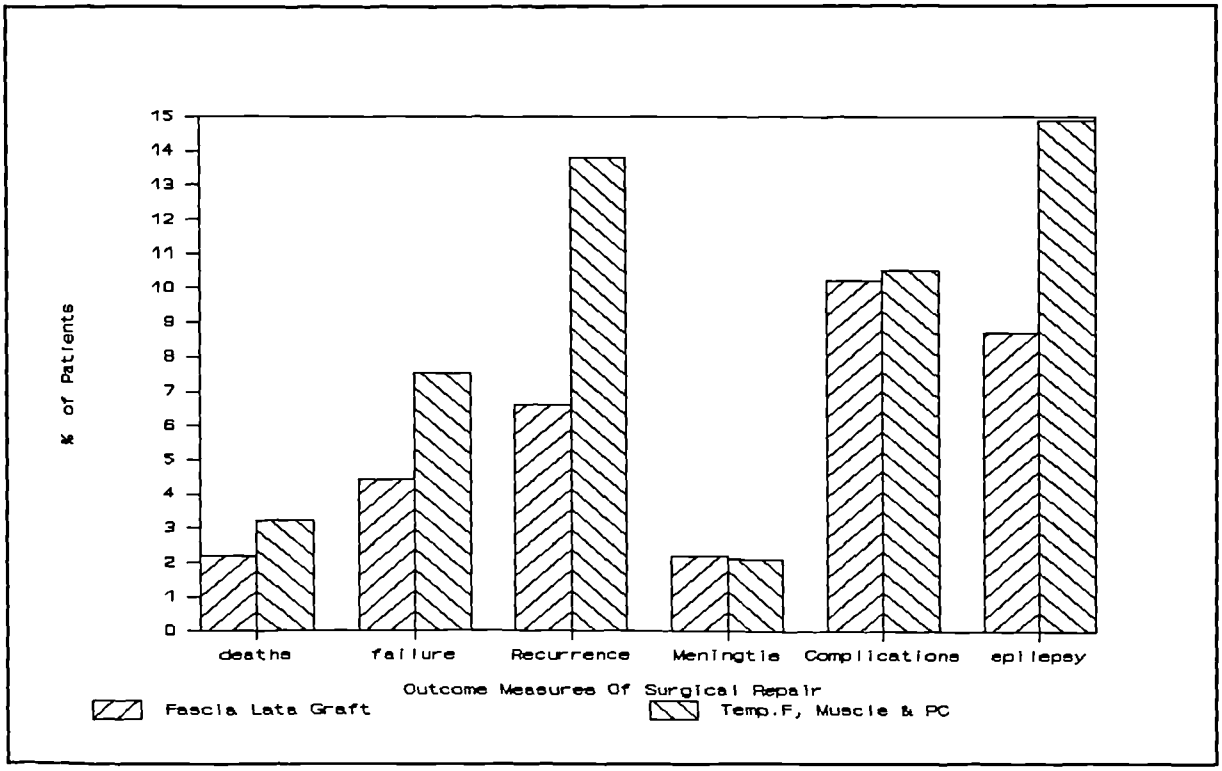


Figure 4-9; The mortality and morbidity after surgical repair using fascia lata (number=136) or pericranium (PC), muscle or/and temporalis fascia (Temp.F) (number=80).

4,5-5 Prognosis:

The long-term prognosis of those who had a successful dural repair is excellent with normal life expectancy. Up to 99.8 % were free from meningitis and up to 85 % remained free from recurrent CSF leakage 6 years following surgical repair. The most significant adverse prognostic factors for developing post-operative meningitis were recurrent CSF leakage and failed repair and the adverse prognostic factor for the recurrence of CSF leakage was non-traumatic CSF fistula.

The acute surgical risk of less than 3 % mortality and less than 11 % morbidity outweighed the mortality and morbidity of meningitis. The adverse prognostic factors for post-operative morbidity were repair during the third week of CSF leakage and presence of skull fractures.

4,6 Summary and Conclusions

203 patients with dural fistulae underwent 232 surgical repairs between 1944 and 1990. 116 patients were treated before the introduction of microsurgery and computed tomography. 183 CSF fistulae were of traumatic origin (158 were associated with head injuries). The mean follow up was 5 years (range 1 - 32 years). The life-tables of these patients were calculated using the Kaplan-Meier product limit technique and a proportional hazards analysis was performed using biomedical software based on the Cox's proportional hazards regression model.

The mean (Standard Deviation) age was 31.5 (18) years.

The male to female ratio was 3.2 to 1.

The operative mortality was 2.5 % and it was adversely affected by age (> = 60 years Hazard ratio 1.37), failed surgical repair (hazard ratio 1.39) and meningitis (hazard ratio 1.39). The operative mortality was reduced (by 20 %) by microsurgery and CT scanning, but the difference was not significant. The negative exploration and failure rates were also reduced by microsurgery and CT scanning, but again the difference was not significant. The immediate surgical complication rate was 10.3 % and it was adversely affected by timing of surgery (Repair during the third week of CSF leakage hazard ratio 1.51), increasing age (> = 60 years hazard ratio 1.2) and head injury with skull fracture (hazard ratio 1.16).

After the introduction of microsurgery and computed CT scanning, 99.8% of patients survived for 6 years free from meningitis. The most significant adverse prognostic factors for meningitis were recurrent CSF leakage (hazard ratio 2.09)and failed repair (hazard ratio 1.06). 85.2 % remained free from recurrent CSF leakage for 6 years and the most significant adverse factor for recurrence was non-traumatic CSF fistula (hazard ratio 2.6). The incidence of epilepsy after surgical repair was 11.2 % and it was adversely affected by the presence of skull fractures (hazard ratio 1.27) and intracranial post-operative complications (hazard ratio 1.88).

Conclusions:

(1) The long-term prognosis of patients with surgically repaired CSF fistulae is excellent and those who survive the surgery have normal life expectancy. Surgical repair provides a long-term protection against meningitis (logrank tests 1p & 2p < 0.001). The most significant adverse prognostic factor for meningitis was recurrent CSF leakage (hazard ratio 1.39).

(2) The short-term complications (mortality and morbidity) of surgical repair were not unduly increased by the surgical approach (p value > 0.05) and the complications were not greater than the risks of meninigitis if no surgical repair was undertaken. While the timing of surgery did not alter significantly the mortality, failure, recurrent and meningitis rates, repair during the third week of CSF leakage adversely affected the morbidity rate (hazard ratio 1.51). Although, microsurgery and computed tomography have reduced the mortality rate (by 26 %) and the negative exploration

rate (by 65 %), the difference was not significant. Again microsurgery and computed tomography have improved the results of surgery in terms of survival free from meningitis and recurrence, though the results did not reach statistical significance (logrank tests 1p & 2p > 0.05).

(3) Intradural surgical repair offers the best chances of sealing the CSF fistula and direct inspection of the associated cortical damage, it is not associated with an increased morbidity or mortality (p > 0.05). Unilateral exploration is the operation of choice when the CSF fistula is lateralized. This can be extended to the contralateral side without an increased morbidity or mortality. Extracranial extradural approaches should be reserved for selected patients, particularly with CSF fistulae through the tuberculum sellae.

(4) It is ethically justifiable to recommend surgical repair to every patient with a proven CSF fistula and to undertake the repair when the patient is fit for surgery, preferably within two weeks of the onset of CSF leakage.

Chapter 5

The Role of Facial Manipulation and CSF Drainage in the Management of CSF fistulae

5,1 INTRODUCTION:

Although, surgical dural repair remains the main cornerstone in the management of CSF fistulae, it is not the only surgical procedure used to treat this complex problem. Adjuvant surgical operations directed to treat the underlying disease causing the CSF fistula are as important as dural repair itself. Simple closure of the CSF fistula without treating the underlying pathology (such as hydrocephalus or intracranial mass), is doomed to failure and a high recurrence rate.

Reduction of facial fractures in traumatic CSF fistulae provides a strong bony support for the repair and approximates the dural tear edges, increasing the success of repair (Dawson & Fordyce 1953 and lewin 1964). Similarly, reduction of CSF pressure to that of the atmosphere has been advocated in the treatment of high pressure and recurrent CSF fistulae (Spetzler & Wilson 1978). This can be achieved by repeated lumber punctures or by an external syphoning device. CSF is diverted away from the fistula, allowing a coagulum of blood and a fibrin network to bridge the dural defect and form a scaffolding along which dural repair progresses. On the other hand, if CSF continues to leak through the fistula, the arachnoid and the contused brain cortex adhere to the lips of the dural tear preventing adequate healing of the dural defect.

In this chapter, the possible values and complications of manipulation of facial fractures and CSF drainage will be discussed and the relevant literature will be critically reviewed.

5,2 Facial fractures & manipulation:

Facial fractures are common in patients with CSF leaks. They occur in 47 % (89/188) of traumatic CSF fistulae. The incidence of CSF leaks in patients with facial fractures is about 25 % (Dawson & Fordyce 1953). Therefore, it is essential to examine these patients systematically to detect such fractures. The forehead is palpated for depressed fractures and frontal sinus injury. The orbital ridge is palpated for irregularity and an ophthalmological examination may reveal damage and / or displacement of the eye ball. Nasal asymmetry and / or depression and nasal septal haematoma may suggest nasal fractures. The malar eminences and zygomatic arches are palpated for deformity and dental occlusion is noted. The maxillary bones are palpated intra- and extra- orally and midface stability is checked by grasping the upper incisors and alveolar ridge and gently attempting to move these structures anteriorly or posteriorly. Finally, the mandible is examined by intra- and extra- oral palpation. If a facial fracture is suspected, the facial bones should be assessed radiologically by posterior-anterior, lateral, submental-vertex and Water's views (Posterior-anterior-oblique view). In selected patients, an axial, coronal and three-dimensional computed tomography may be required to evaluate the extent of these fractures.

The commonest facial fractures associated with CSF rhinorrhoea are fractures of the middle third of the face (Dawson & Fordyce 1953, Lewin 1954 and Dawson 1962). These fractures are classified into three types
(Le Fort 1972), Figure 5-1;

(1) The transverse (Le Fort I) fracture; it separates the lower maxilla, hard palate and pterygoid processes from the rest of the maxilla (this fracture can be simple,

comminuted or compound).

(2) The pyramidal (Le Fort II) fracture; it runs along the nasofrontal suture, the floor of the orbit, the zygomatico-maxillary sutures and the pterygoid processes.

(3) The cranio-facial disjunction (Le Fort III); the fracture separates the midface from the cranium. It runs through the zygomatico-frontal sutures, the naso-frontal suture and the floor of the orbit.

Fractures of the middle third of the face are often a mixture of Le Fort fractures and their treatment requires inter-maxillary fixation with fixation of the mandible and maxilla to the first stable bony structure immediately above the fracture . This can be achieved by reduction and wiring or miniplate and screws.

Although the management of facial fractures is well documented, its timing and role in patients with CSF fistulae is still open to debate and controversy. Neurosurgeons may be reluctant to authorize early reduction of facial fractures, in the presence of CSF leakage, because of the extra risks of general anaesthesia and the fear of introducing infection (Lewin 1964). On the other hand, reduction of facial fractures may stop the CSF leak (Collin 1973) and thus reduces the risk of introducing virulent hospital bacteria into the CSF. Delaying facial fracture-reduction not only makes the job of the facio-maxillary surgeon more difficult, but it also may reopen a closed CSF fistula (Dawson & Fordyce 1953 and Collin 1973). However these controversial views are based on personal experiences with small number of patients as their are no published trials addressing this problem. The following study evaluates facial manipulation in 89 facial fractures associated with CSF rhinorrhoea.

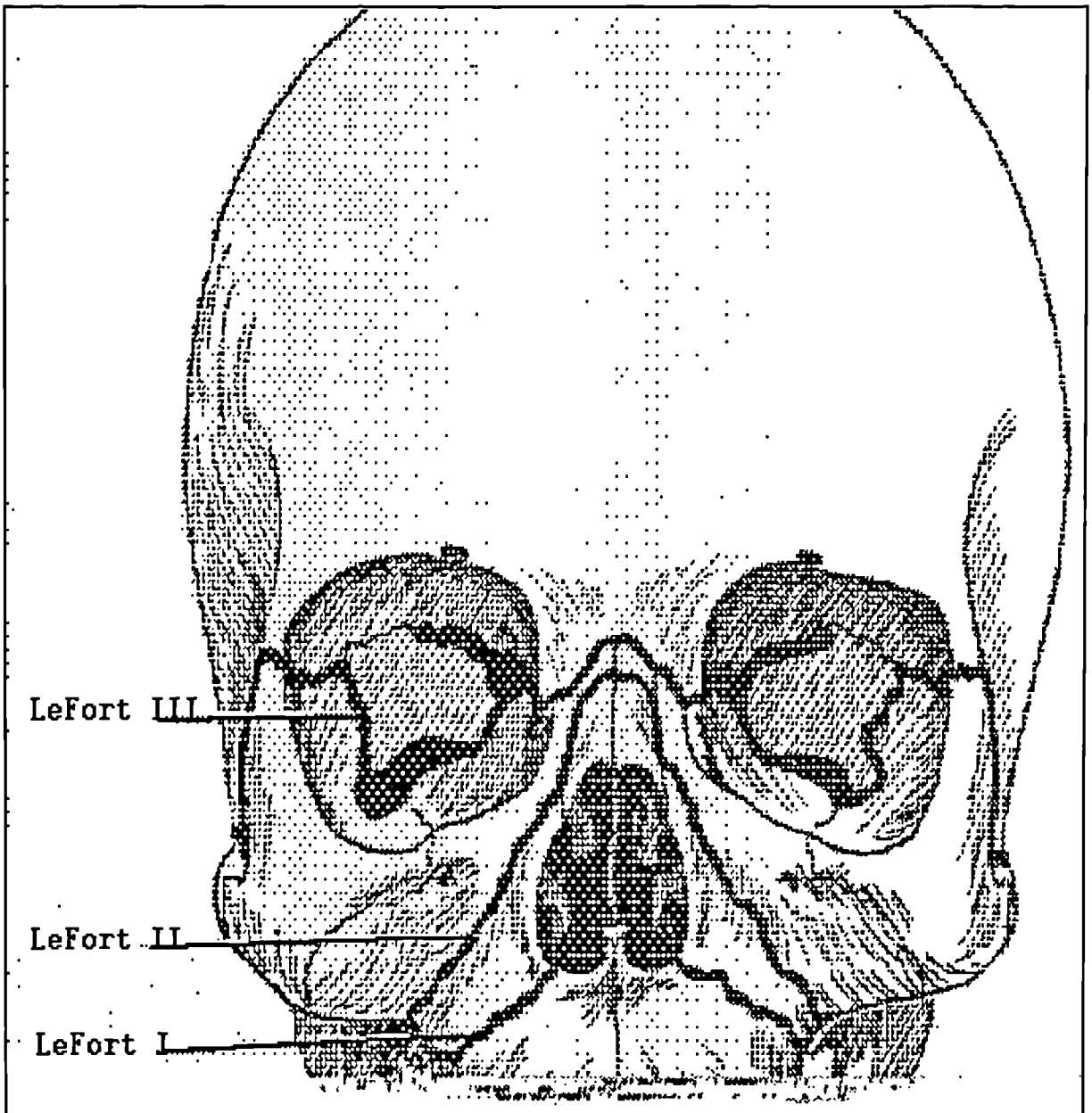


Figure 5-1: Classification of Facial Fractures;

5,2,1 Objective:

To determine the value of facial reduction and fixation in the management of patients with CSF fistulae.

5,2,2 Patients:

Eighty-nine patients with facial fractures associated with CSF rhinorrhoea were studied. These represent 47 % of all patients with CSF fistulae treated in the Mersey Regional Department of Medical and Surgical Neurology between 1944 and 1990 and 9.5 % of all facial fractures treated during the same period.

The medical records of these patients were critically reviewed and up to date information about these patients was obtained by writing to the family practitioners and the Family Health Services Authorities (FHSA's). The mean follow up was four years (range 1 - 32 years). The mean age was 32.8 years and the male to female ratio was 4 to 1. The facial fractures were reduced in 26 patients (29 %) and the CSF fistula was repaired in 75 patients (84 %). Three patients (3.4 %) had facial reduction alone and 11 (12 %) had neither manipulation nor repair. The CSF leakage started within a week in 80 patients (90%) and lasted for less than 8 days in 48 patients (54 %). Meningitis developed in 15 patients prior to surgical intervention. 81 had associated vault skull fractures and 18 were associated with pneumocephalus.

5,2,3 Results:

The baseline characteristics of these patients are summarised in table 5-1.

Table 5-1; The baseline characteristics of 89 patients with facial fractures and CSF rhinorrhoea;

Factors	No. Patients	Per cent %
Mean Age in years	32.8	
Male to Female ratio	4 : 1	
CSF Leakage; Onset in 7 days Stopped in 7 days Recurrent	89 80 48 10	 89.9 53.9 11.2
Fractures; Face Skull vault Pneumocephalus	89 81 18	 91.0 20.2
Surgical Intervention; Dural Repair Facial Reduction Neither	78 75 26 11	87.6 84.3 29.2 12.4
Intracranial infections; Pneumococcal	15 7	16.9 7.9
Antibiotic Prophylaxis	45	50.6

Facial Reduction as complementary procedure to surgical repair:

Twenty-three (25.8 %) had facial reduction and dural repair with no deaths, failure or recurrence of the CSF leak. There was no case of postoperative meningitis in this group of patients. On the other hand 52 patients had surgical dural repair without facial reduction. From the latter group of patients, one died, one developed meningitis,

the repair failed in 4 and the CSF leakage recurred in 4 patients. Therefore, facial manipulation had significantly increased the chances that the dural repair will succeed in stopping the CSF leak and preventing its recurrence (Chi-square with Yates' correction 4.21, d.f.=1, p value < 0.05) Table 5-2. Three patients had facial reduction without dural repair, one of which developed recurrent CSF leakage 9 days following the facial reduction. Eleven (12.2 %) patients underwent neither facial reduction nor dural repair, of which three developed meningitis with one death (Table 5-2).

Table 5-2; The results of surgical intervention in 89 patients with facial fractures and CSF rhinorrhoea;

Surgery Type	Dural Repair only	Facial reduction only	Both	Neither
Facial fracture & CSF leakage	52	3	23	11
Vault skull fractures	48	0	23	10
Leak Stopped after Surgery	48	3	23	-
Leek Persisted after surgery	4	0	0	-
Recurrent leak after surgery	4	1	0	-
Meningitis after surgery	1	0	0	3 *
Deaths	1	0	0	1 *

* 3/11 developed meningitis, one was fatal in those who had neither facial reduction nor dural repair .

Timing of facial manipulation:

Fifteen patients had facial reduction before surgical dural repair was undertaken. In ten (66.7 %) of these patients, the CSF leak was made worse or the leak restarted following facial manipulation. Subsequent dural repair was undertaken in 12 patients without recurrence or meningitis (Figure 5-2). Three patients underwent facial reduction alone, one of which developed recurrent CSF leak and refused dural repair. No cases of meningitis occurred in these three patients during the follow up period.

Eleven patients had facial manipulation immediately after surgical repair at the same setting (6 patients) or shortly after dural repair (5 patients). No deaths, recurrent CSF leaks or meningitis occurred in these 11 patients. If facial manipulation was not combined with dural repair, the CSF leak either worsened or recurred (Chi-square with Yates' correction 6.3, d.f. = 1, p value < 0.01).

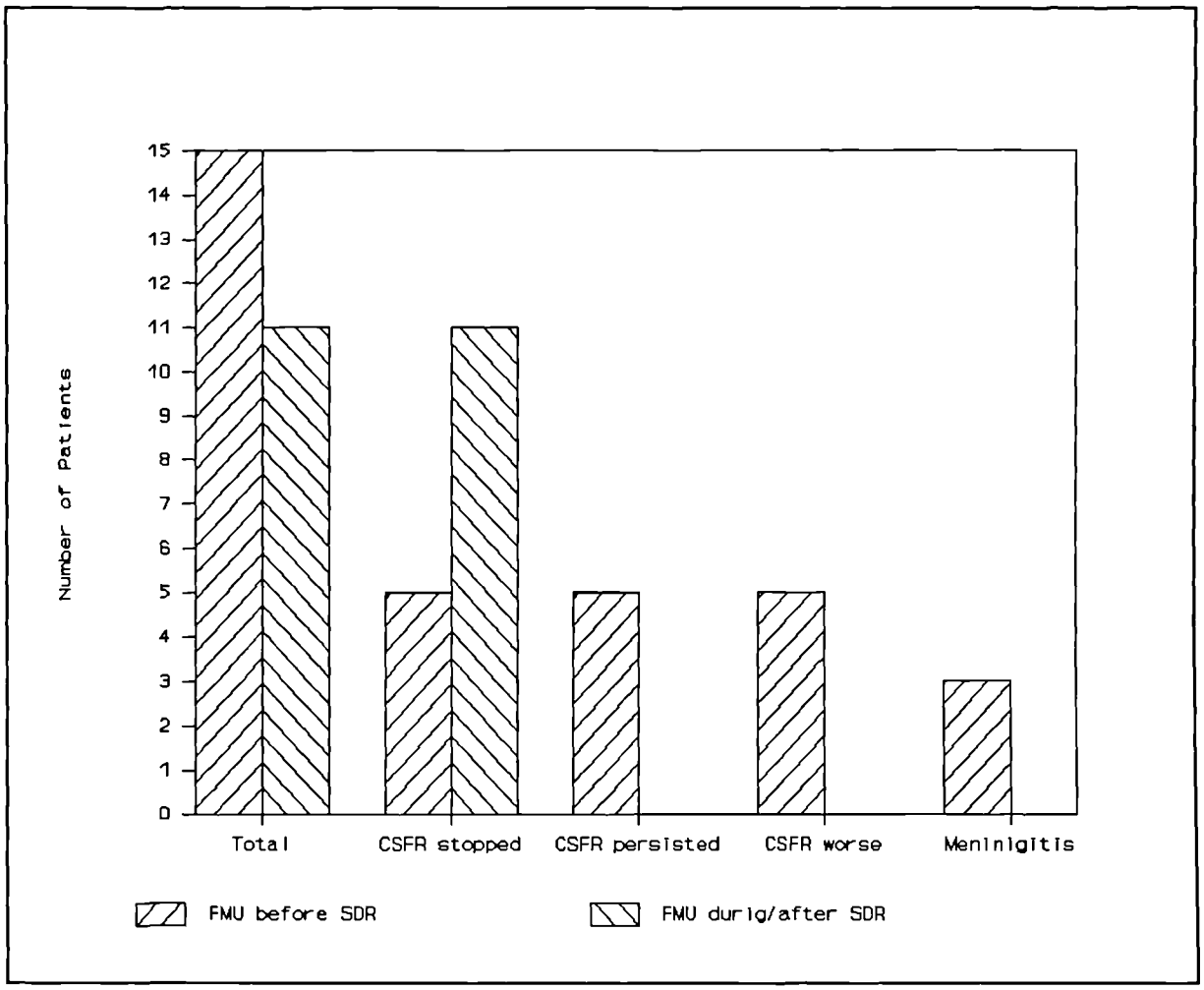
Four (27 %) out of the 15 patients, who underwent facial manipulation before surgical dural repair, developed meningitis prior to subsequent surgical dural repair (Figure 5-2).

5,2,4 Discussion:

Facial fractures, that carry a continuing risk of CSF leakage, are often associated with fractures of the skull vault (Jefferson and Reilly 1972). Early reduction of the facial fractures stopped the CSF leakage in 17 out of 19 patients (Collin 1973). However, stoppage of CSF leak is not a reliable sign of dural repair. The arachnoid and brain are often found adherent to the lips of the dural tear, preventing adequate healing

(Lewin 1954). Ten out of 15 patients, who underwent facial reduction before dural repair, either continued to leak CSF or the leak was made worse. Furthermore, four of these patients developed meningitis. In comparison, none of the 11 patients, who underwent facial reduction at the same sitting or shortly after surgical dural repair, developed meningitis or recurrent CSF leak. Furthermore, facial manipulation did not increase the morbidity or mortality of surgical dural repair when the surgery was combined.

Figure 5-2; Effect of timing of facial reduction on the CSF leak, FMU=facial manipulation, SDR= surgical dural repair;



As the objective of surgery is to seal the CSF fistula and prevent intracranial infection, the earlier surgery is undertaken the better. Early surgery not only makes the facial reduction easier, but it also prevents intracranial infection with virulent, resistant hospital micro-organisms. Surgical dural repair in the first two weeks of CSF leak was not a significant adverse prognostic factor for the operative morbidity and mortality (Chapter 4). The cumulative risk of meningitis within the first two weeks of CSF leakage was 4.6 % (Chapter 2).

Surgical repair, without reduction of associated facial fractures, was associated with 15.4% (8/52) rate of failure and / or recurrence. This significant failure rate is due to graft necrosis (Lewin 1964) and lack of strong bony support (Dawson and Fordyce 1953). Patients who had no dural repair and no facial reduction came out worst; 3 out of 11 patients developed meningitis with one death.

Clearly, patients with CSF rhinorrhoea and facial fractures benefit from early surgical dural repair and facial manipulation, which can be undertaken at the same setting without an increased morbidity or mortality. The contention, that isolated facial fractures (without fractures of the skull vault) can be treated by facial reduction alone (Jefferson and Reilly 1972), cannot be supported because most the patients in this study were associated with fractures of the skull vault (91 %). Only three patients had facial reduction alone for isolated fractures of the middle third of the face, one of which developed recurrent CSF leak 9 days after reduction. Furthermore, no recurrent leaks or negative explorations occurred in those who underwent surgical dural repair after facial reduction (12 patients). Although, isolated facial fractures are not common in

patients with CSF rhinorrhoea (8/89), it is wise to investigate these patients for persistence of CSF fistula even when the CSF leak stops after reduction. If a fistula can be demonstrated or cortical brain damage can be seen adjacent to an anterior fossa fracture, surgical repair is advisable (Jefferson and Reilly 1972).

5,3 CSF Drainage in CSF fistulae:

The advantages of draining CSF and reducing the intracranial pressure to that of the atmosphere in patients with CSF fistulae include;

(1) Stopping CSF flow through the fistula allows blood and fibrin coagulum to form and bridge the dural defect so that healing progresses.

(2) Removes the underlying aetiology in high pressure CSF fistulae.

(3) During surgery, reduces the amount of frontal lobe retraction required to expose the anterior cranial fossa.

However, CSF drainage in the presence of an open dural fistula is not without risks to the patient. Apart from the local complications of the spinal drainage procedures,(such as local infection, root leg pain and spinal haematomas), intracranial complications include;

(1) Introduction of intracranial infection through the CSF fistula.

(2) Introduction of intracranial air and the development of tension pneumocephalus.

(3) The development of intracranial haematomas.

The following review evaluates the effects of CSF drainage in patients with CSF fistulae with a critical review of the relevant literature.

5,3,1 Objective:

To evaluate the possible effects of CSF drainage in patients with CSF leakage.

5,3,2 Patients:

Sixteen patients in the present series had primary (8 patients) or secondary (8 patients) CSF diversion procedures to manage the CSF leak. Secondary CSF diversion was performed after failure of surgical dural repair, while primary procedures were undertaken without previous dural repair. The mean age of these 16 patients was 47 years and the mean duration of CSF leakage was 3 weeks. There were 8 males and 8 females and the CSF fistulae were traumatic in origin in 15 and one patient had benign intracranial hypertension. The CSF drainage procedure was lumbar in 14 and cranial in two patients. Eleven of the CSF diversion devices were eventually removed (2 because of shunt infection and 9 temporary lumbar drains which were intended to be removed). The mean follow up was 3.3 years (range 1 to 10 years).

5,3,3 Results:

The effects of the CSF diversion on the CSF leakage;

The CSF leak stopped after the CSF drainage procedure in 14 patients (14/16). The CSF drainage was successful in stopping the CSF leak in all those who had recurrent CSF leaks following previous surgical dural repair (8/8), while it failed to stop the CSF leak in two of those who had no previous surgery directed at the CSF fistula (2/8). Eleven drains were removed, of which seven were secondary to previous repair and four as primary procedures. No recurrence of the CSF leak occurred in those who had previous surgical dural repair and subsequent drain removal (0/7). Three of four patients, who had no previous repair and their CSF drain was removed, developed recurrent CSF leakage shortly after the drain was removed (Table 5-3).

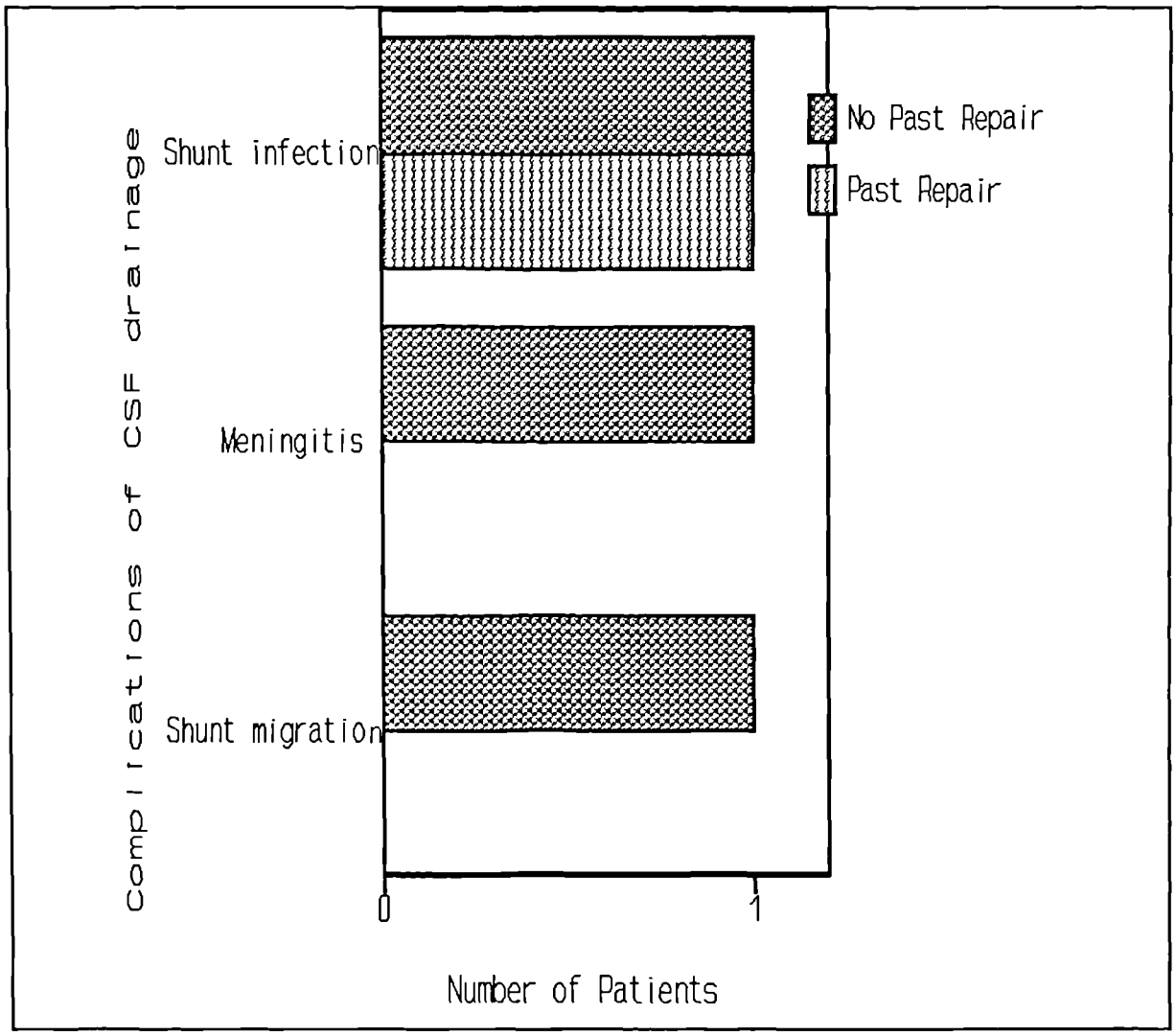
Table 5-3; The effects of CSF drainage on the CSF leakage;

Effects \ Repair	CSF fistula Repaired	NO Dural Repair
Effect of CSF drainage:	8	8
CSF leak Stopped	8	6
CSF leak continued	0	2
Effect of drain removal:	7	4
CSF leak recurred	0	3
NO recurrence	7	1

Complications of CSF drainage:

There were no deaths, pneumocephalus or intracranial haematomas in this study. However, three patients developed septic complications, meningitis in one and shunt infection in two patients. The isolated case of meningitis in this study (1/15) occurred in a patient who had no previous surgical dural repair of the CSF fistula. The infection was successfully eradicated by judicious use of antibiotics and removal of the CSF drain. Figure 5-3 summarizes the complications of CSF drainage in this study.

Figure 5-3; Complications of CSF drainage in 16 patients with CSF leaks; 8 had previous attempt of dural repair and 8 had not:



5,3,4 Discussion:

CSF drainage is advocated during intradural exploration of the anterior cranial fossa to minimize the amount of frontal lobe retraction and therefore avoid retraction haematomas. IIowever, CSF drainage has also been advocated as treatment of recurrent CSF leakage following previous repair and as primary treatment in high pressure CSF fistulae (Greenblatt & Wilson 1973, Spetzler & Wilson 1977 & 1978, Selman & others

1980, James & Tibbs 1981 and Bret & Others 1985 & 1986). CSF shunting is more suitable for recurrent CSF leaks after previous attempts at dural repair and as an adjunct procedure to treat high pressure CSF fistulae. In a compiled series (Table 5-4) CSF diversion was successful in controlling the CSF leak in 32 out of 35 recurrent CSF leaks collected cases (Success rate of > 91 %). The complication rate in this collected series was very low (2.9 % meningitis, 2.9 % shunt infection and 8.6% pneumocephalus - Table 5-4).

Table 5-4; The results of CSF diversion in 35 recurrent CSF leaks following previous surgical dural repair;

* Authors-Year	Total	Success	Mening	ShuntI	Pneumo
Greenblatt & Wison 1973	2	2	0	0	0
Muizalaar & Wilson 1977	1	1	0	0	1
Spetzler & Wilson 1978	7	7	0	0	0
Ahmadi & Others 1985	1	1	0	0	0
Bret & Others 1985	15	12	1	0	1
Komisar & Others 1986	1	1	0	0	1
Present Series 1991	8	8	0	1	0
Total Cases (%)	**35**	**32(91.4)**	**1(2.85)**	**1(2.85)**	**3(8.6)**

* Selman & Others 1980 has reported another 15 successful cases of CSF shunts in 15 CSF leaks, but it was not clear from their paper whether these cases were recurrent after previous repair or not and the follow up in some cases was only one month. This is why I have not included this series in this table.

Mening=meningitis, ShuntI=shunt infection & Pneumo=pneumocephalus.

CSF diversion as the only treatment of CSF leaks was associated with a significant failure rate. In 36 collected cases of CSF leaks treated with CSF shunts without dural repair (Table 5-5); in 16 (42 %) the shunt failed to stop the CSF leak, 4 (11 %) developed meningitis, one (2.8 %) developed shunt infection and 6 (17 %) developed pneumocephalus (Table 5-5).

Table 5-5; The results of CSF diversion in 36 collected cases, who had no previous attempts of surgical dural repair;

Authors Year	No.*	Success	Failure	Mening.	Sh. Inf.	Pneumoc	SMF
Little & Others 1975	4	2	2	0	0	0	0
Spetzler & Wilson 78	3	3	0	0	0	0	0
Ikeda & Others 1978	1	0	1	0	0	1	0
Tanaka & Others 1980	2	0	2	0	0	2	0
Tames & Tibbs 1981	4	3	1	0	0	0	0
Clayton & Others 85	1	1	0	0	0	0	0
Hubbard & Others 85	6	1	5	2	0	3	0
Bret & Others 1986	4	4	0	0	0	0	1
Flynn & Others 1987	2	1	1	1	0	0	0
Olofsson & Bynke 88	1	0	1	0	0	0	0
Present Series 1991	8	6	2	1	1	0	1
Total cases %	**36**	**21 58%**	**15 42%**	**4 11%**	**1 2.8%**	**6 17%**	**2 6%**

Mening. = meningitis, Sh.Inf. = shunt infection, Pneumoc = pneumocephalus, SMF = shunt malfunction.

* Most these patients were elderly with a short life-expectancy, the site of leak was not possible to localize, patient was not fit for intradural repair or the leak was small.

Clearly, CSF diversion in CSF fistulae, without previous dural repair was associated with a low success rate (Chi-square (with Yates' correction) was 8.6, d.f = 1 and p value < 0.01) and higher intracranial complications (28 % with no previous repair versus 12.5% when repair was previously performed). However, CSF drainage may be the alternative procedure to treat symptomatically the CSF leak in the elderly patient, when the site of CSF leak cannot be identified or direct dural repair is contraindicated.

5.4 Summary and Conclusions:

89 patients with CSF rhinorrhoea and fractures of the middle third of the face were studied. 26 (29 %) had facial reduction at some stage and 75 (84 %) had dural repair. There were no deaths, failure, recurrent leaks or meningitis in the 23 patients who underwent surgical dural repair and facial reduction. One death, one meningitis, four failures and four recurrent leaks occurred in the 52 patients who underwent surgical dural repair without facial reduction. One CSF leak recurred after facial reduction in three patients who had facial manipulation alone. Of the 11 patients who did not undergo surgery three developed meningitis of whom one died. The CSF leak persisted or made worse in 10 out of 15 patients, who had facial reduction before dural repair, while it stopped in all those who underwent facial reduction during or shortly after dural repair (11 patients).

Sixteen patients had CSF diversion procedures to manage the CSF leak. Eight were recurrent after previous dural repair, all of which stopped leaking CSF after the CSF drainage. The other eight patients had CSF drainage without previous dural repair and two continued to leak CSF. 11 CSF drains were removed; 7 of those who had a

previous repair did not leak after the removal of the drain and of the rmaining 4 who had no previous repair 3 had recurrent leaks after drain removal. There was only one patient who had no previous repair and who went on to develop meningitis after CSF drainage. Two shunt infections and one shunt malfunction occurred in this study.

CONCLUSIONS:

(1) Facial reduction of fractures of the middle third of the face in patients with CSF fistulae should be performed as soon as possible at the same sitting as surgical dural repair. This will significantly increase the success rate of dural repair. Facial reduction alone failed to stop the CSF leak in most of the cases in this study (10/15). Therefore, it should be looked at as a complementary and not as a competitive procedure to dural repair. A facio-maxillary surgical opinion, in conjunction with a neurosurgical opinion should be sought early and a joint plan of action should be formalized for each individual patient with CSF leak and facial fractures.

(2) CSF drainage is recommended in the treatment of difficult CSF fistulae after direct surgical attempts fail to cure the CSF leak and when direct repair is contraindicated. It has a very low success rate of curing the CSF fistula if it is not combined with previous repair. Furthermore, CSF diversion, on its own, does not protect against meningitis and predisposes to tension pneumocephalus.

Chapter 6

The Value of B_2-Transferrin in the Diagnosis of CSF Fistulae

6,1 Introduction:

It is often difficult to be certain that the leaking fluid is CSF, particularly when the fluid may be mixed with blood, nasal secretions or wound discharge. There are no pathognomonic clinical signs of CSF fistulae and chemical analysis of the fistular fluid for glucose and protein, carries a 45 to 75 % false positive rate (Gadeholt 1964, Kirsch 1967, Healy 1969 and Kosoy & others 1972). Testing the fistular fluid for glucose and protein is not reliable diagnostic test because:

(1) Glucose & protein are normally present in blood and nasal and lachrymal secretions. Therefore, testing for glucose and protein cannot differentiate between traumatic CSF leakage and traumatic nasal or aural bleeding. Similarly, these tests cannot distinguish with certainty non-traumatic CSF rhinorrhoea from allergic rhinitis and runny nose.

(2) In the presence of meningitis, the glucose level in the CSF may reach very low levels so that it cannot be detected in the fistulous fluid. Furthermore, the protein content of the CSF may reach very high levels under these circumstances.

On the other hand cisternography has been used to confirm CSF leakage with more success. Fluorescien, radioisotope tracer and water-soluble nonionic contrast media have been used extensively. but they have the following disadvantages:

(1) Invasiveness, requiring intrathecal injection of the dye or contrast.

(2) Require expertise and technology that may not be readily available in many hospitals.

(3) Patients need to be detained in hospital to carry out such investigations.

(4) Cisternography is contraindicated in some patients:

(a) Patients with intracranial mass lesions.

(b) Patients with previous allergy to iodine or fluorescien.

(b) Patients with previous allergy to iodine or fluorescien.

(c) Patients, who are too ill to be moved from intensive care units.

(4) They carry small risk to the patient:

(a) May induce allergy to iodine and fluorescein.

(b) May cause seizures (In contrast-CT-cisternography).

(5) Relatively time consuming and expensive.

The value of cisternography to localize the site of CSF fistulae will be discussed in the following chapter.

B_2-Transferrin is a byproduct of the neuroaminidase activity of the brain and practically has been found only in the CSF. It contains fewer sialic acid radicals and therefore migrates slower on electrophoresis than its counterpart B_1-Transferrin. B_1-Transferrin is a B_1-globulin essential to maintain iron in a soluble form (Fe^{2+}, ferrous form). It is a member of a wider family of iron-binding proteins distributed in the cellular and extracellular body fluids (Yang & others 1984). It contains 679 amino acid residues and two asparagine-linked oligosaccharide chains (Calculated molecular weight = 79,570). It consists of two homologous domains, each of which contains a single iron-binding site (MacGillavry & others 1983 and Metz-Boutique & others 1984). Human transferrin serves the following functions:

(1) Iron transport from the sites of absorption to the sites of storage and utilization (Fletcher & Huehns 1968).

(2) Protection of the human body against iron intoxication (Laurell 1960).

(3) Preservation of iron by preventing its loss in the urine (Putnam 1975).

(4) Recycling of iron derived from catabolism of iron-containing proteins.

(5) Special role in the growth and normal function of the central nervous system (Espinosa de los Monteros & others 1989).

B_1-Transferrin occurs normally in three main forms of similar structure and function. These isoforms include:

(1) Serotransferrin, which is synthesized predominantly in the liver and crosses the blood brain barrier via a specific receptor-mediated transport (Jefferies & others 1984). It is also synthesized locally in the brain by the oligodendrocytes and the choroid plexus (Bloch & others 1985, Dickson & others 1986 and Aldred & others 1987).

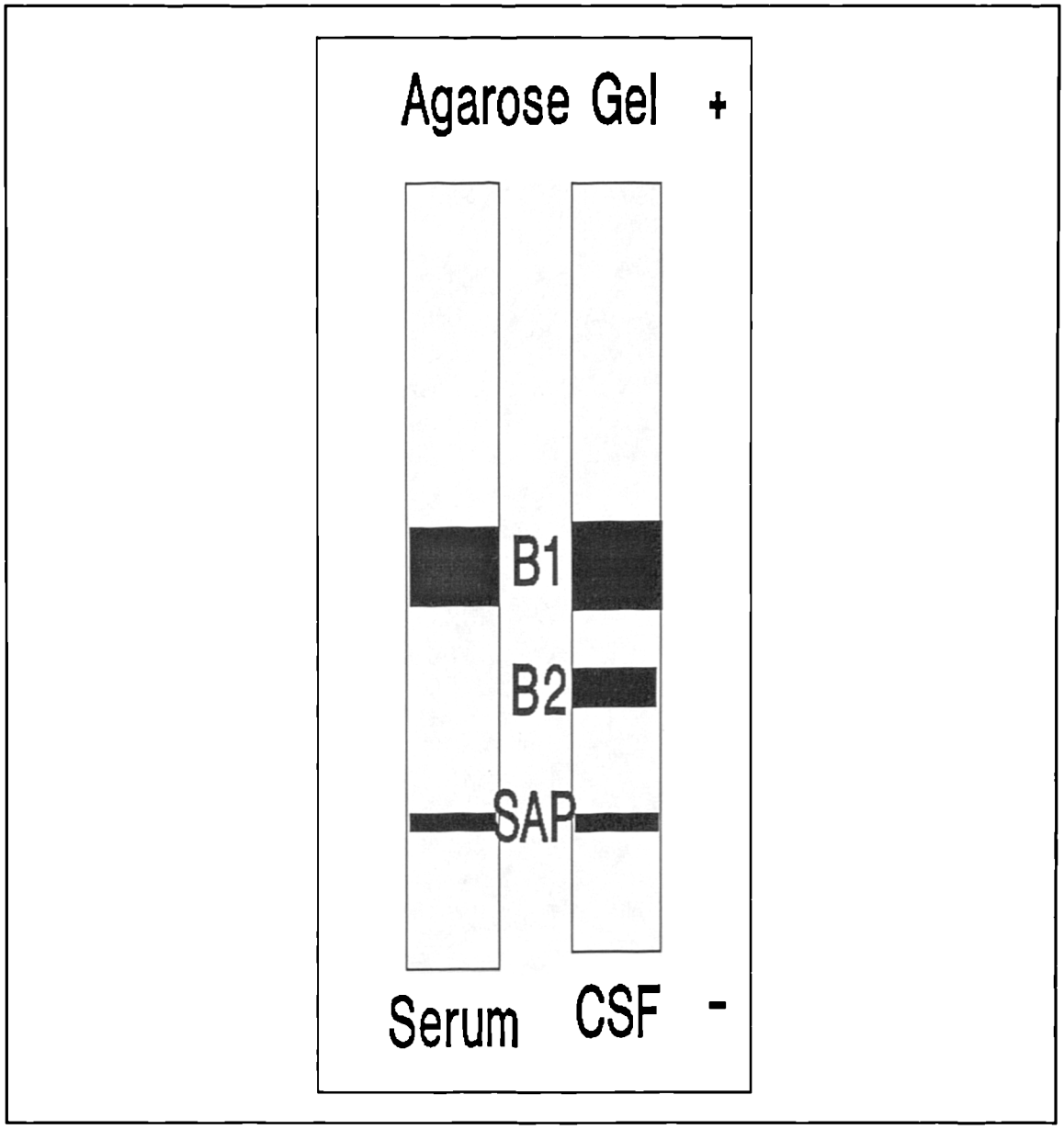
(2) Lactotransferrin, which occurs in milk and tears and is secreted by lymphocytes.

(3) Ovotransferrin (conalbumin), which is found in the egg-white.

These isoforms of B_1-Transferrin cannot be separated by polyacrylamide and agarose gel electrophoretic techniques and produce a single transferrin band when electrophoresed. Neuroaminidase splits off the sialic acid molecules from B_1-Transferrin producing B_2-Transferrin, which migrates slower than its precursor, when electrophoresed under the same buffer. In vitro studies have shown that when B_1-Transferrin was treated with neuroaminidase and then the resultant enzymatic mixture was electrophoresed, the transferrin band was split into one major component (B_1-Transferrin band) and a smaller cathodal band (B_2-(asialic) Transferrin band) Figure 6-1, (Kilar & Hjerten 1989). Because the neuroaminidase activity is restricted to the central nervous system, B_2-Transferrin is practically present in the cerebrospinal fluid only.

Therefore, developing a simple technique to identify the B_2-Transferrin band will make CSF identification possible and the diagnosis of CSF leakage certain.

Figure 6-1; Diagram of transferrin bands on electrophoresis;



B1=B_1-Transferrin, B2=B_2-Transferrin and SAP=sample application point.

6,2 Aim of this Study:

The aim of this study is to determine the reliability of B_2-Transferrin identification, using Paragon^R gel immunofixation techniques, to differentiate CSF from its contaminants during CSF leakage.

6.3 Methods:

114 samples of CSF and potential CSF contaminants during CSF leakage (Blood, Wound discharge or Nasal secretions) were examined blindly by the usual Glucose-Oxidase Stick Test and the Paragon^R Gel Immunofixation technique to identify B_2-Transferrin.

B_2-Transferrin identification technique,

(The Paragon^R Gel Immunofixation technique):

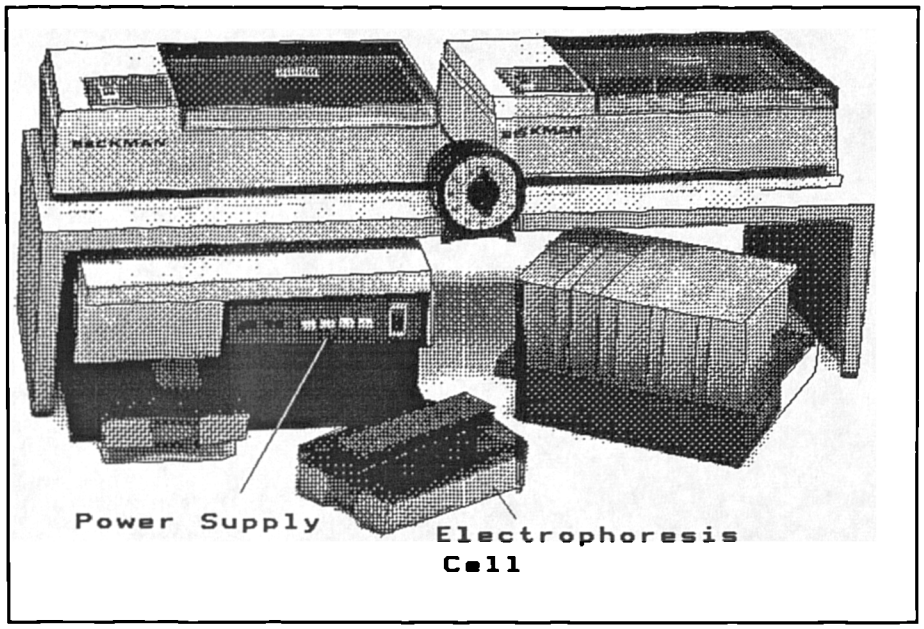
The technique is based on the immunofixation procedure, which combines the principles of protein electrophoresis and immunoprecipitation. The Immunofixation technique was originally described in 1964 (Wilson 1964 and Afonso 1964) and was refined in 1969 (Alper & Johnson 1969). The principle technique is to electrophorese a specimen such as CSF in multiple positions on an agarose gel. Following electrophoresis, the monospecific antiserum is applied to the gel and incubated to form immune complexes between the protein in the specimen and the specific antiserum. The gel, then is stained to detect the position of the immune complexes.

Equipment:

I used the following pieces of equipment, which is available in the Buxton Neurobiochemistry laboratory, The Mersey Regional Department of Medical & Surgical Neurology, Walton Hospital, Liverpool:

(1) The Paragon^R Electrophoresis Accessory Package - 240 volts which consists of: Power supply, two electrophoresis cells, Dryer, Incubator, Wet Processor, Press dryer, Applicator, Manual and Timer (Beckman Instruments (U.K) Ltd) Figure 6-2.

Figure 6-2: Beckman, Paragon Electrophoresis System:



(2) Centrisart^{R} I (Sartorius AG, West Germany).

(3) Centrifuge (Heraeus Christ, Heraeus Equipment Ltd.).

(4) Sample Mixer (Chiltern, MT17).

(5) Digital Concentration Photometer to measure the protein concentration.

(6) Test tubes, multirange pipettes 0.5 to 80 microlitres, multirange pipettes' capillary and multirange pipette piston, Sample stand and Washing dishes.

(7) Refrigerant aggregate with thermoregulator from -10° to 50° Celsius.

Preparation of Reagents:

(1) Standard Universal Agarose Gels: I used the pre-packed Immunofixation-Electrophoresis kits (IFE). Each pack contains 10 Paragon^{R} gels (Beckman Instruments (UK) Ltd), gel blotters, sample and antiserum templates and sample blotters and gel drying blotters. These packs are stored at room temperature (18°C to 26°C).

(2) Barbital buffer pH 8.6, consists of:

Diethyle-barbituric acid 4,0 grams.

Sodium barbitone 20.6 grams.

Distelled Water 5.0 litres.

(3) Polyethylene glycol buffer pH 8.6 made by;

Adding 100 millilitres of Barbital buffer to 8.0 grams of Polyethylene glycol 6000.

(3) Working Anti-Transferrin prepared by adding equal parts of;

Polyethylene glycol buffer pH 8.6 and

Monospecific rabbit anti- human transferrin (Dakopatts, Dako Ltd. Denmark).

(4) Glutaraldehyde 4 % in aqueous solution.

(5) Saturated Ammonium sulphate solution.

(6) Silver stain solution composed of;

21.0 millilitres of 0.1N Sodium hydroxide,

1.4 millilitres of 25 % Ammonia solution,

Add Distilled water to make 100 millilitres and

Add 1.0 millilitre of 20 % Silver nitrate.

Sample preparation:

(1) If the specimen contains blood, centrifuge at 10^4 g for 15 minutes to remove the red cells. Separate the supernatant and measure its protein content. If the protein concentration is more than 5 grams per litre, add ammonium sulfate to the specimen in a ratio of 1 to 1. Centrifuge at 10^4 g for 15 minutes and discard the supernatant. The precipitate is dissolved in 15 millilitres of distilled water and mixed very thoroughly. The resultant solution is concentrated ten fold using the centrisart^R I.

(2) If the specimen is clear, measure its protein content. If the protein content is above 5 grams per litre, proceed as above in 1. If the protein content is less than 5 grams per litre, concentrate the sample ten fold using the centrisart^{R} I. The centrisart^{R} I consists of an outer test-tube (centrifuge tube) in which 0.1 to 2.5 millilitres of the sample are poured and an inner test-tube (floater tube) which filters the supernatant leaving a concentrated sample in the outer test-tube. After the sample is poured into the outer test-tube, wait for 5 minutes to soak the membrane of the floater. The outer tube is closed and centrifuged at 1,000 g. Remove the inner test-tube (floater containing the supernatant) and discard. The concentrated sample in the outer test-tube is now ready to be processed (Figure 6-3).

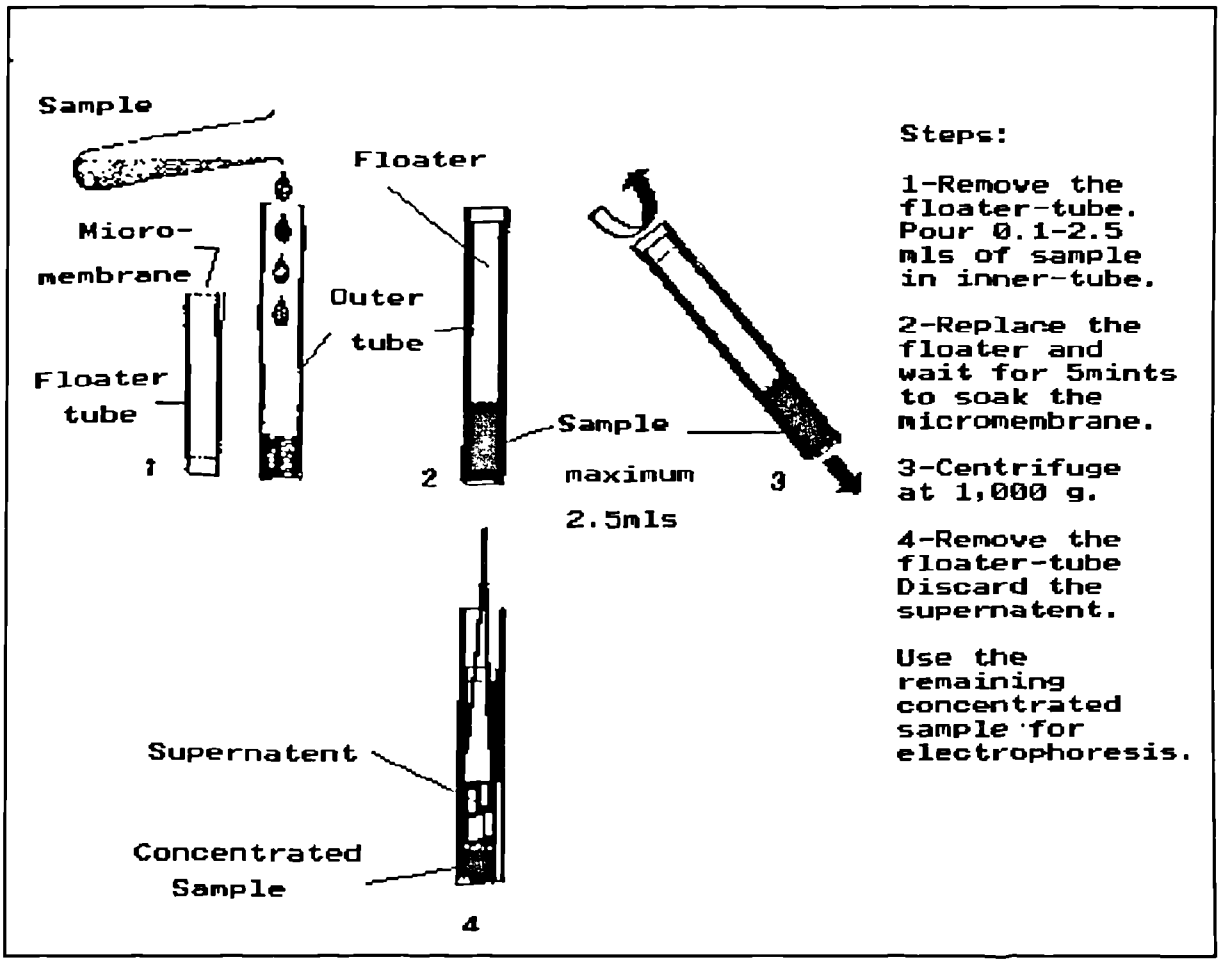


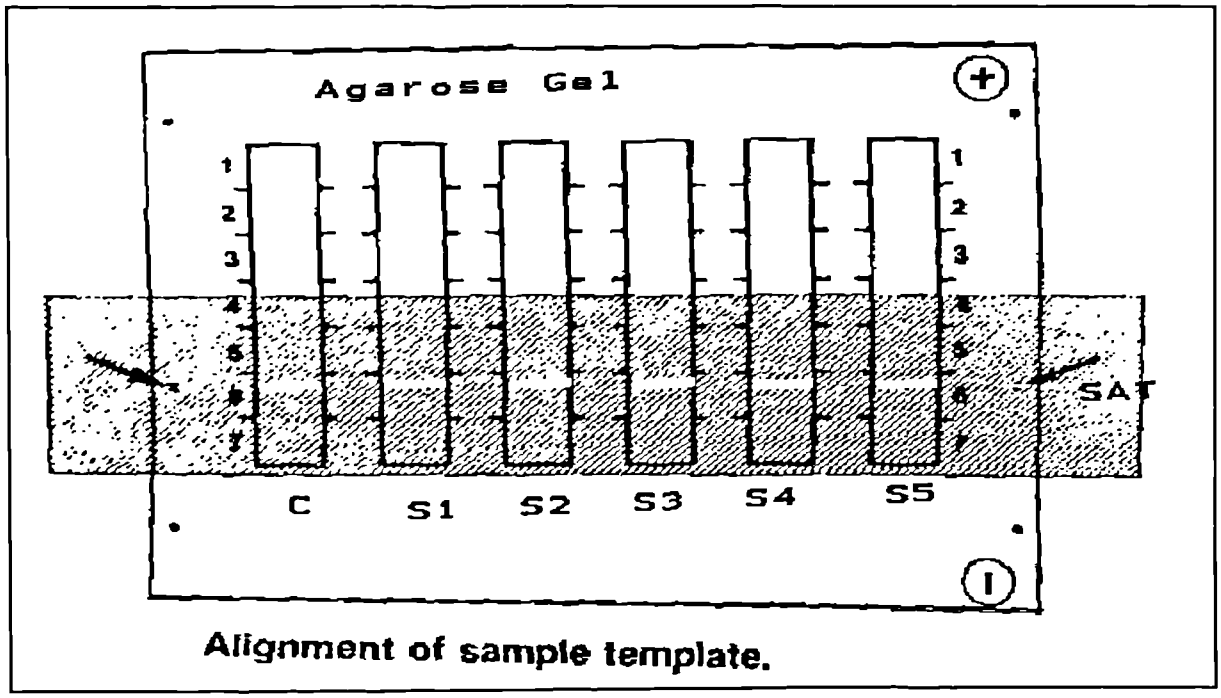
Figure 6-3: Summary of sample concentration using the Centrisart^{R} I.

Sample Application:

(1) Blot the gel with a gel blotter to remove excess moisture.

(2) Align the sample application template (SAT) with the alignment dots in the centre position on the side margins of the gel. To get good results, accurate alignment of the template is essential (Figure 6-4).

Figure 6-4; Sample Application Template (SAT) alignment, C= control, S1 to Samples 1 - 5:



(3) Gently press the sample template against the gel surface to remove any air bubbles.

(4) Dispense 3 to 5 microlitres of appropriately prepared sample (as explained in the sample preparation step) to the sample positions on the sample template.

(5) Wait for 5 minutes for the sample to diffuse into the gel.

(6) Blot excess sample with a template blotter. Remove the template blotter and the

sample template and discard them.

(7) Proceed to electrophoresis.

Electrophoresis:

(1) Fill the electrophoresis cell with fresh barbital buffer pH 8.6. The recommended amount is 90 millilitres and the two compartments of the electrophoresis cell should contain equal amount of the buffer.

(2) Place the gel in the cell. Make sure that the gel edges are submerged in the barbital buffer.

(3) Electrophorese at 100 volts for 30 minutes.

(4) Proceed to immunoprecipitation.

Immunoprecipitation:

(1) Remove the gel from the electrophoresis cell and blot the excess moist with a gel blotter.

(2) Align the antiserum template (AST) with the four corner dots on the gel. Accurate template alignment is essential for good results (Figure 6-5).

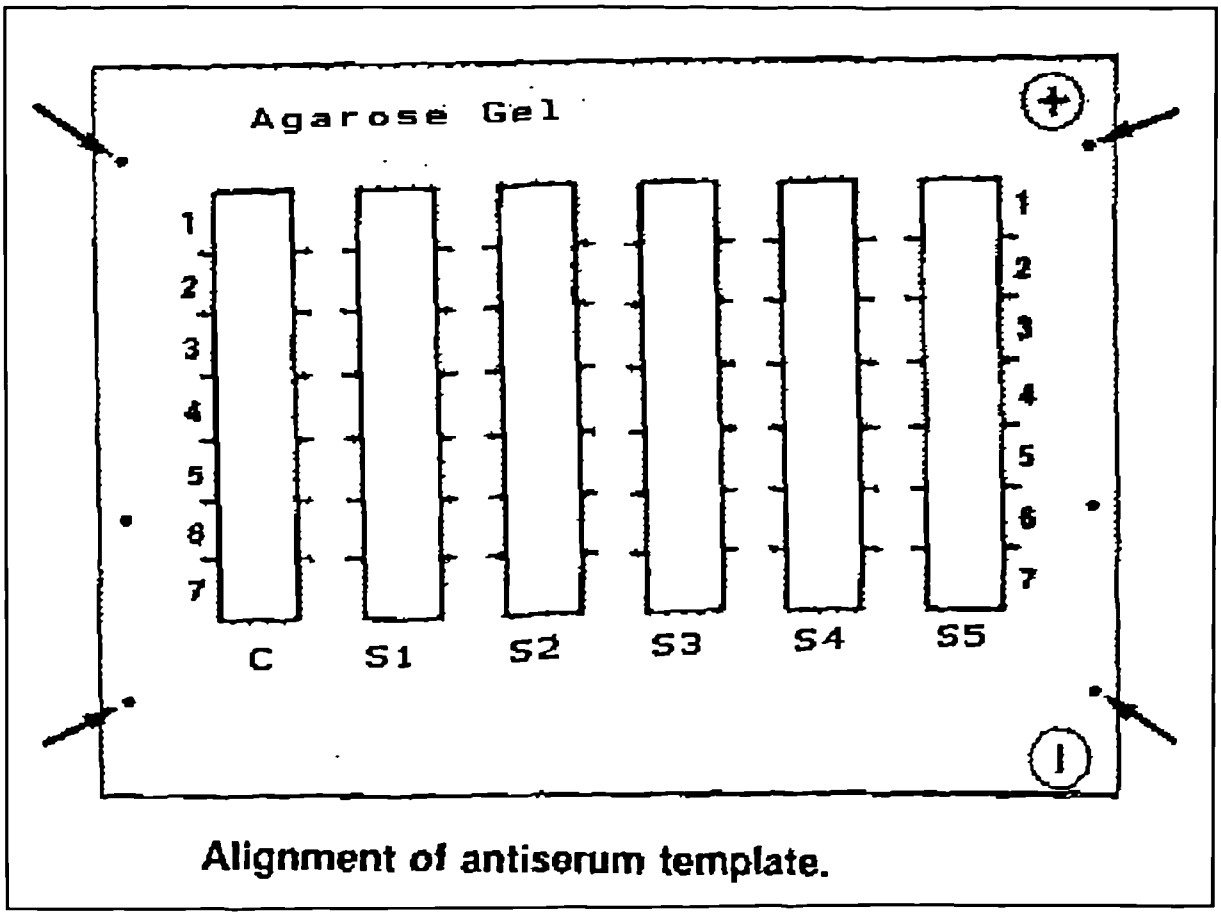
(3) Gently press the margins of the template against the gel surface to ensure a complete seal.

(4) Apply 40 to 80 microlitres of the monospecific antiserum against human transferrin to the trough positions. Do not touch the gel surface with the micropipette tip.

(5) Place gel and antiserum template, gel side up, in black incubator box on top of a moistened gel blotter. Close the box and incubate for at least 30 minutes.

(6) Proceed to staining.

Figure 6-5; Antiserum template (AST) alignment, C=control, S1-5= samples1-5.



Staining:

(1) Remove the gel from the incubator box and discard the antiserum template.

(2) Wash the gel in distilled water three times (60 minutes).

(3) Fix the gel in 4 % glutaraldehyde for at least 15 minutes.

(4) Wash the gel again in distilled water.

(5) Place the gel in silver staining solution until the desired intensity is reached (2 to 20 minutes). The staining has to be done under constant inspection to avoid heavy staining of the background.

(6) Destain the gel in 5 % acetic acid solution to remove excess darkening of the

background.

(7) Dry the gel in room temperature.

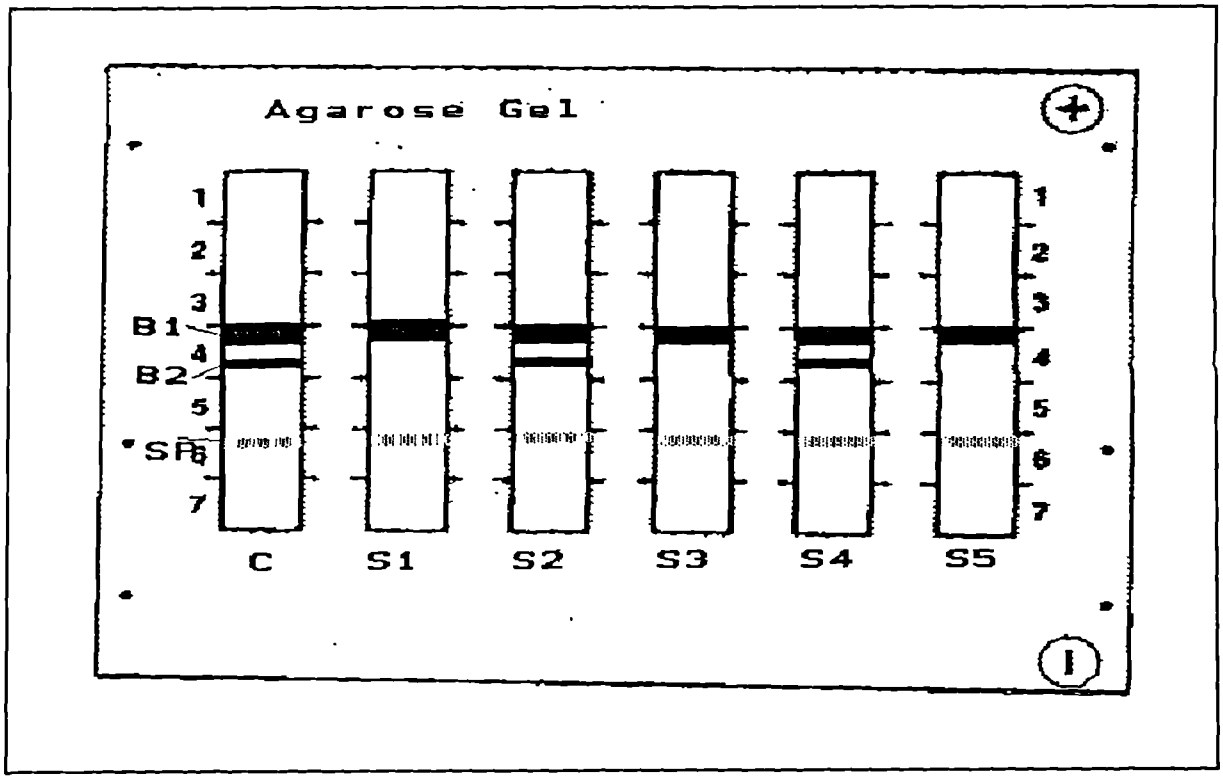
Quality control:

For every set of samples, a sample of known pure CSF should be included as a control. The control sample should always give two bands of transferrin at 4-5 position of the Paragon^{R} gel. If the control sample fails to show the expected results, then the process has to be repeated.

Evaluation:

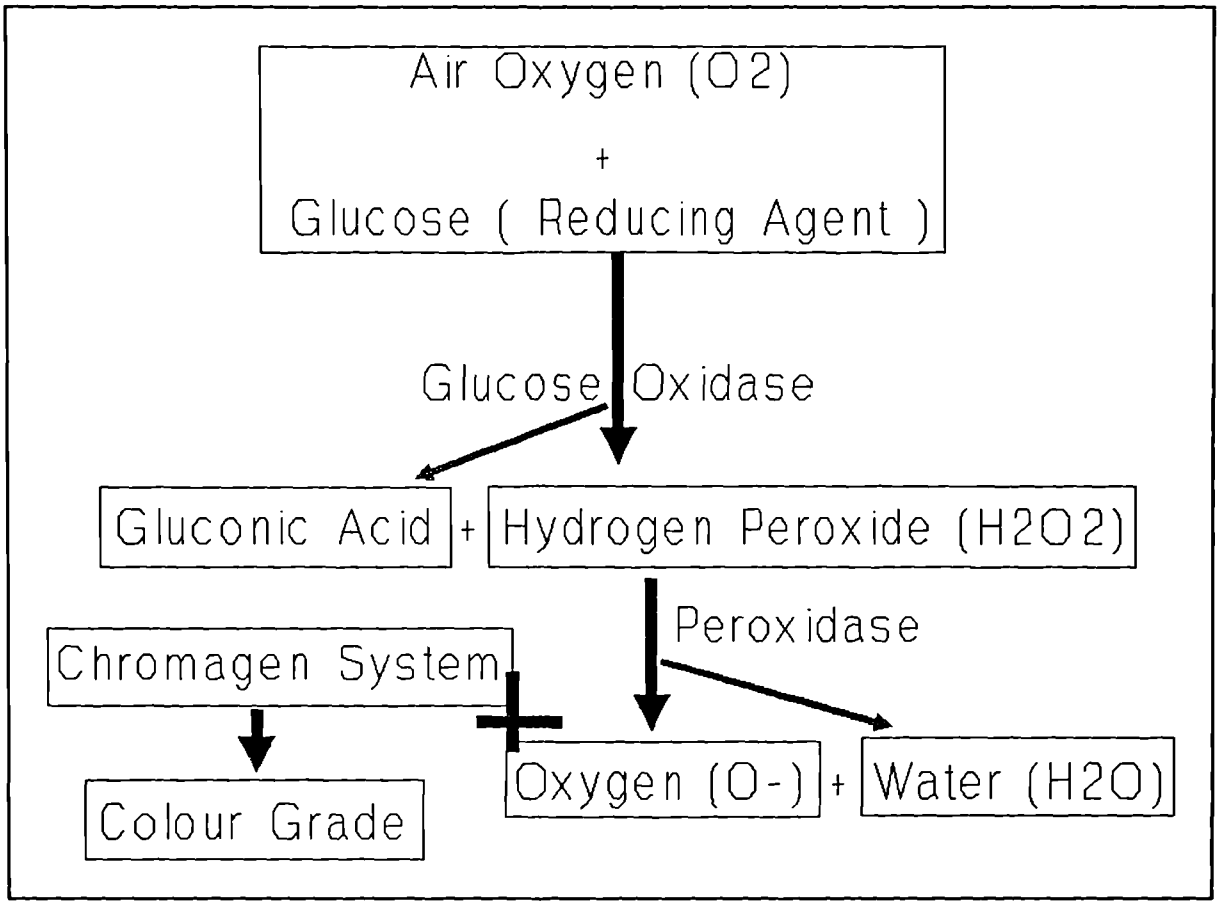
Compare the location of protein band(s) in the samples to that of the control. If the sample showed two bands, it must have contained CSF (Figure 6-6 & AppendixB page 224).

Figure 6-6; Diagram of Transferrin bands in Specimens containing CSF (C,S2,S4) and those which do not contain CSF (S1,S3,S5), B1 = B_1-Transferrin, B2 = B_2-Transferrin, SP = Sample application position.



Glucose-Oxidase Stick Test:

The Glucose-Oxidase Stick Test is based on the following chemical reactions:



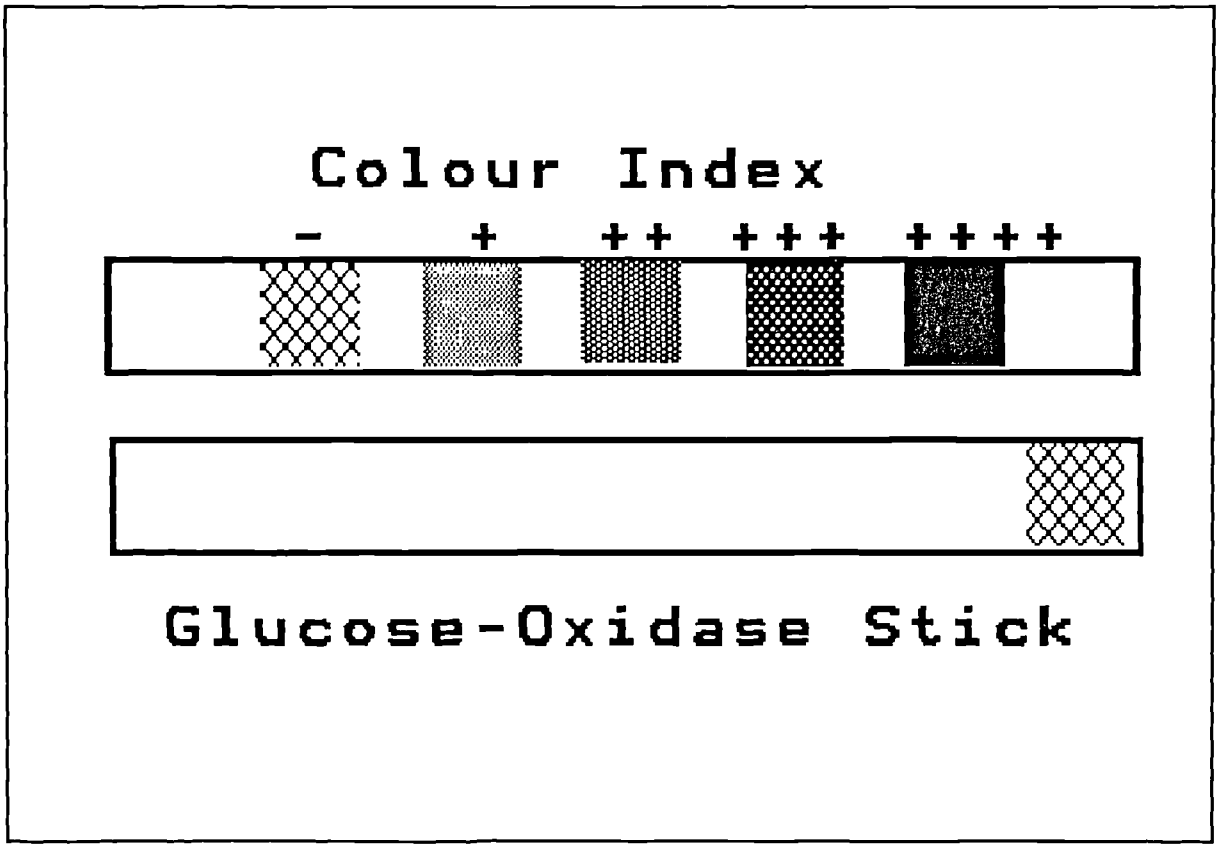
The test stick has a strip impregnated with a mixture of glucose-oxidase, peroxidase and a chromogen system. In the presence of glucose-oxidase, glucose is oxidised by atmospheric oxygen to gluconic acid and hydrogen peroxide. The latter, in the presence of peroxidase, oxidizes the chromogen system to a shade of the colour. I used MAXI SCREEN (Combi 6A) sticks because they test for ascorbic acid as well as glucose. Therefore, false positive results due to the presence of ascorbic acid are avoided (MAXI SCREEN, Combi 6A, Cambridge Selfcare Diagnostics Ltd, Newcastle upon Tyne).

The technique is very simple:

(1) Dip the test strip of the stick into the sample.

(2) Wait for 60 seconds in room air and then compare the colour of the strip to the colour index on the stick's container (Figure 6-7).

Figure 6-7; Diagram of the Glucose-Oxidase stick test:



6,4 Materials:

Cerebrospinal fluid (CSF) samples were collected during lumbar punctures (17 patients, 7 of which during myelography), lumbar drainage (29 patients), ventricular drainage (1 patient) and shunt procedures (11 patients). The details of the underlying disease for which the CSF was drained are summarised in Table 6-1.

Table 6-1: Details of the source and method of CSF collection:

Disease	Lumbar puncture	Lumbar drain	Ventricular drain	During shunts
Subarachnoid haemorrhage	6 Diagnostic	25 Intraoperative	-	-
Hydrocephalus (postoperative)	5 Therapeutic	-	1 Shunt infection	11 Shunt malfunction
Normal CSF	6 Diagnostic	4 Therapeutic	-	-

Potential contaminants of leaking CSF, included blood (24 patients), wound discharge (15 patients) and nasal secretions (17 patients). The clinical details of these patients are summarised in Table 6-2.

Table 6-2; Clinical details of non-CSF samples:

Disease & Method of Collection of sample	Sample	Number
Postoperative blood sample (Arterial line)	Blood (Serum)	24
Postoperative wound discharge (radiovac drainage system)	Blood & tissue fluid	15
Runny nose without CSF leakage	Nasal secretion	17

Each sample was given a random number (1 to 114), prepared for analysis and tested by the Glucose-Oxidase stick test and the Paragon^{R} Immunofixation for B_2-Transferrin band. The results of the two tests were compared using biomedical statistical software package. All the Chi-square values are with Yates' correction and the p values are two tailed.

6,5 Results:

Protein Content Results:

The protein contents of the 114 samples are summarized in Figure 6-8.

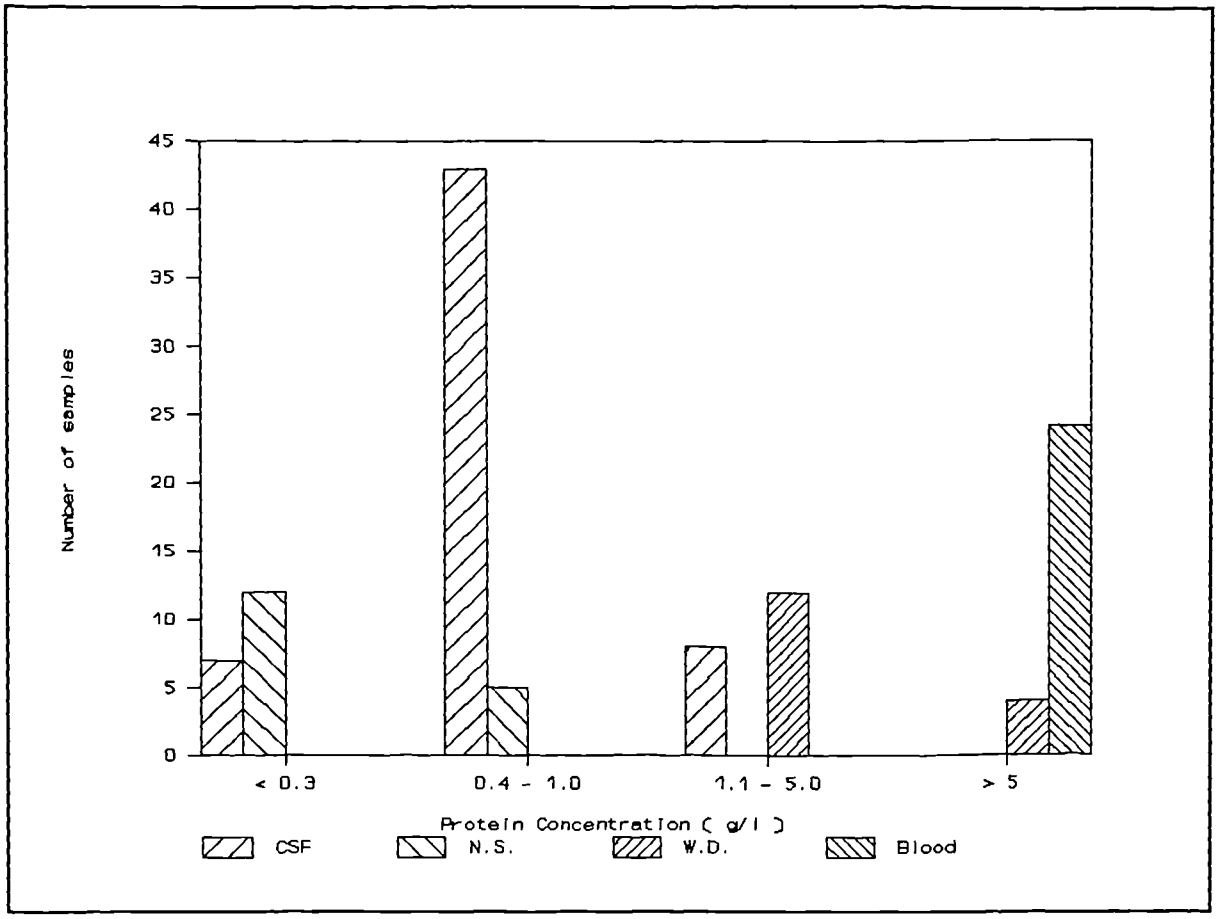


Figure 6-7: Summary of protein concentration: W.D. =wound discharge, N.S. =nasal secretion & CSF=CSF containing samples.

The Glucose-Oxidase Stick Test:

Specificity:

97 samples were positive for glucose, of which only 57 contained CSF. All specimens containing blood (Blood & Wound discharge) were positive and only one

sample containing nasal secretions was positive for glucose. The specificity of the glucose-oxidase stick test in this study was 64 % and even if the threshold of the positive result is increased to > 2.8 mmol/l (+ + +), the specificity of the test remains low at 64.9% (Table 6-3 & Figure 6-9).

Table 6-3: The results of Glucose-Oxidase Stick Test:

Specimen	CSF	Blood	Wound Discharge	Nasal Secretion
Number	58	24	15	17
Negative	1	0	0	16
+ <1mmol/l	0	0	1	1
+ + 2.8mmol/l	2	1	0	0
+ + + 8.3mmol/l	26	20	14	0
+ + + + >8.3mmol/l	29	3	0	0

False+ve results: 35.1 % (40/114) False-ve results 0.9 % (1/114).

False positive tests:

The false positive rate for CSF identification was 35.1 %, and if the threshold of positive results is increased to > 2.8 mmol/l, then the false-positive rate is reduced to 32.5 % (Table 6-3 & Figure 6-8).

False negative results:

The false negative results of CSF identification was 0.9 % (1/114) and if the threshold for positive results is increased to > 2.8 mmol/l the false negative rate increases to 2.6 % (Table 6-3 & Figure 6-9 & Figure 6-10).

Figure 6-9; Histogram of the Glucose-Oxidase Sticks Test Results: CSF=cerebrospinal fluid samples, W.D=wound discharge & N.S=Nasal secretion.

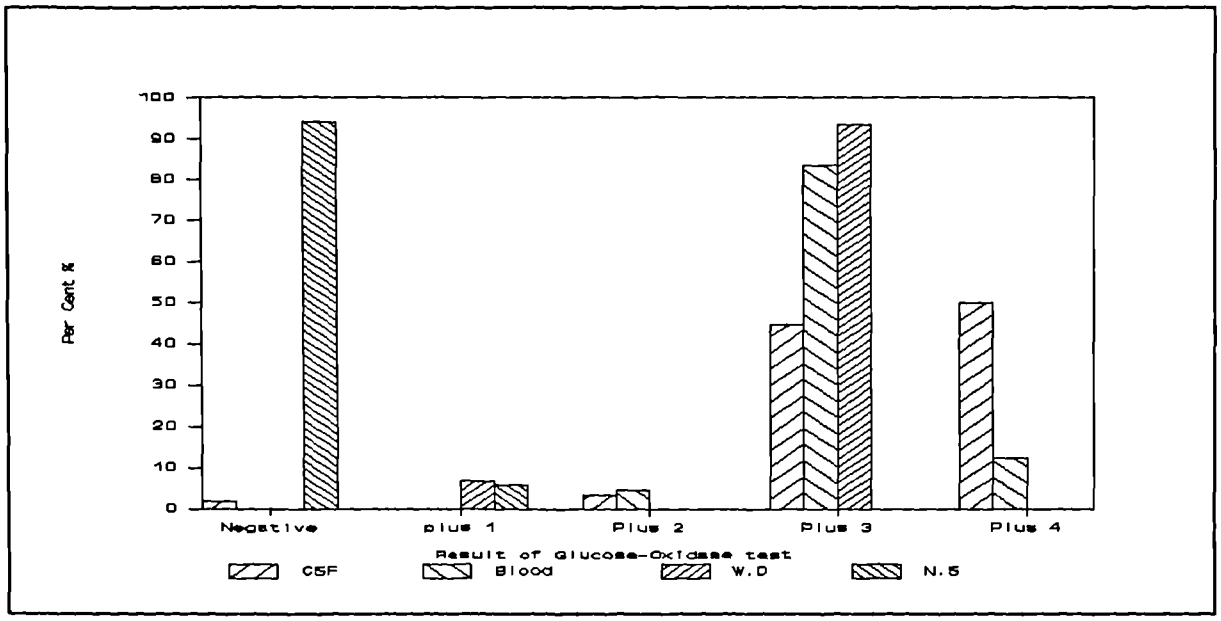
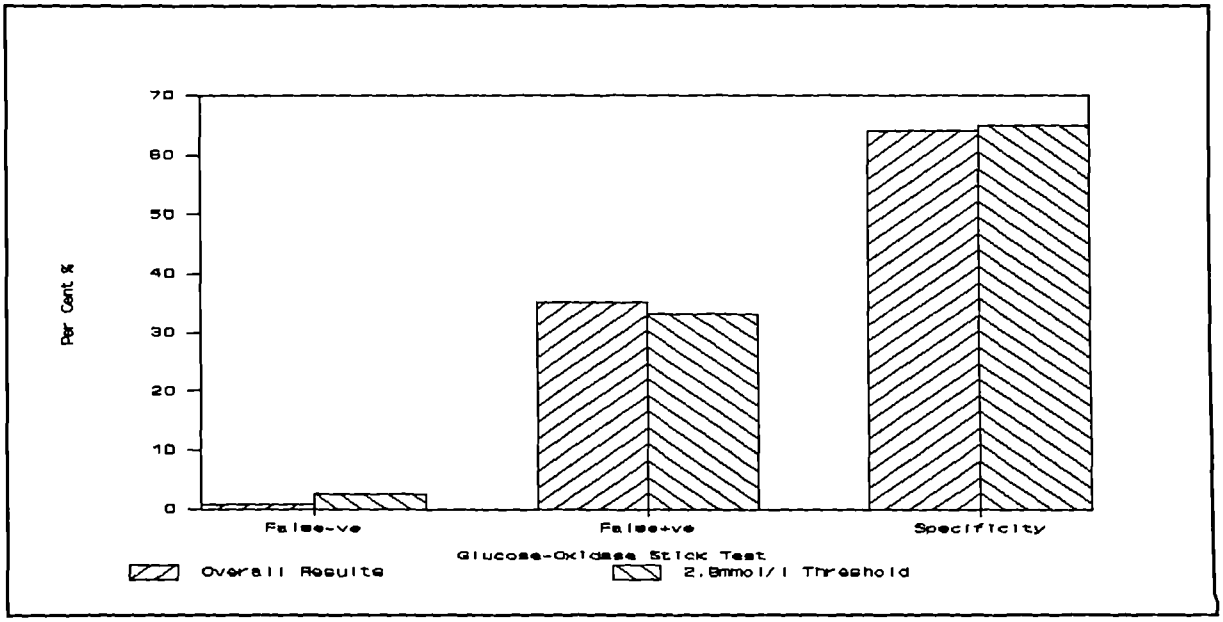


Figure 6-10; Histogram of specificity & False results of Glucose-Oxidase stick test for identifying CSF containing samples (n=114),



The Paragon^{R} Immunofixation (B_2-Transferrin) Results:

Specificity:

98.3 % (57/58) of the samples containing CSF showed B_2-Transferrin band as well as the B_1-Transferrin band. None of the other samples were positive for the B_2-Transferrin band. All blood and wound discharge samples and two nasal secretion specimens showed a single (B_1-Transferrin) band. The specificity of the B_2-Transferrin band was 99 % (Table 6-4 & Figure 6-11).

Table 6-4; Summary of the results of B_2-Transferrin:

Samples	Total Number	B_2-Transferrin	B_1-Transferrin
CSF containing	58	57	58
Blood & Sera	24	0	24
Wound Discharge	15	0	15
Nasal Secretion	17	0	2

* Specificity of B_2-Transferrin band 99 % .

False positive results:

There were no false positive results in this study.

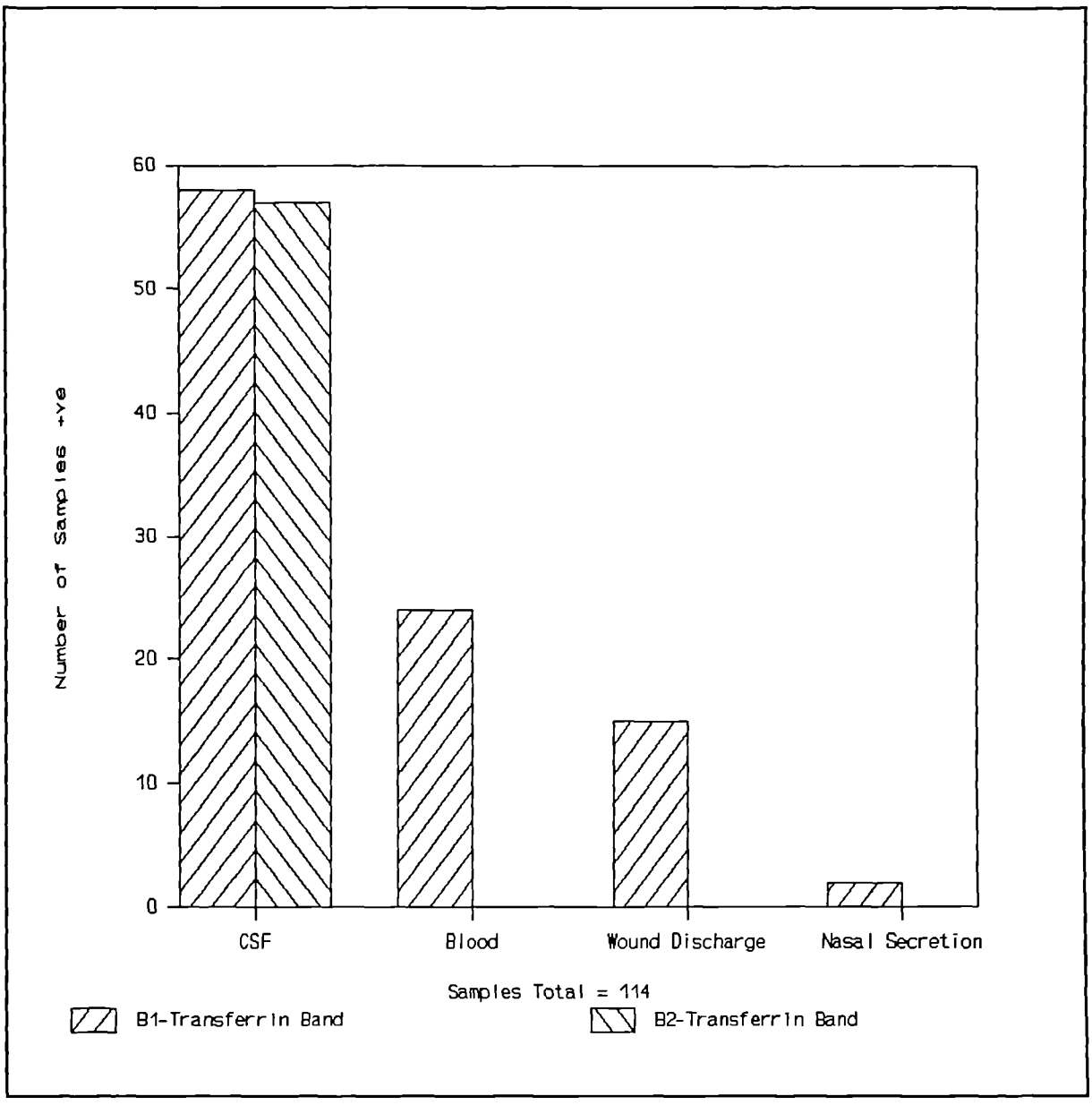
False negative results:

One sample containing CSF obtained through an external ventricular drainage system was negative for the B_2-Transferrin band. Subsequent measurement of the protein content of this sample was unusually low (10 mg %).

Sensitivity:

The lowest concentration of CSF detectable with this method was 10 % of any sample. If the CSF contaminant to pure CSF ratio was more than 10 to 1 the B_2-Transferrin band was not detectable.

Figure 6-11; Results of Transferrin Bands in 114 samples:



6,6 Discussion:

Study Sample:

The study sample included known CSF, blood, wound discharge and nasal secretions obtained from patients with wide range of neurological conditions. None of the blood samples, wound discharges or nasal secretions were contaminated with CSF. When the CSF sample contained blood such as that obtained from recent subarachnoid haemorrhage, the blood of the same patient was obtained for analysis as an extra control. None of the patients was suffering from rheumatoid disease, melanoma or chronic liver disease.

Techniques:

The glucose-oxidase stick test used in this study is quick and semi-quantitative. The stick also tests for ascorbic acid, a reducing substance that can lead to false positive tests for glucose.

The Paragon^R immunofixation method used in this study to detect the B_2-Transferrin band is quicker than the conventional immunoelectrophoresis, because the monoclonal antibody is applied directly to the surface of the gel, overlying the electrophoresed antigens (Ritchie & Smith 1976). The sample volume and the quantity of the antiserum required to perform this test, are relatively very small. With the Paragon^R technique up to 12 samples can be processed simultaneously. Its sensitivity is enhanced by using silver staining techniques (Oberascher 1988), but the lowest concentration of CSF, detectable by this method, was 500 microlitres of pure CSF per 5 millilitres of discharge. The Paragon^R immunofixation technique to detect B_2-Transferrin band offers the following advantages over conventional immunoelectrophoresis and other methods of immunofixation:

(1) The maximum number of samples that can be processed simultaneously is 12 (6 samples in each cell).

(2) The amount of buffer required for electrophoresis is reduced to 90 millilitres in each cell (i.e 90 mls per 6 samples).

(3) The electrophoresis time is reduced to 30 minutes at 100 volts.

(4) The amount of the antitransferrin required can be reduced to 40 microlitres per sample, provided that the expected positions (4-5 positions) of the transferrin bands on the gel are covered by the antiserum.

In short, the Paragon^{R} immunofixation technique saves considerable time and money.

Specificity:

The Glucose-Oxidase stick test was non-specific for CSF with a false positive rate of 35 %. These results are marginally better than the 45 - 75 % false positive rate found in previous studies using the Glucose-Oxidase test paper (Gadeholt 1964, Kirsch 1967, Healy 1969 and Kosoy & others 1972). The test specificity depends on the glucose-oxidase, which is essentially a dehydrogenase enzyme. The test may give false results because the glucose-oxidase and peroxidase enzyme activities can be affected by several factors (Fales 1963):

(1) Presence of reducing agents, such as ascorbic acid, mannose or ribose, may give false positive results.

(2) Low pH, fluoride and chloride inhibit the peroxidase activity.

On the other hand, the Paragon^{R} immunofixation technique (B_2-Transferrin band identification) was highly specific and accurate. The only false negative result was a sample of CSF obtained from an external ventricular drainage system with a very low CSF protein concentration (10 milligrams per 100 millilitres of CSF). In comparison to

the Glucose-Oxidase Stick Test, the Paragon^R immunofixation for B_2-Transferrin is more accurate and specific (Chi-square (with Yates' correction) = 44.39, df = 1 , 0.01 > p value < 0.00001).

Sensitivity:

The lowest concentration of pure CSF, that can be detected with the Paragon^R immunofixation for B_2-Transferrin was 10 % (i.e. 500 microlitres of pure CSF per 5 millilitres of discharge). This confirms the results of sensitivity in a previous study using different immunofixation techniques for B_2-Transferrin (Oberascher 1988).

False-positive results and Quality assurance:

There was no false-positive tests in this study for the B_2-Transferrin band, using the Paragon^R method. However, false-positive results have been reported, using other techniques of immunofixation (Oberascher 1988). These false-positive results were attributed to genetic variants and liver cirrhosis (Oberascher 1988). Other possible confusing results can occur due to presence of abnormal transferrin forms, such as transferrin-C in rheumatoid arthritis (El-Hazmi & others 1991), melanoma associated antigen p97 (Brown & others 1982 and Rose & others 1986) and human Burkitt's lymphoma transformation factor (Diamond & others 1983). To avoid confusing results, due to the presence of these abnormal transferrin and transferrin-like proteins, a serum sample from the same patient should be analyzed simultaneously with the fistulous fluid.

For quality control a known sample of pure CSF should be analyzed to detect the possible failure of electrophoresis and to compare the transferrin bands in the samples to those of the control. During this study, only one gel failed to electrophorese and the test was repeated with good results.

Trouble-Shooting of Paragon^R Immunofixation:

(1) No electrophoretic bands visible: If the control sample did not show the expected transferrin bands then this indicates failure of the electrophoresis. Repeat the test, make sure that the correct amount of buffer is poured into the cell and the edges of the gel are submerged in the buffer.

(2) Grey or brown precipitate appearing as dust, smudges or swirling on the gel surface. This non-specific silver deposition appears to be due to low temperature or silver reagent carry-over. Soak the gel in de-ionised water for 5 minutes three times and make sure that the silver stain reagent is at least 25° C.

(3) Dark uniform yellow, mottled brown or mottled green background with poor sensitivity. This usually indicates water-contaminants or incomplete removal of the gel buffer. Use the purest water you can get and wash the gel thoroughly before staining.

6,7 Conclusion:

Accurate and specific diagnosis of CSF leakage is now possible, by using the Paragon^R immunofixation technique to detect the B_2-Transferrin band. This technique is very sensitive and highly specific with the following advantages:

(1) It carries no risk to the patient.

(2) It is highly specific (> 99 % in this study).

(3) Highly sensitive (can detect 100 microlitres of pure CSF per 1 millilitre of fluid).

(4) It can be carried out as an outpatient test.

(5) It can be performed on both fit and unfit patients as it does not require the patient to be moved from intensive therapy units.

(6) It is non-invasive.

(7) It is cheaper and quicker than immuno-electrophoretic techniques.

Chapter 7

Preoperative Localization of CSF Fistulae and Selection of Patients for Surgery

7,1 Introduction:

Accurate localization of CSF fistulae has always been a difficult problem for both the neuro-radiologist and the neuro-surgeon. Several techniques have been developed to localize CSF fistulae. Lateralization and preferably precise localization of CSF fistulae is very important, when surgery is being contemplated. Not only does it make the planning for surgery easier, the operation quicker and the operative morbidity less, but it also increases the chances of a successful repair and reduces the negative exploration rate.

Plain skull radiographs and complex motion tomography were the most commonly used investigations to localize CSF fistulae until recently, when computed tomography (CT) and cisternography have taken over the lead. The arrival of non-ionic, water-soluble contrast media (such as Metrizamide, Lopamidol and Iohexol) and more stable isotope materials (such as Technetium-99m) provided new modes of investigation. Metrizamide-Computed Tomographic-Cisternography (MCTC) was used first in 1977 (Drayer & Others 1977) and radio-isotope cisternography (RIC) has been used since 1968 (Di Chiro & Others 1968). Since then, many case reports and short series of CSF fistulae, localized using these techniques, have been reported and several modifications of these techniques have been developed.

7,2 Objective:

To determine the values of tomography and cisternography in the localization of CSF fistulae.

7.3 Techniques of Cisternography:

Contrast-Computed Tomographic-Cisternography (CCTC):

Premedication:

Thorough explanation of the procedure is as important as premedication. The most commonly used premedication is Diazepam 10 mg, given 30 minutes before the procedure (Ghoshhajra 1980, Manelfe & others 1982 and Brandt & others 1983). Anticonvulsants should be continued and neuroleptic drugs (such as phenothiazines) should be discontinued 48 hours before and 12 hours after cisternography.

Intrathecal injection of the contrast:

A water-soluble, non-ionic contrast agent is injected intra-thecally, through a lumbar puncture or C1,2 lateral cervical puncture, using a 22 gauge spinal needle. 5-7 millilitres of the contrast medium are injected and 3 absorbent sponges or pledgets are placed in each nostril (Figure 7-1). The position of the table is tilted 60 to 70° head down (Trendlenburg position) for 1-2 minutes and then returned to - 10°. Then, the patient is transferred in this position to the scanner.

Contrast Media:

The most commonly used contrast media in cisternography are the water-soluble, non-ionic iodine based contrast media, such as;

(1) Metrizamide (Nyegaard, Oslo, Norway and Winthrop, France) in a concentration of 190 to 220 mg Iodine / millilitre (Naidich & Moran 1980, Ghoshhajra 1980, Cooper & Kassel 1982, Manelfe & others 1982, Afshar & Thomas 1982, Park & others 1983, Brandt & others 1983, Ahmadi & others 1985 and Okada & others 1991).

(2)Iohexol (Omnipaque, Noromed Ltd), concentration of 240 mg Iodine / millilitre (Olofsson & Bynke 1988 and Byrne & others 1990).

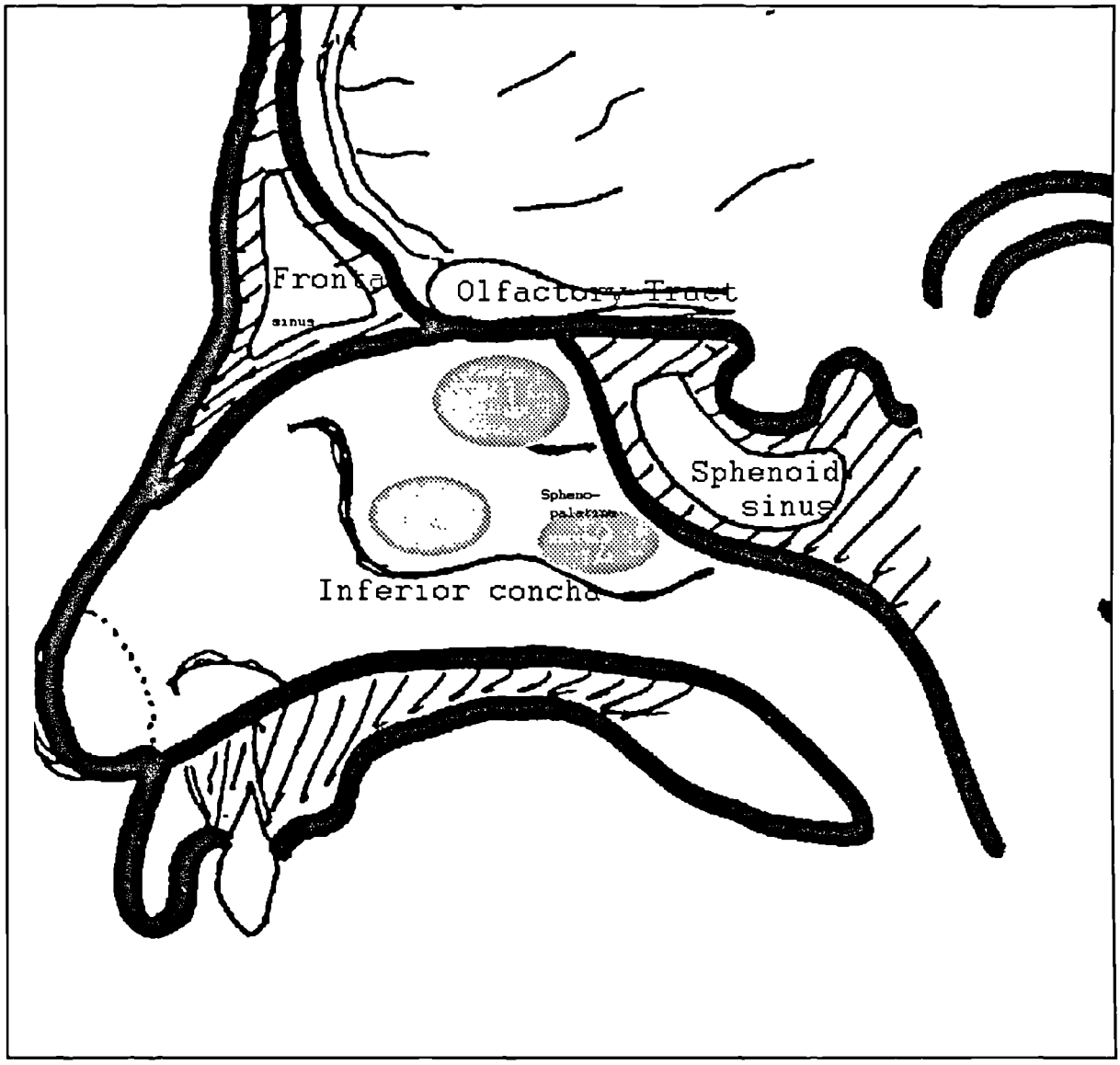
(3) Lopamidol (Bracco, Milan, Italy and Schering, France).

Figure 7-1; Diagram of the site of Nasal pledgets;

(Pledget 1) Near the Cribriform plate.

(Pledget 2) in the Spheno-palatine recess.

(Pledget 3) near the Roof of the Middle meatus.



Scanning:

Pre-scan computed tomogram (" Scout View ") is performed to allow a better coronal slice selection and gantry angulation to avoid artifact-producing dental fillings (Cooper & Kassel 1982). The patient is scanned in the brow-up position starting at the lower spheno-ethmoidal region. Then, the scan is repeated in a decubitus position with the leaking nostril inferior to demonstrate contrast-fluid shift in the air sinuses (Naidich & Moran 1980). A coronal scan is obtained with the patient in the prone position covering the particular area of interest, such as anterior fossa fractures (Ghoshhajra 1980). The collimation of the scanner is set for 4-5 millimetre slices with 1-3 millimetres overlapping to increase the sensitivity of the technique (Ghoshhajra 1980, Manelfe & others 1982 and Ahmadi & others 1985). Images should be monitored in the standard and reverse video modes preferably using two simultaneous monitors (Ghoshhajra 1980). Sagittal reconstruction is not helpful (Manelfe & others 1982).

Modifications to show intermittent and small leaks:

If the previous technique did not show the CSF fistula, the following manoeuvres may demonstrate the site of a small or intermittent CSF leak;

(1) Asking the patient to cough or perform a Valsalva manoeuvre then repeating the scan (Manelfe & others 1982).

(2) Electively raising the CSF pressure by injecting normal saline or artificial CSF intra-thecally using an infusion pump and a CSF manometer (Spetzler & Wilson 1978 and Naidich & Moran 1980). The recommended rate of infusion is 0.5 to 5 millilitres of fluid / minute until the CSF leak is demonstrated or the CSF pressure has reached 600 millimetres of water (H_2O) and has been maintained at this level for 15 minutes

(Magnaes & others 1977 and Spetzler & Wilson 1978).

(3) Digital subtraction fluoroscopy of the images after the intra-thecal injection of contrast (Byrne & others).

Contraindications:

This procedure is contraindicated in patients with previous allergy to iodine and those who have an intracranial mass lesion. Neuroleptic drugs should be stopped 48 hours before and 12 hours after the test, while anticonvulsants should be continued.

Positive results:

The test is considered positive if the contrast was demonstrated leaking through a bony or dural defect (Figure 7-2) or a bony defect is demonstrated and the contrast is detected in one of the nasal pledgets (Figures 7-3 & 7-4). The test is considered doubtful if only a bony defect is shown or the contrast is detected in the nose without a bony defect (Manelfe & others 1982).

Figure 7-2; Diagram of Contrast computed tomographic cisternography (CCTC) showing the contrast leaking through a bony defect;

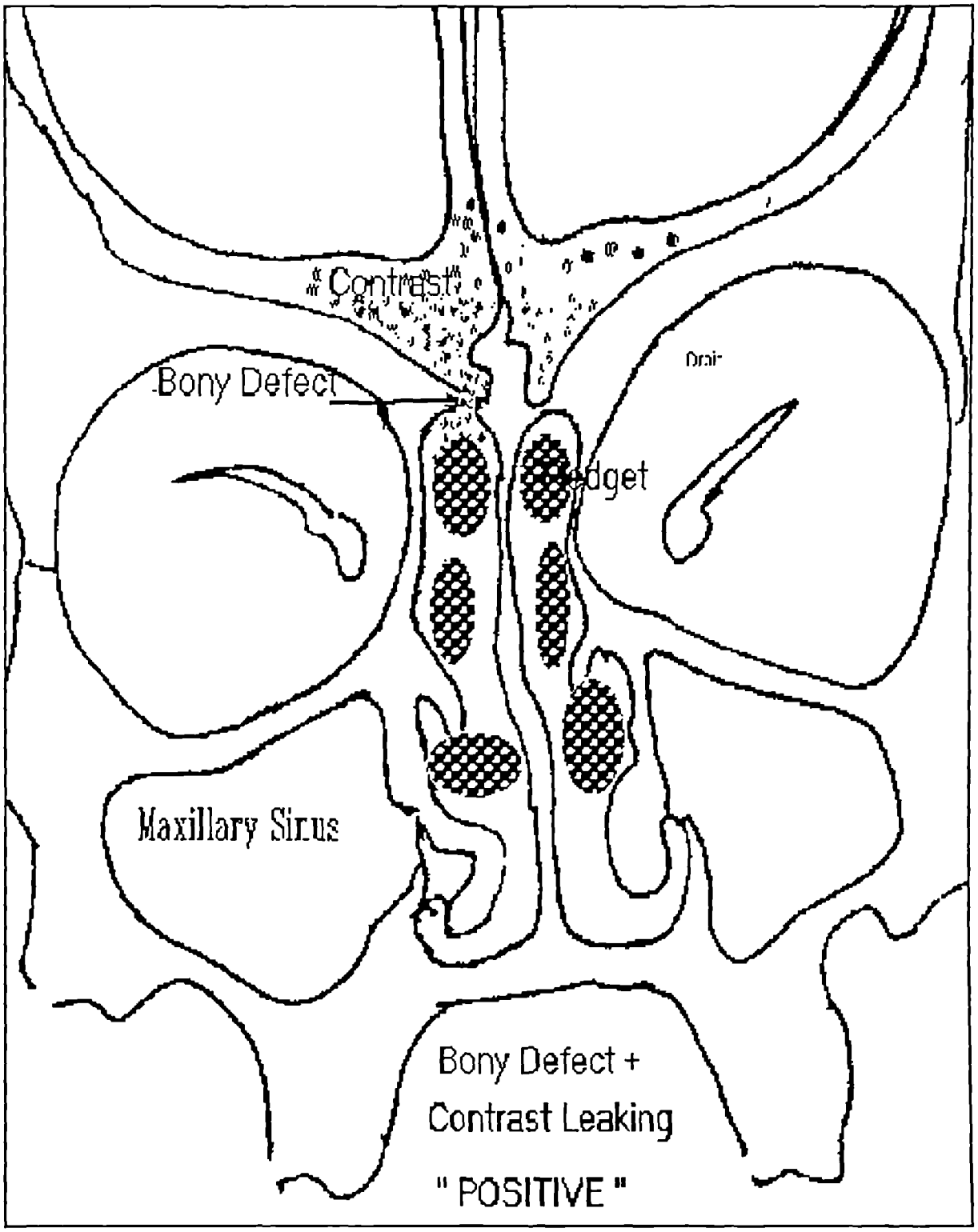


Figure 7-3; Diagram of CCTC showing a bony defect but no leak of contrast,(doubtful result);

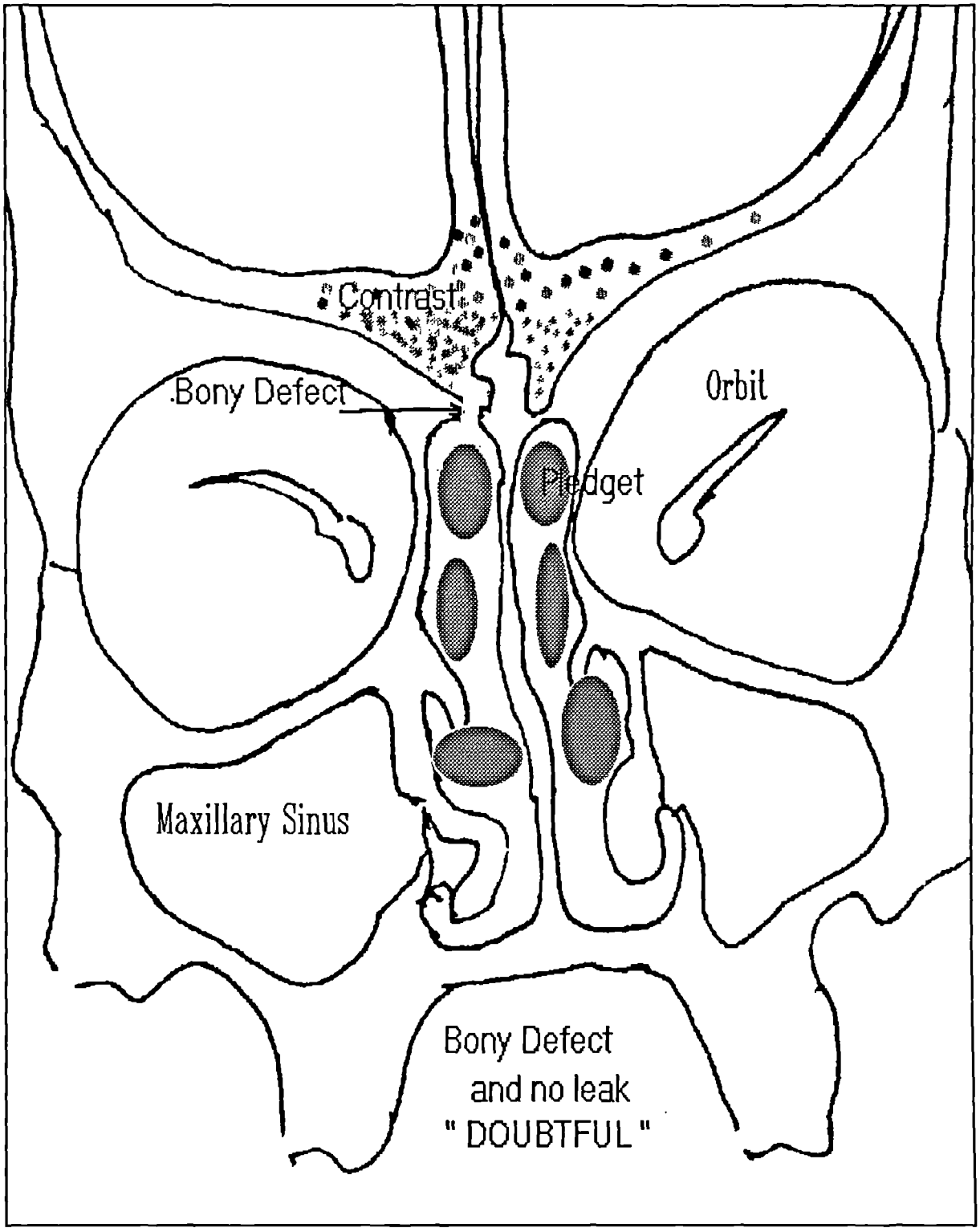
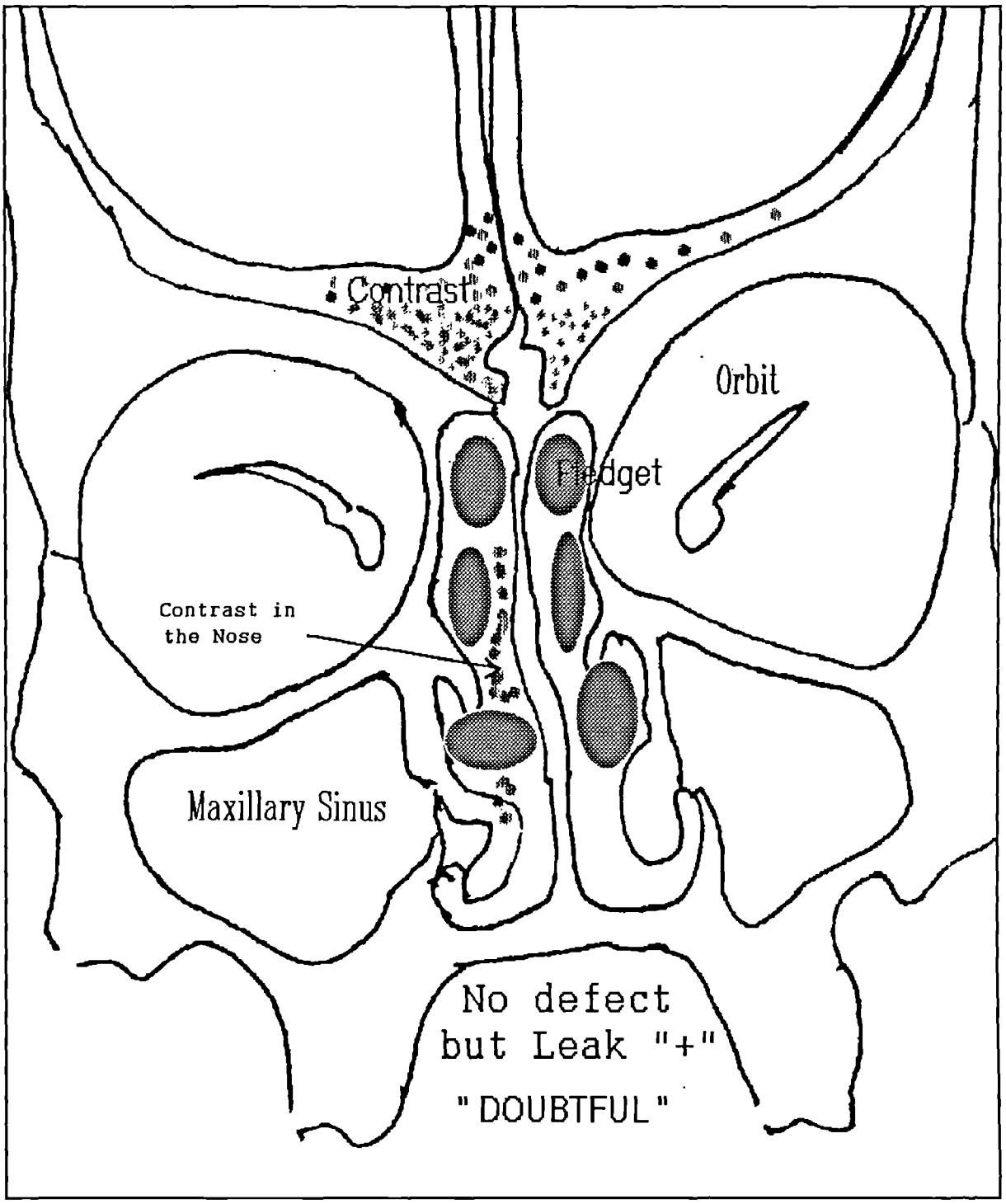


Figure 7-4; Diagram of CCTC showing no defect but contrast is present in the nose, Result = doubtful;



* If both a bony defect and a contrast leak are shown = Positive test.

Radioisotope Cisternography (RIC):

The technique of intra-thecal injection of radioisotopes is the same as that employed in contrast-computed tomographic-cisternography (CCTC). There are many suitable radioisotopes, that have been used to localize CSF fistulae. However, the most widely used radioisotopes include;

(1) Technetium-99m (^{99m}Tc) or ^{111}Indium (^{111}In) - labelled diethylenetriamine pentaacetic acid (DTPA), ^{99m}Tc 100 MBq or ^{111}In 18.5 MBq (Glaubitt & others 1983, Park & others 1983, Kok & others 1985, Bret & others 1985, Flynn & others 1987 and Bleach & others 1988).

(2) ^{99m}Tc- pertechnetate, 1 mCi (Mamo and others 1982).

(3) ^{99m}Tc- labelled human albumin (Spetzler & Wilson 1978).

After intra-thecal injection of the radioisotope, the nose is packed with absorbent pledgets and scintigraphy is performed. Anterior, left and right scintigram are obtained using a gamma camera with low energy, all purpose, parallel hole collimator. Scintigraphy is performed at several intervals after the radioisotope injection. The nasal pledgets are replaced twice daily and their radioactivity is counted. Blood samples are obtained immediately after the removal of the nasal pledgets. The nasal pledgets' radioactivity is compared with aliquots of 2 millilitres of serum using a well scintillation counter (Glaubitt & others 1983). Scintigraphy after 3, 6 and 24 hours of the radioisotope injection is the minimum number of counts, but to increase the sensitivity of this technique, 48 and 72 hours counts are recommended (Ommaya 1976 and Glaubitt & others 1983).

Premedication with potassium pertechnetate is recommended to avoid impregnation of the salivary glands with the tracer, so as to reduce false positive results

(Mamo & Others 1982). Furthermore, using 10 % dextrose solution as a vehicle for the tracer has been suggested to increase the success rate and the count efficiency and to decrease the radiation exposure (Alazraki & others 1973).

7,4 Clinical Material and Results:

Anterior Cranial Fossa Tomography (ACFT):

Anterior cranial fossa tomography was performed in 59 patients with traumatic, definite CSF leaks. A bony defect was found in 11 patients (18.6 %), which were all confirmed at surgery. However, another 40 patients underwent surgical dural repair of CSF fistulae, despite a negative anterior cranial fossa tomography (False negative rate of 78.4 %). The success rate and sensitivity of anterior cranial fossa tomography is shown in figure 7-5.

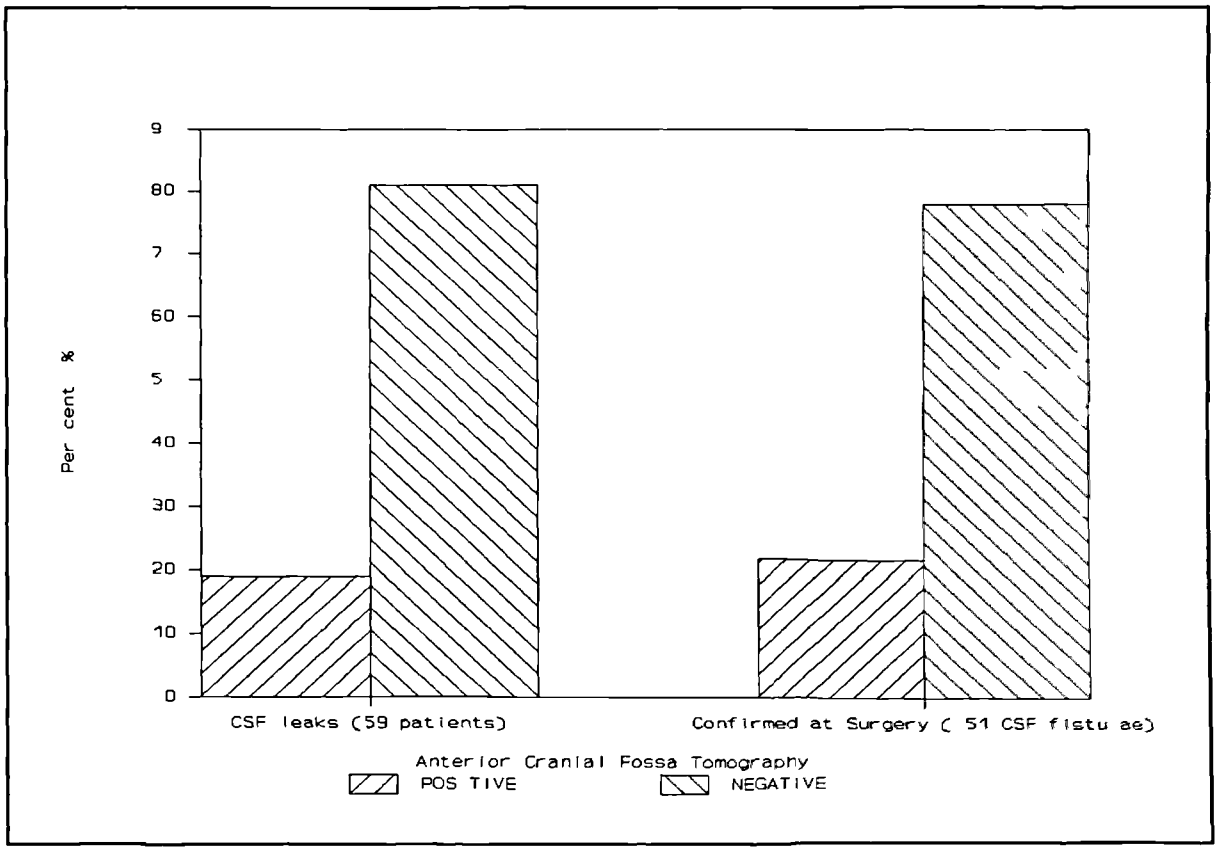


Figure 7-5; The value of anterior cranial fossa tomography.

Computed Tomography (CT):

Computed tomography (CT) was performed in 66 patients with suspected CSF fistulae, of which 33 patients underwent surgical exploration. The CT scan showed the possible site of CSF leak in 13 patients (19.7 %), which were confirmed at surgery (Success rate of 39.4 %, nearly twice as that of anterior cranial fossa tomography). The CT scan not only doubled the detection rate of bony defects, but it also was helpful in showing other intracranial lesions, such as haematomas, contusions, hydrocephalus and pneumocephalus (Figures 7-6 & 7-7).

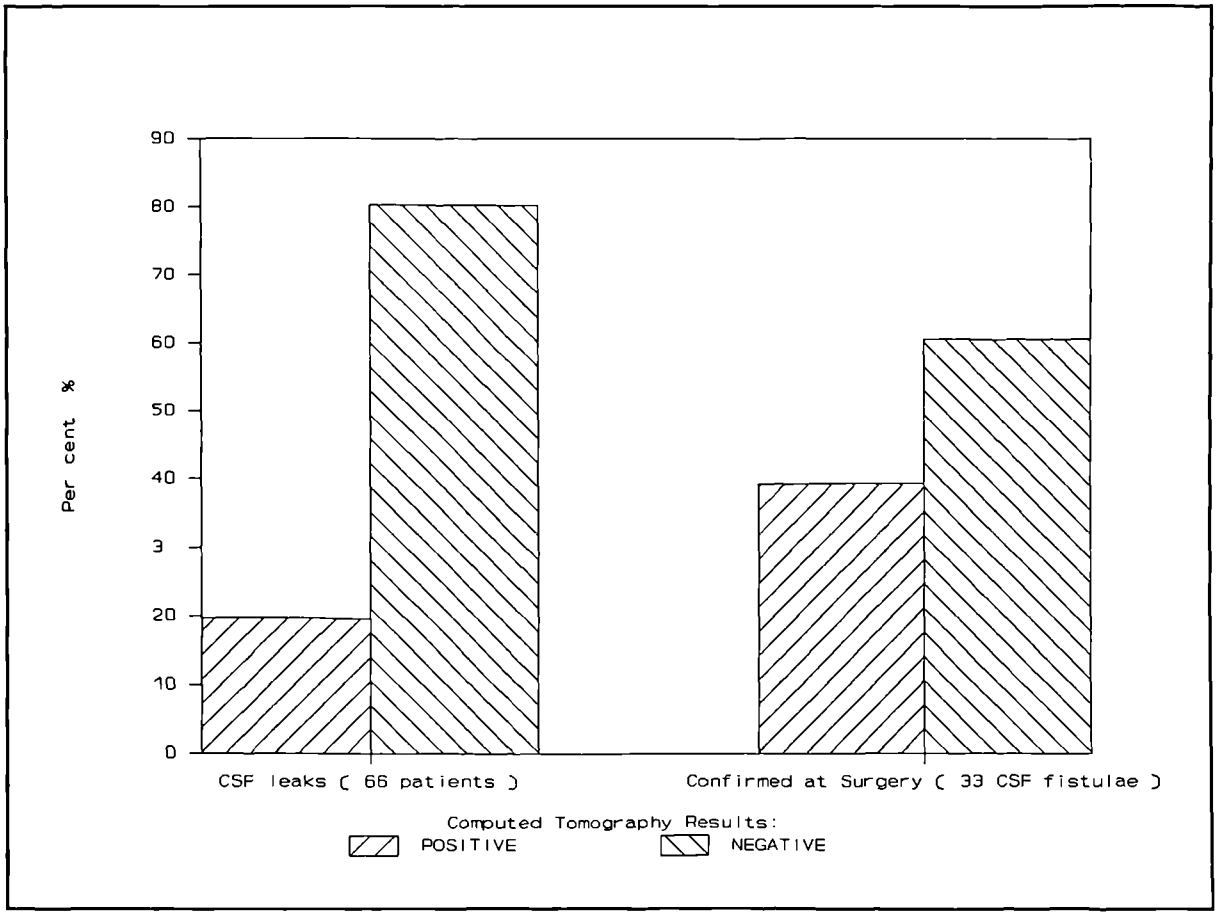
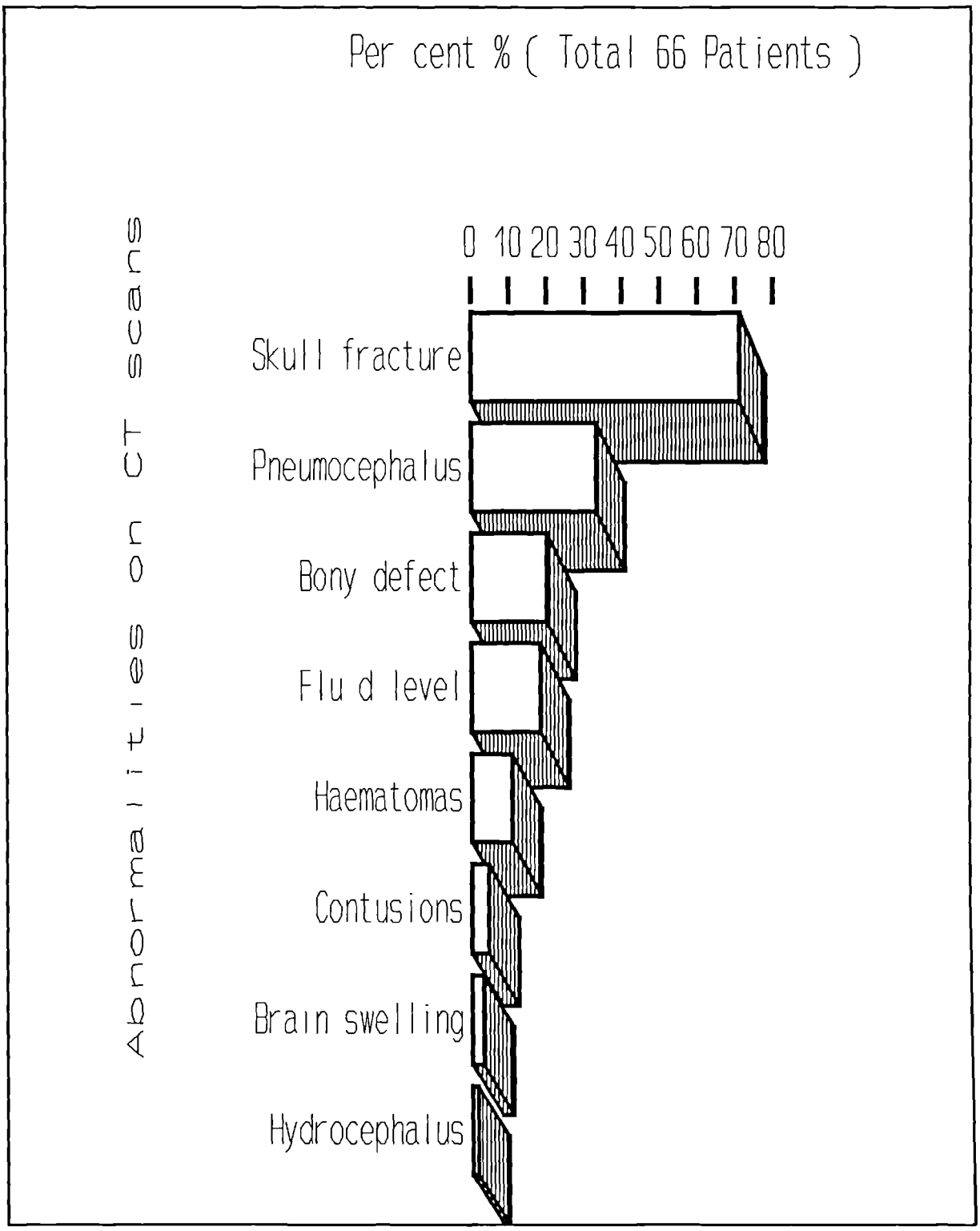


Figure 7-6; The results of Computed Tomography in CSF leaks.

Figure 7-7; Abnormalities shown by Computed Tomography (CT) in 66 patients with CSF leaks;



Iohexol-Computed Tomographic-Cisternography (ICTC):

The precise location of the CSF fistula was shown in 22 out of 34 patients, using Iohexol computed tomographic cisternography (ICTC). Twenty-three were definite CSF leaks and proceeded to surgery, which confirmed the site in 22 patients (Success rate of ICTC = 95.7 % and false negative rate = 4.3%). The value of ICTC is presented in figure 7-8.

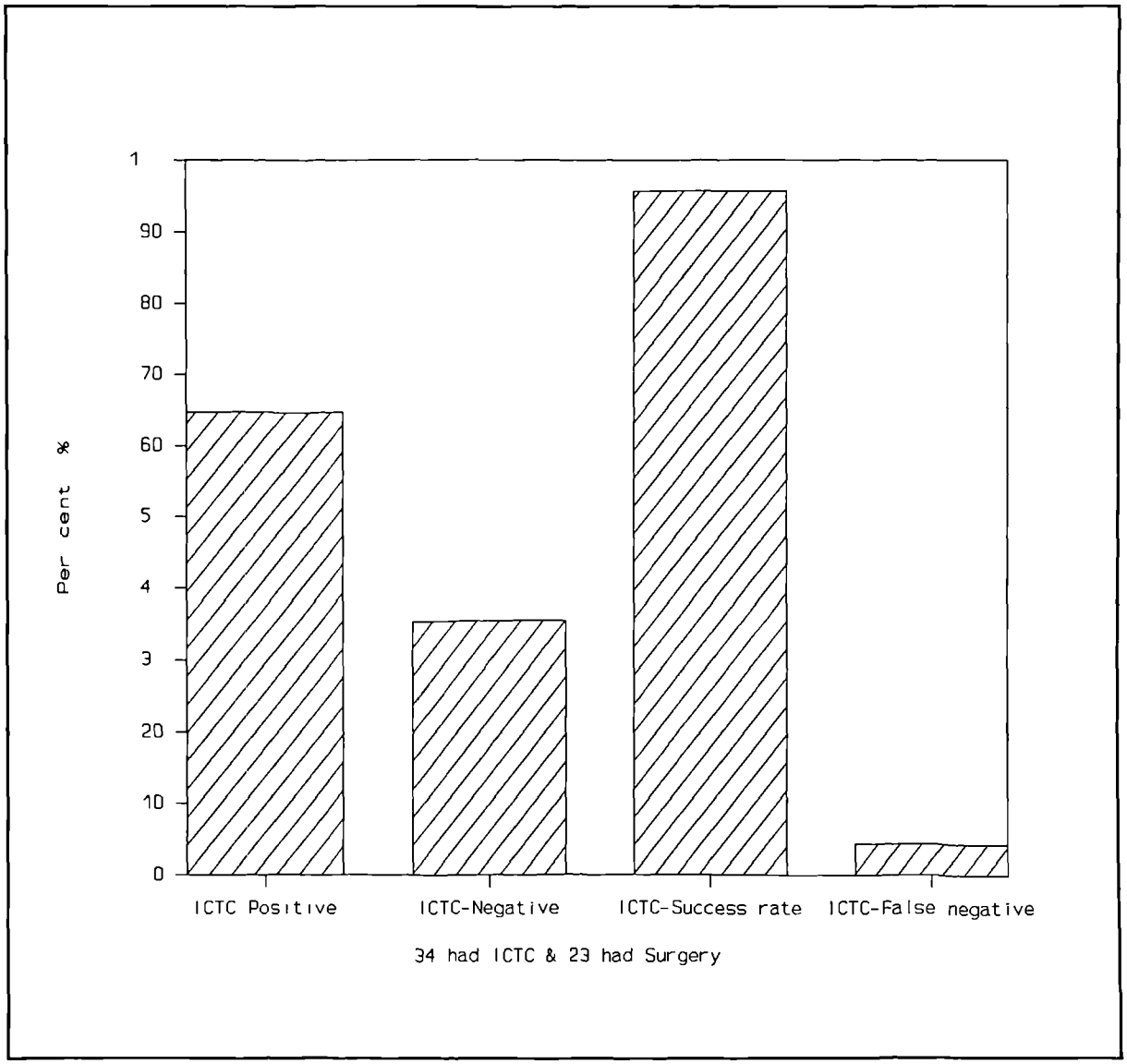


Figure 7-8; The results of Iohexol-Computed Tomographic-Cisternography (ICTC) in 34 patients with suspected CSF fistulae.

Radioisotope Cisternography (RIC):

Radioisotope cisternography was positive in 5 out of 18 patients (28%). Surgical exploration was performed in 8 patients, 5 patients had a positive RIC and 3 had a negative test (Success rate of 62.5 % & false negative rate of 37.5%, Figure 7-9).

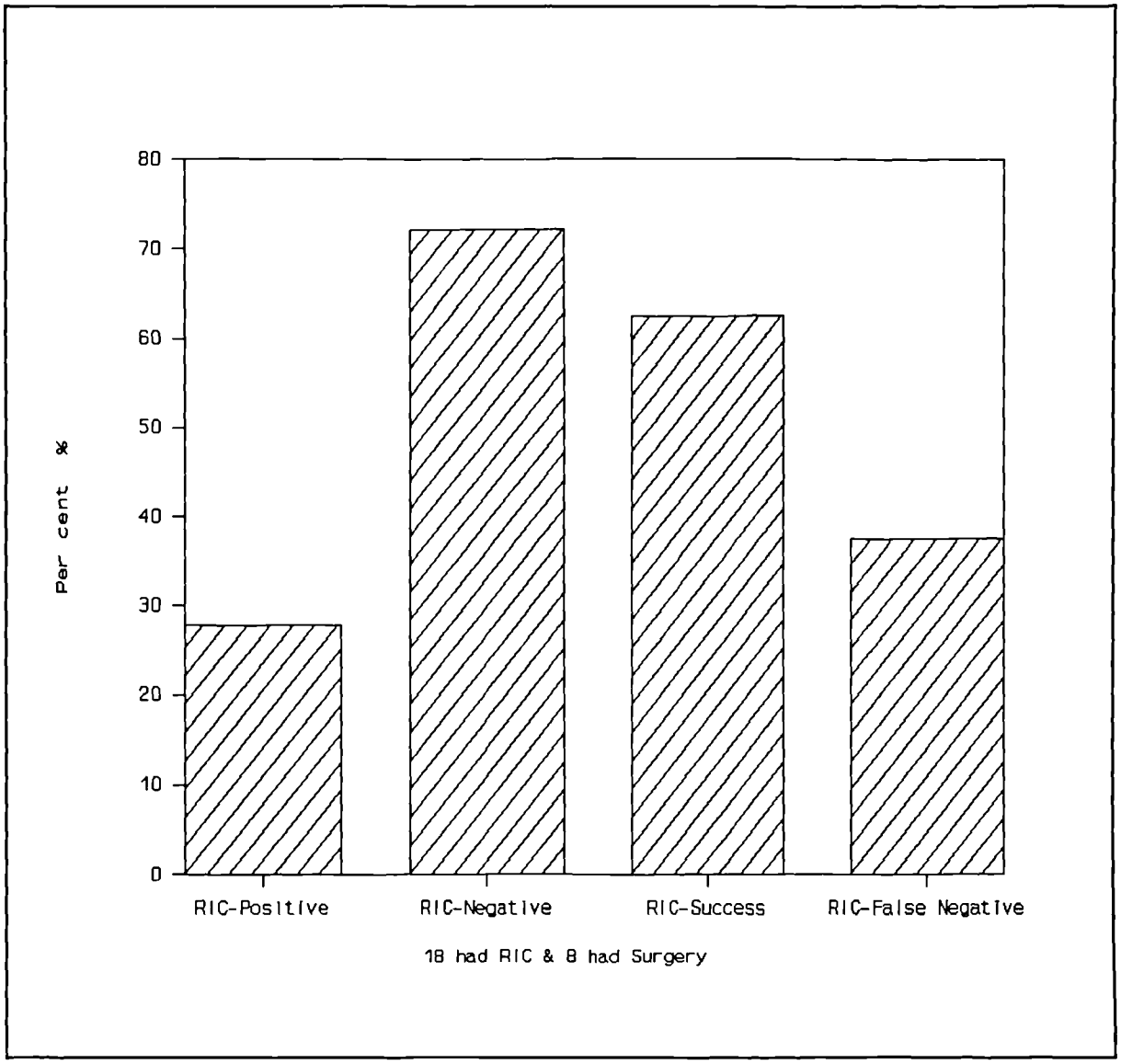


Figure 7-9; Summary of the results of radioisotope cisternography (RIC) in 18 patients with suspected CSF fistulae.

Table 7-1 summarizes the results of preoperative localization of CSF fistulae in the present study. Statistical analysis of proportions showed;

(1) Anterior cranial fossa tomography (ACFT) did not have any advantages over computed tomography (CT) of the anterior cranial fossa (Chi-square with Yates' correction = 0, d.f = 1, $p > 0.05$).

(2) Iohexol-computed tomographic-cisternography (ICTC) was the best pre-operative investigation to localize CSF fistulae. Its success rate was 2.4 times that of plain CT (Chi-square (Yates' correction) = 18.1, d.f = 1, $p < 0.001$) and at least 1.5 times the success rate of radioisotope cisternography (Chi-square (Yates' correction) = 5.04, d.f = 1, $p < 0.05$).

Table 7-1; Summary of the results of pre-operative localization of suspected CSF fistulae;

Radiology	Anterior Cranial Fossa Tomography ACFT	Plain Computed Tomography CT	Radio-isotope Cisterno-graphy RIC	Iohexol Computed Tomographic Cisternogr-aphy (ICTC)
Total No.	59	66	18	34
Positive *	11 (18.6%)	13 (19.7%)	5 (27.8%)	22 (64.7%)
Negative	48 (81.4%)	53 (80.3%)	13 (72.2%)	12 (35.3%)
Surgery No.	51	33	8	23
Success %	21.6	39.4	62.5	95.7
False % negative	78.4	60.6	37.5	4.3

* Positive means; in ACFT & CT showed a bony defect and in ICTC & RIC showed the possible site of CSF leak.

7,5 Discussion:

Accurate localization of CSF fistulae is very important to limit the extent of surgery, avoid negative exploration and reduce the operative morbidity. However despite modern technology, localization of CSF fistulae remains a difficult problem for both the neuro-radiologist and neuro-surgeon.

Anterior cranial fossa tomography (ACFT) has been used extensively to localize CSF fistulae in the past (Jefferson & Lewtas 1963). Anterior cranial fossa tomography demonstrated the possible site of CSF leak in 53 to 66 % of traumatic CSF leaks (Lantz & others 1980 and Manelfe & others 1983). However, it was positive in only 18.6 % of 59 CSF leaks of mixed aetiology in the present study. Furthermore, anterior cranial fossa tomography has been superseded by the high resolution of computed tomography (CT), confirming previous reports that anterior cranial fossa tomography has no advantages over CT scanning (Levy & others 1978 and Manelfe & others 1983). CT scanning, not only, showed the possible site of the CSF leak in 20-70% of cases studied, but it has also shown a significant number of intracranial aetiological and associated lesions. It is an essential initial investigation to detect intracranial mass lesions and obstructive hydrocephalus before embarking upon cisternography.

Cisternography using water-soluble, non-ionic contrast media (such as Iohexol or Metrizamide) and computed tomography with overlapping, fine slices, has shown a consistently high success rate (Drayer & others 1977, Dohrmann & others 1979, Ghoshhajra 1980, Naidich & Moran 1980, Cooper & Kassel 1982, Park & others 1983, Manelfe & others 1983 and Ahmadi & others 1985). It has replaced radioisotope

cisternography in some institutions (Cooper & Kassel 1982) and a success rate of 100% has been reported (Naidich & Moran 1980, Ghoshhajra 1980 and Ahmadi & others 1985). Contrast (Metrizamide or Iohexol)- computed tomographic cisternography has the following advantages;

(1) More precise in localizing CSF fistulae due to the high resolution of the CT scanner.

(2) Readily available, as most neurosurgical units possess CT scans and fluoroscopy, but not many units possess a gamma camera. The contrast is stable and can be stored in the department.

(3) Safe, simple, easier to handle and repeatable.

(4) Quicker than radioisotope cisternography.

Contrast-CT-Cisternography is more sensitive and more precise than radioisotope cisternography, (Chi-square with Yates' correction = 5.04, d.f=1 , $p < 0.05$). It is also more accurate than plain CT (Chi-square with Yates' correction = 18.1, d.f=1, $p < 0.001$). The combined results of this study and published data showed that the success rate of contrast-computed tomographic-cisternography was 92 % (Table 7-2 and Figure 7-10 & 7-11). Furthermore, its sensitivity can be enhanced, in the intermittent or slow CSF leaks, by electively raising the CSF pressure (Spetzler & Wilson 1978 & Naidich & Moran 1980) or by performing digital subtraction of the images (Byrne & Others 1990). There were no serious side effects and the reported complications, such as low pressure headaches and seizures, are not different from those reported after myelography.

*Table 7-2; The results of contrast-computed tomographic-cisternography in 114 cases of suspected CSF leaks (34 studied and 80 cases reported in the literature *);*

Type of CSF leak	Active Leak	Inactive leak	Total leaks
Total Number	99	15	114
Site localized	81 (81.8%)	9 (60%)	90 (79%)
Negative test	18 (18.2%)	6 (40%)	24 (21%)
Surgery No.	85	6	91
Confirmed at Surgery (Success)	78 (92%)	6 (100%)	84 (92%)
False negative %	7 (8%)	0	7 (8%)

* Break down of the 80 collected cases from the literature;

Authors (Year)	No.	Positive	Authors (Year)	No.	Positive
Ghoshhajra 1980	6	6	Naidich & Moran 80	3	3
Manelfe & Others 82	27	21	Cooper & Kassel 82	2	2
Park & Others 1983	7	5	Brandt & others 83	12	10
Ahmadi & others 85	7	7	Hubbard & others 85	3	2
Olofsson &Bynke 88	4	4	Byrne & others 1990	8	7
Okada & Others 1991	1	1 (Total = 80).			

Radioisotope cisternography (RIC) has been used extensively in the evaluation of CSF leaks before the arrival of CT scans (Ommaya 1976, Spetzler and Wilson 1978, Lantz and others 1980 and Mamo and others 1982). It demonstrated the possible site of CSF leakage in 25 to 80 % of cases (Ommaya 1976, Spetzler & Wilson 1978, Lantz & others 1980, Mamo & others 1982, Glaubitt & others 1983, Park & others 1983, Bret & others 1985 and Flynn & others 1987). The sensitivity of radioisotope cisternography

can be increased by delivering the radioisotope directly into the anterior cranial fossa via bifrontal burr holes (Mamo & others 1982). However, radioisotope cisternography can be misleading (Hubbard & others 1985) and despite using more invasive techniques to deliver the radioisotope, such as that employed by Mamo and his co-workers, the success rate did not exceed 85 % in the presence of active leakage. Furthermore, this invasive technique carried a false negative rate of 8.7 % and a false positive rate of at least 1.5% (Mamo & others 1982).

The only advantage of radioisotope cisternography is that it can confirm CSF leakage in suspected cases. For localisation of the leak, it is less precise, more time consuming (48 or 72 hours) and more difficult to handle. The radioisotope has to be preordered every time the test is required, as the isotope is less stable and requires quality assurance testing before its use. This makes radioisotope cisternography not readily available, when it is needed. The average success rate of radioisotope cisternography in 211 patients was 66.9 % (Table 7-3). Radioisotope cisternography was not as sensitive and successful in localizing CSF leaks as metrizamide-computed tomographic- cisternography (Chi-square with Yates' correction = 18.8 , d.f 1, $p < 0.0001$) Figure 7-10 & 7-11.

Adequate localization of CSF fistulae (22 patients using Iohexol-CT-cisternography and 5 patients using radioisotope cisternography) has reduced the failure rate and recurrence rate to 3.4 %. Furthermore, unilateral exploration was sufficient in 85 % of these patients (25/27), with no deaths or meningitis.

*Table 7-3; The results of radioisotope cisternography (RIC) in 211 suspected CSF leaks; (18 studied cases and 193 cases reported in the literature *);*

Type of Leak	Active leak	Inactive leak	Total leaks
Total number	186	25	211
RIC-positive	90 (48.4%)	7 (28%)	97 (46%)
RIC-negative	96 (51.6%)	18 (72%)	114 (54%)
No.had Surgery	129	16	145
Confirm at surgery (Success)	90 (69.8%)	7 (43.8%)	97 (66.9%)
False negative	39 (30.2%)	9 (56.2%)	48 (33.1%)

* Break down of the collected series from the literature:

	Authors	No.	Positive	Authors	No.	Positive	
1973	Greenblatt & others	2	2	1976 Ommaya		63	27
1978	Spetzler & Wilson	14	6	1980 Lantz & others	12	7	
1980	Naidich & Moran	5	5	1982 Mamo & others	40	11	
1982	Manelfe & others	2	2	1983 Glaubitt & others	12	3	
1985	Bret & others	10	8	1985 Kok & others	1	1	
1985	Hubbard & others	6	3	1987 Flynn & others	13	6	
1988	Bleach & others	1	1	1989 Bronstein & others	1	1	
1991	Okada & others		1	1 (Total cases 193)			

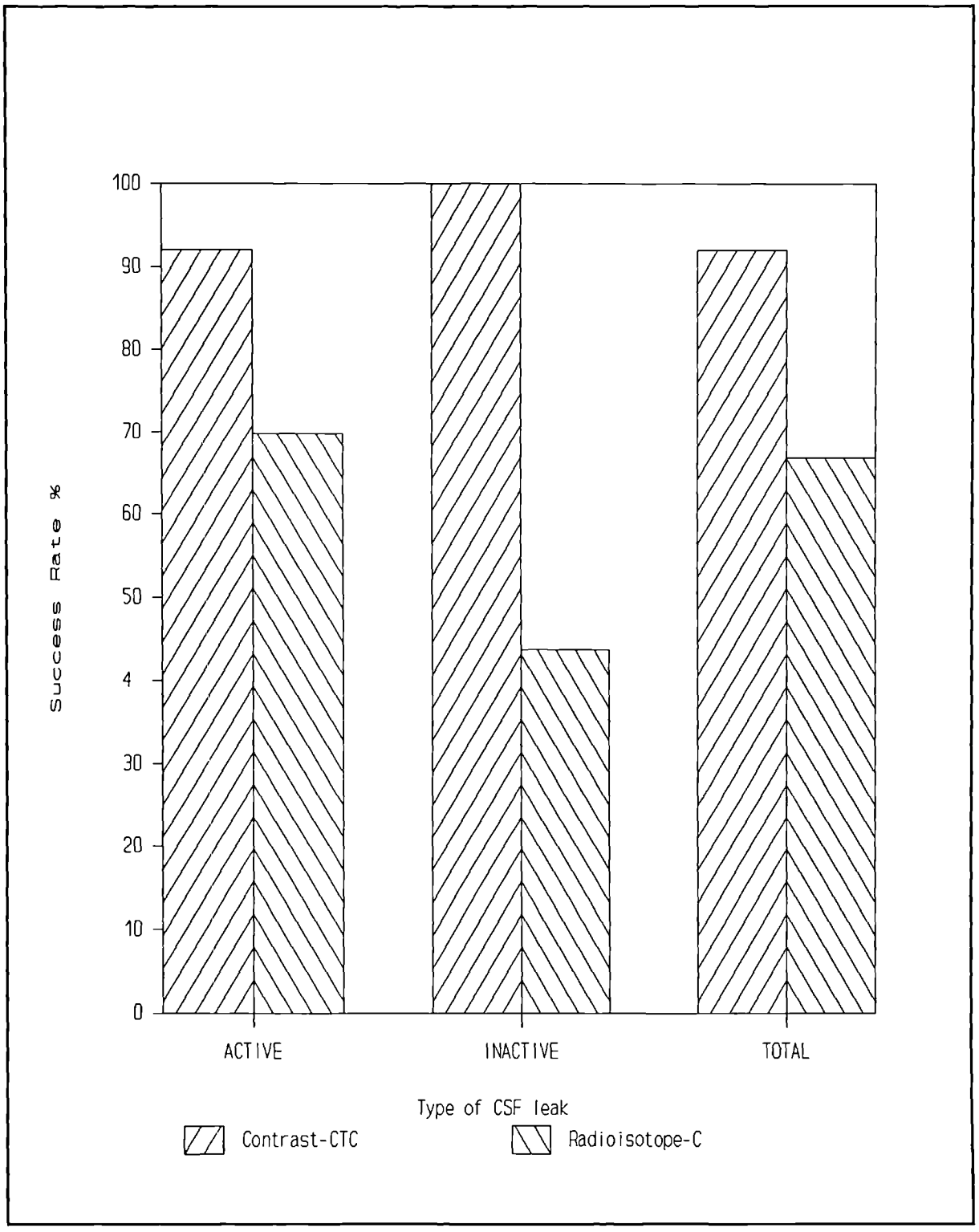
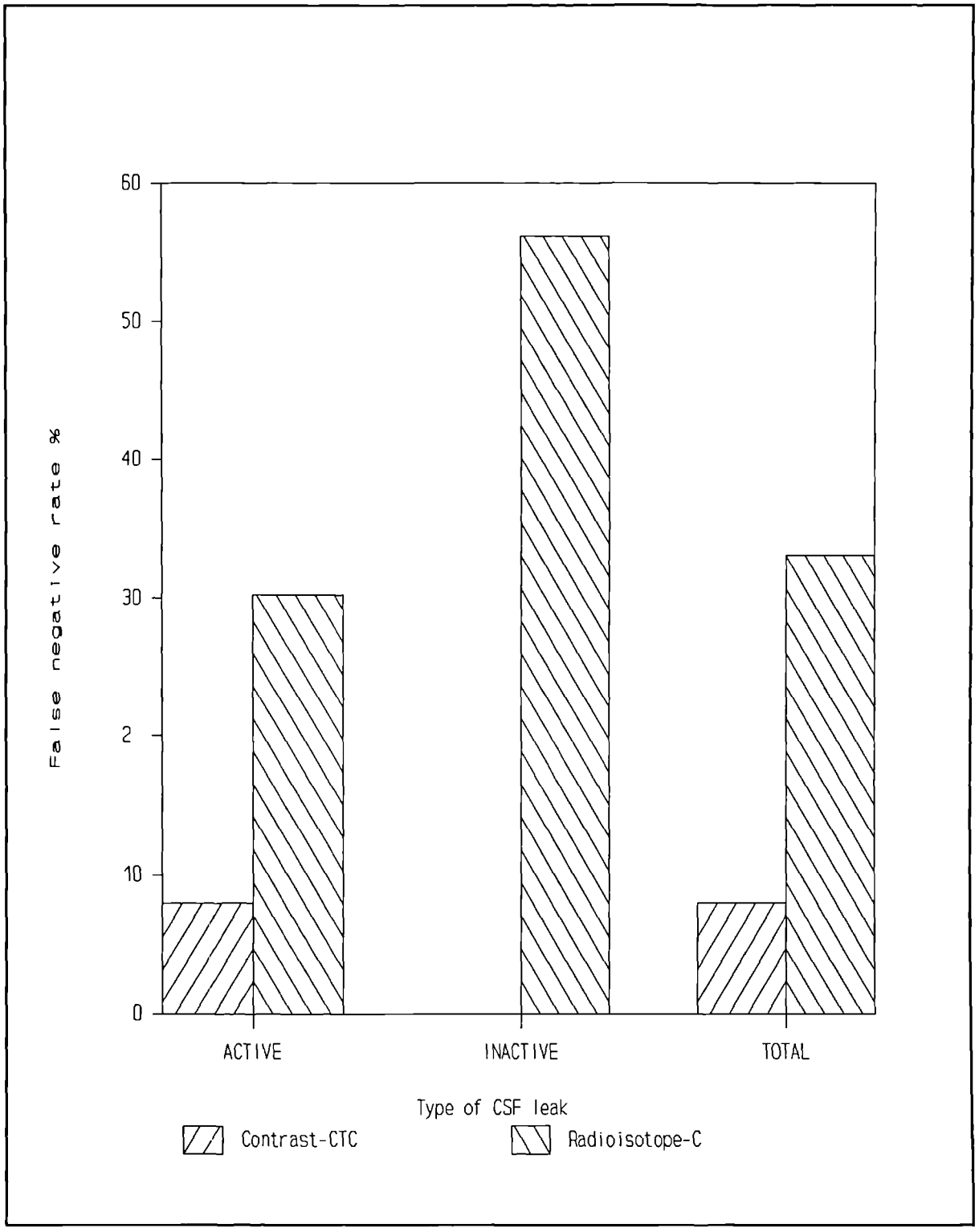


Figure 7-10; The success rate of Contrast-CT-cisternography (Contrast-CTC 114 cases) and of Radioisotope cisternography (Radioisotope-c 211 cases).

Figure 7-11; The false negative rate of contrast-Ct-cisternography (Contrast-CTC 114 cases) and of radioisotope cisternography (Radioisotope-C 211 cases).



7,5 CONCLUSIONS:

(1) Precise preoperative localization of CSF fistulae is very important to limit the extent of the surgical exploration and, therefore, reduce the operative morbidity. It is also important to increase the success rate of surgical repair and avoid negative exploration.

(2) With the arrival of high resolution computed tomography, anterior cranial foss tomography does not add to CSF leak localization. Furthermore, CT scanning is an important initial investigation in demonstrating associated intracranial lesions.

(3) Radioisotope cisternography is less efficient than contrast-CT-cisternography. It takes longer time to perform, more difficult to handle and less precise. However, it may be helpful in confirming suspected CSF leaks, when contrast-CT-cisternography is negative.

(4) Contrast (Iohexol or Metrizamide) computed tomographic cisternography is safe and readily available. It is easier to handle, more sensitive and quicker to perform than radioisotope cisternography. It has a high success rate of at least 92 % and it is more precise in localizing the site of the CSF leak due to the high resolution (bone / soft tissue differentiation) of computed tomography. The inactive CSF leaks can be demonstrated using this technique either by digitally subtracting the images or electively raising the CSF pressure.

Chapter 8

CONCLUSIONS

<*><*><*><*><*>

The literature on the management of cerebrospinal fluid fistulae remains controversial and at best unsatisfactory, because:

(1) The data on the long-term outcome of treated and untreated CSF fistulae is lacking and insufficient. There were no published studies of the long-term survival of patients with CSF fistulae and there was no comparison found between those who had surgery before and after the introduction of microsurgery and CT scanning.

(2) The lack of accurate and precise diagnostic tests to identify patients with CSF leakage.

The purpose of this thesis was to provide this vital information and examine a new technique of CSF identification, so as to provide guidelines for the management of CSF fistulae. The following is a summary of the conclusions reached in this thesis:

(1) CSF identification and the diagnosis of CSF leakage:

The diagnosis of a CSF leak can be made beyond doubt by analyzing the fistulous fluid, using the Paragon^{R} immunofixation technique to identify the B_2-Transferrin band. The sensitivity of this technique is very high and the specificity is over 99 %. It is non-invasive, carries no risk to the patient, has no contraindications and is relatively cheap and quick. In comparison, the Glucose-Oxidase stick test proved to be non-specific and inaccurate (X^2 44.39, df = 1, $p < 0.00001$).

(2) The natural history and the long-term survival free from meningitis of unrepaired CSF fistulae:

Patients with unrepaired CSF fistulae are at continuing risk of meningitis, irrespective of the onset, the duration and the aetiology of the CSF leakage. The survival free from meningitis was less than 42 % at 10 years follow up. The actuarial risk of developing meningitis was 2.4 % per week (1-4 weeks after CSF leakage), 3 % per month (1-12 months from the onset of CSF leak) and 9.8 % per year thereafter. The most significant adverse prognostic factor for developing meningitis, in patients with unrepaired CSF fistulae, was CSF rhinorrhoea (Hazard ratio 2.34). Meningitis, complicating unrepaired CSF fistulae, was potentially fatal and carried substantial morbidity. This treacherous course of meningitis in some patients is the result of regional deficiency of both humoral and cell-mediated immunity (Scheld & Kealy 1983, Simberkoff & others 1980 and Bernbardt & others 1981). Prophylactic antibiotic treatment, in patients with unrepaired CSF fistulae, did not significantly reduce the risk of developing meningitis (logrank test $Chi^2(2)$, $p > 0.05$). Furthermore, it was associated with an increased number of cases of Gram negative meningitis and failure to isolate the pathogen from the CSF (Chi^2 5.7, df1, $p < 0.01$).

(3) The role of surgical dural repair in the management of CSF fistulae:

The long-term prognosis of patients, who underwent surgical dural repair is excellent. Surgical dural repair has significantly reduced the risk of meningitis with very low morbidity and mortality (logrank test $Chi^2(2)$, $p < 0.001$). The most significant adverse prognostic factors for post-repair meningitis were recurrent CSF leak (hazard

ratio = 2.09) and failure of dural repair (hazard ratio = 1.06). Intradural surgical repair carried a very high success rate and a low mortality and morbidity rates. It can be performed through a unilateral exploration, which can be extended to the other side or middle cranial fossa without increasing the morbidity and mortality of surgery. The repair can be undertaken as early as possible in the fit patient without increasing the morbidity or mortality of the operation. Pericranial and / or temporalis fascial graft were as good as fascia lata in achieving dural repair without the added risk of the thigh procedure. Microsurgery and computed tomography have led to improvements in both the short- and the long-term results of surgery. The differences were not statistically significant because microsurgery & computed tomography were introduced gradually and there was a learning curve of the newly adopted techniques.

(4) The value and timing of reduction of fractures of the middle third of the face in patients with traumatic CSF fistulae:

Facial reduction, of the associated middle third facial fractures in patients with CSF fistulae, increased significantly the success rate of surgical dural repair (Chi^2 = 4.21, df1, $p < 0.05$). HIowever, when it was performed before dural repair it did not prevent meningitis and it significantly worsened the CSF leak (Chi^2 = 6.3, df1, $p < 0.01$). This could be due to the fact that most patients in this study had skull vault fractures and significant head trauma. The value of facial reduction in patients with CSF rhinorrhoea and facial fractures without skull vault fracture was not possible to determine in this thesis because there were only three such patients in this study. Facial reduction can be performed early at the time of surgical dural repair without additional morbidity or mortality.

(5) CSF drainage in CSF fistulae:

CSF diversion procedures were helpful in treating patients with recurrent CSF leaks. However, on their own, they did not prevent meningitis and were not successful most of the time. Furthermore, CSF drainage without repair predisposes to tension pneumocephalus.

(6) Preoperative localization of CSF fistulae and selection of patients for surgery:

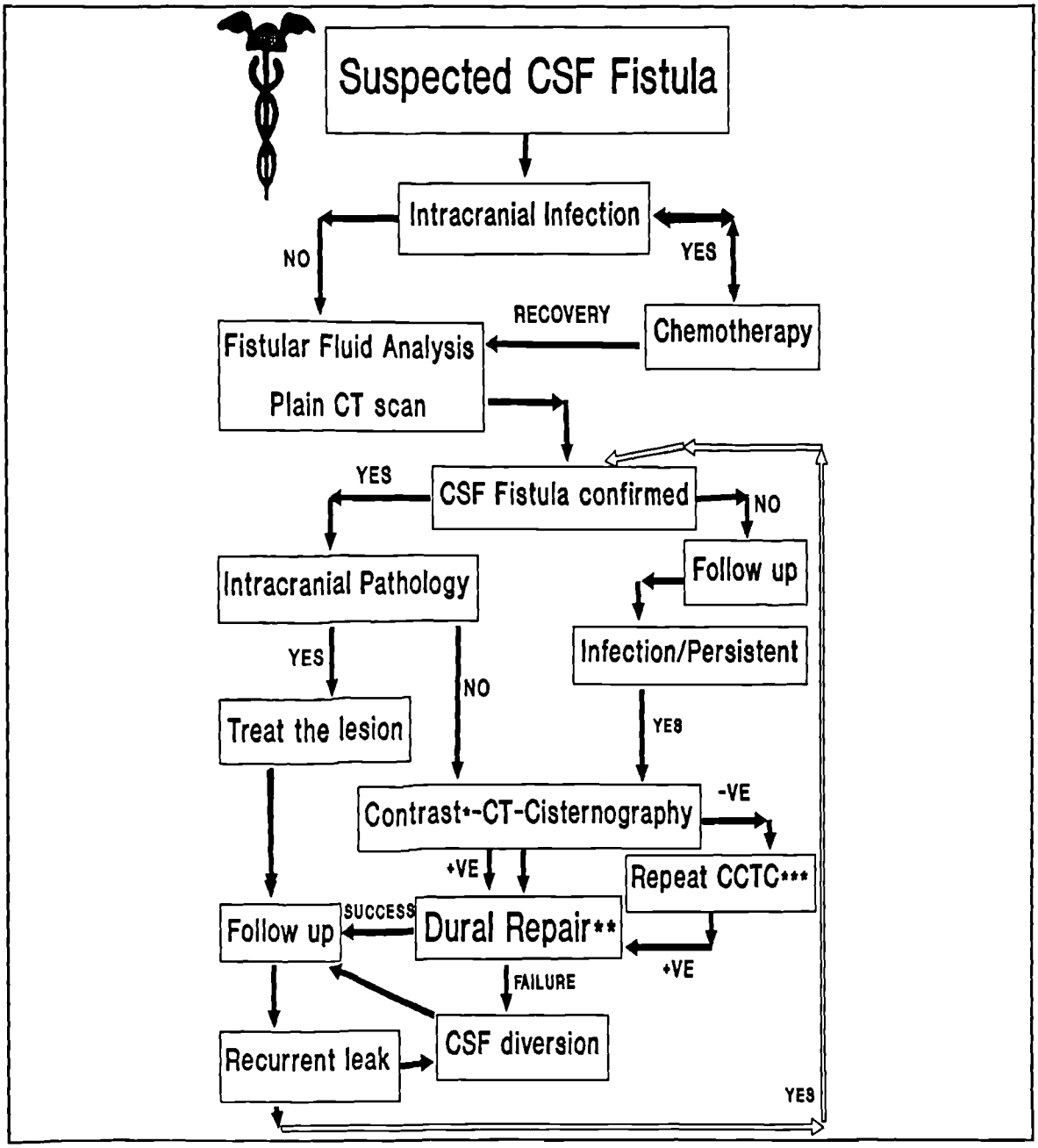
Preoperative localization of CSF fistulae was helpful in limiting the extent of surgical exploration and increasing the success rate of the dural repair.

Polytomography did not have any advatages over computed tomography in patients with CSF fistulae. Computed tomography (CT) was a valuable initial investigation in patients with suspected CSF fistulae. Although its identification of the site of CSF leak was limited, it was important in detecting or excluding associated intracranial lesions. Radioisotope cisternography (RIC) was inefficient and sometimes misleading. However, it may have a place in investigating CSF fistulae, when computed tomography is not available. Water-soluble, non-ionic contrast-computed tomographic cisternography was the most sensitive and the most successful preoperative localization technique in CSF fistulae. It is safer and more precise than radioisotope cisternography. This study confirms the findings of previous studies of smaller number of patients.

This thesis, therefore, has established that accurate diagnosis of CSF leakage is possible using the Paragon^{R} immunofixation technique for B_2-Transferrin . Surgical dural repair combined with early facial reduction or CSF drainage when indicated, in the post microsurgery and computed tomography era, is safe and highly successful in preventing meningitis. The long-term prognosis of these patients with CSF fistulae is excellent after surgical dural repair. Preoperative localization, using water-soluble, nonionic contrast computed tomographic cisternography, and surgical dural repair, therefore, should be offered to any patient with a definite CSF fistula. Surgical repair should be performed as soon as the patient is fit for surgery. While the patient is waiting for surgery, a constant vigil for early detection of intracranial infection should be maintained, introducing appropriate therapy should meningitis develop.

Based on this thesis and the relevant previous clinical studies, the management of patients with CSF fistulae can be formalized according to the guidelines outlined in the following flow chart.

Flow chart for CSF fistulae management:



* Water-soluble, nonionic contrast medium

** Reduction of fractures of middle third of the face or CSF diversion in high pressure CSF fistulae.

*** Repeating the contrast-CT-cisternography, should involve maneouvers to increase CSF pressure.

Appendix A: Data Collection Form:

Patient identification:
Surname Initials Study No.
Date of birth Age
Address Sex []M []F

Tracing records:
Hospital No.
Date of admission Consultant
Family Practitioner
Address

CSF fistula details:
Symptoms;[] Rhinorrhoea [] Otorrhoea
[] Both [] Neither
[] Other
Type [] Traumatic;A=accidental;Type.....
B=postsurgical .....
[] Non-traumatic A=normal pressure
B=high pressure

Course of CSF leakage:
Onset; []Immediate [] Early (1-7 days)
[] late > 7 days [] Recurrent
Duration
Stopped;[]spontaneously []surgically
[] Persistent

Associated factors: [] None [] Yes if yes ;
[]Skull fractures type; {}frontal {}temporal {}basal {}other.....
[]Facial fractures type; {}nasoethmoid {}Le Forte II {}Le Forte III {}other.....
[]Intracranial mass; {}haematoma type..... {}Tumour type.....
[]Previous head injury; Date [] Previous surgery; Date
Outcome..... {} ENT nasal {}ENT ear
Type of trauma {}Transphenoidal {}ACF crani.
{]PCF craniectomy {}Other
[]Other
[] aeroceles {} No {} Yes

Antibiotic prophylaxis ; [] NO [] Yes if yes;
Type (Specify)..... [] Duration
Time of start from CSF leak [] immediate [] early (1-7 days) [] late (>7 days)

Meningitis; [] No [] Yes if yes;
Number Time from CSF leak of each episode;
Organism Antibiotic treatment
Complications; [] *none* [] death [] abscess [] recurrence
[] hydrocephalus [] neurological deficit (specify)......

Relation of CSF leak to facial manipulation:
[] not applicable [] leak stopped before manipulation of face (FM)
[] leak stopped before and recurred after FM [] leak began after FM [] no effect
[] leak stopped following FM [] leak made worse after FM .
[] type of FM.....

Maximum follow up prior to dural repair;
Duration Source
Result; [] dead [] meningitis [] recurrent meningitis [] other

Preoperative investigations:

[] Plain Skull radiographs: [] Yes [] No
Findings;.....

[] Polytomography: [] Yes [] No
Findings;.....

[] CT scan: [] Yes [] No [] Fracture..... [] Aerocele
[] Haematoma [] Bony defect [] Other.....

[] Iohexol-CT-cisternography: [] Yes [] No
[] Negative [] Fistula localised [] Suspected site
Site .....
[] Reactions.....

[] Radioisotope cisternography: [] Yes [] No
[] Negative [] Fistula localised [] Suspected site.....
Site suspected.....
[] Reactions .....

[] Other investigations: .....
Findings: .....

Surgical intervention:

[] Dural Repair:
[] Yes [] No
[] Intradural [] Extradural
[] Unilateral [] Bilateral
[] others .....
[] Reason of repair:
[] Intracranial infection.
[] Persistent CSF leakage (>7day)
[] Recurrent CSF leakage.
[] Prophylactic
[] Time from the onset of CSF leak .....
[] Graft:
[] Fascia lata [] Pericranium
[] Temporalis fascia [] Temporalis muscle
[] Tisseel glue [] Xenaderm
[] Other .....

[] CSF drainage:
[] Yes [] No
[] Lumbar [] Ventricular
[] Drain [] Shunt
[] Timing of CSF drainage:
[] Before repair [] After repair
[] Reason:
[] Recurrent CSF leakage.
[] Hydrocephalus.
[] High CSF pressure.
[] Time from CSF leak

Operative Findings:

[] Negative exploration. [] Repaired [] No repair
[] Number of fistulae found;.....
[] Fistula site:
[] Frontal sinus [] Cribriform plate
[] Ethmoids [] Sphenoid sinus
[] Petrous bone [] Internal auditory meatus

Surgery-associated complications:

[] None [] Death [] Focal neurological deficit .....
[] I C Haematomas [] Thrombo-embolism .....
[] Chest infection [] Wound & flap infections .....
[] Other .....

Long-Term outcome measures:

[] Meningitis (number & pathogen).....Time from repair.....
[] Recurrent leak time from repair.....
[] Seizures time from repair .....

Subsequent Surgery:

[] Number..... [] Type.....
[] Indication.....
[] Outcome.....

Details of Follow up:

[] Maximum follow up period from surgery .....
[] Follow up source [] Medical records [] Family Health Services Authority
[] General practitioner [] Outpatient visit.
[] Outcome at 3 months .....
[] Outcome at 6 months .....
[] Outcome at 12 months .....
[] Final outcome .....
[] Cause of death .....

COMMENTS:

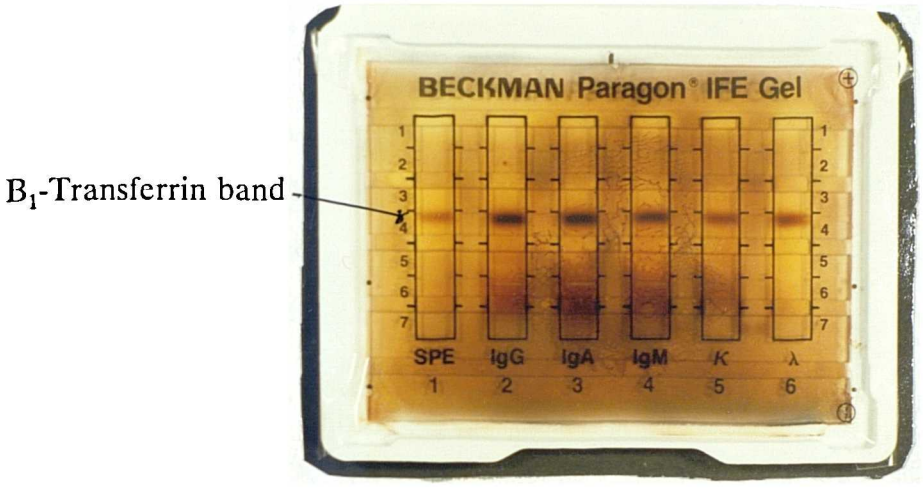
Appendix B

Photographs of the results of two Paragon^{R} immunofixation

Gel (A) Shows 6 samples all of which show a single transferrin band B_1-transferrin;

Samples 1,5 & 6 containing Wound Discharges

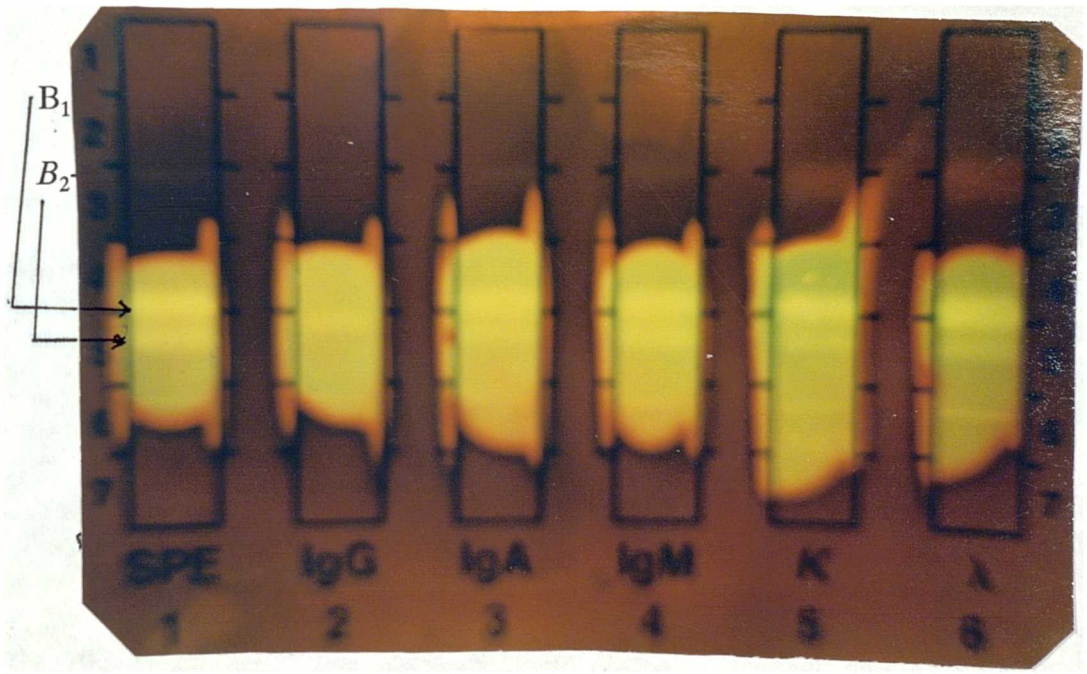
Samples 2,3 & 4 containing blood.



Gel (B) Shows:

Samples 1,3,4,5 & 6 show two transferrin bands and they are CSF samples

Sample 2 shows single transferrin band and it is Nasal Secretion



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MY CONTRIBUTION IN THE WORK PRESENTED IN THIS THESIS:

I have collected all the samples used in this study, with the exception of those obtained during myelography, which were collected for me by the neuroradiologists. I carried out all the necessary preparations of the samples, silver stain reagents and the working antiserum solution. The barbital buffer and polyethylene glycol buffer were prepared by the M.S.L.O's of the neurobiochemistry laboratory. I carried out the electrophoresis, immunoprecipitation, staining and the glucose-oxidase testing of the 114 samples. The sensitivity of the Paragon^{R} immunofixation technique was performed in conjunction with the M.S.L.O's in the neurobiochemistry laboratory.

I have traced the clinical material from the medical records and the neuro-radiology, neuro-theatres, disease index and patient information data bases. I reviewed all the clinical records and wrote to the Family Health Services Authorities (FHSA's) and family practitioners to update the follow up data. I created a data-base using an LT 386SX/P computer to store, manipulate and recall the follow up information. I have seen personally the patients with CSF leakage admitted during 1988 to 1990.

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