MANAGEMENT PROBLEMS IN ANEURYSMAL SUBARACHNOID HAEMORRHAGE.

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This thesis is my own unaided work, apart from assistance obtained with the statistical format.

The work has not been submitted previously, nor is it to be submitted for a degree in any other University.

J. Golek

I dedicate this thesis to Lidia and Barnaba whose sacrifices made it possible.

J. Golek

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ABSTRACT

A retrospective review was made of the case records, angiograms and computed tomography (CT) relating to a total of 263 patients with subarachnoid haemorrhage (SAH) due to ruptured berry aneurysms who were admitted to the Department of Neurosurgery, Wentworth Hospital during the four years 1983-1986.

The part of the thesis concerning vasospasm (VS) includes two independent studies on calcium blocker Nimodipine (N®) in the prevention and treatment of VS done by the author.

The aim of the thesis is to analyse the management problems of aneurysmal SAH, and investigate factors influencing outcome in order to establish the best possible management policy.

The results are discussed and related to the recent data from literature. The main factors influencing outcome were: clinical condition of the patient, the timing of admission and surgery, hypertension and hyperglycaemia on admission, presence of vasospasm and related CT appearance of a thick layer of blood or clot in subarachnoid haemorrhage (CT-Fisher 3).

The systemic administration of the calcium blocker nimodipine did not reverse or prevent delayed vasospasm

and caused serious adverse effects i.e. hypotension and hyperglycaemia.

The results of the thesis suggest a change in management policy and timing of surgery should depend on clinical condition of the patient on admission (Hunt & Hess grading)(H&H).

I/II grade (H&H) patients should be operated on as early as possible regardless of timing of admission and results of radiological investigations (CT, angiography). Early surgery (1-3 days) should be the aim of the effort including referral, transport and hospital organisation.

III grade (H&H) patients should be operated on as early as possible, provided radiological investigations do not carry high risk factors i.e. CT-Fisher grade 3, severe angiographic vasospasm. When the latter is present, surgery should be performed soon after day 10 post-SAH. Particular attention should be paid to the careful preparation and selection of patients for angiography.

IV/V grade (H&H) patients should be treated conservatively in specialised units as sooon as possible, preferably neurological or neurosurgical wards, and operated on as soon as their grade improves or, in selected (by surgeon, radiologist and anaesthetist) cases by delayed surgery (after day 10 post-SAH).

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LIST OF ABREVIATIONS (Alphabetically) :

A1	- A_1 segment of anterior cerebral artery
ACoA	- Anterior communicating artery
ATP	- Adenosine triphosphate
BP	- Blood Pressure
CBF	- Cerebral blood flow
CSF	- Cerebro-spinal fluid
CT	- Computerized tomography
CT-Fisher 1 2 3 4	Grading of subarachnoid haemorrhage by computerised tomography according to Fisher et al (35).
EACA	- Epsilon-amino-caproic acid
EC	- Energy charge of adenine nucleotide pool
FFA	- Free fatty acids
FID	- Focal ischaemic deficit
Fig.	- Figure
GCS	- Glasgow Coma Scale
GOS	- Glasgow Outcome Scale
H&H I/II III IV/V	Grading of clinical condition according to Hunt & Hess (49)
HT	- Hypertension
ICA	- Internal carotid artery
ICH	- Intracerebral haematoma
ICP	- Intracranial pressure
ICPM	- Intracranial pressure monitor

Abreviations contd.

LP	- Lumbar puncture
MCA	- Middle cerebral artery
n	- Number, sample size
N®	- Nimodipine (Nimotop®)
N.S.	- Statistically non-significant
Op	- Operation
p	- Level of statistical significance
PCoA	- Posterior communicating artery
pH	- The logarithm, on the base ten, of the reciprocal of the hydrogen-ion concentration
RB	- Rebleed
SAH	- Subarachnoid haemorrhage
SD	- Standard deviation
SEM	- Scanning electron microscopy
V-B	- Vertebro-basilar system of cerebral vessels
VS	- Vasospasm
$\bar{x}$	- Mean

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1. INTRODUCTION

"When a person is pained in the back of the head he is benefitted by having the straight vein in the forehead opened."

Hippocrates on Subarachnoid Haemorrhage (147)

It was only in 1859 that symptoms and signs of a subarachnoid haemorrhage (SAH) were described more lucidly by Gull (135). With the use of lumbar puncture (LP) introduced by Quincke in 1891 (147), a major step towards diagnosis was made and even more important was the initiation of cerebral angiography by Moniz in 1927 (96). He demonstrated an intracranial aneurysm by angiography for the first time in 1933 (95). The next major diagnostic advance was almost fifty years later, in the mid seventies, when the use of computerised tomography imaging (CT) became widespread.

The first malleable clips were introduced by Cushing in 1911 (142), but they were inappropriate for surgical clipping of aneurysm. Thereafter Schwartz introduced spring clips modified by Mayfield and others and these were standard clips for aneurysm surgery for many years (84).

The main approach to intracranial aneurysm was initially

based on the Hunterian principle of ligating the feeding artery to induce thrombosis within the aneurysm. Sir Victor Horsley first accomplished this in 1885 by occluding the cervical carotid artery to treat an ipsilateral intracranial aneurysm (147).

The first planned intracranial operation for saccular aneurysm by wrapping muscle around it was performed by Dott in 1933 (29) and the first successful clipping of the neck of a pre-operatively diagnosed aneurysm was done by Dandy in 1938 (27). Major breakthroughs in modern aneurysmal surgery were - the introduction of intraventricular catheters and principles of intracranial pressure monitoring (ICPM) by Lundberg in 1960 (82), and the introduction of microneurosurgery (72).

Bleeding from a cerebral aneurysm is the major cause of SAH (77%) and is responsible for approximately 28% of all deaths due to cerebrovascular disease before the age of 60 years (59,80,147).

In a forensic series, Pakarinen (103) found ruptured aneurysms in 2-5% of unselected postmortem cases. Based on data from an autopsy series, it was estimated that about 2% of the entire population would have an aneurysm; such an intracranial aneurysm would rupture in less than 1% of the population, and would be the cause of death in 0,5% (57).

Operative results in the pioneer period were not encouraging (32,81). Studies by McKissock and his colleages (87,88,89) comparing conservative and surgical treatment in the early sixties, showed that overall results were not improved by surgery (mortality rate 35%). However, Pakarinen (103) in his superb study of the natural history of aneurysms, showed that those survivors from a first SAH who had been managed conservatively had a 35% mortality within a year and a 51% mortality within five years, the remainder dying subsequently at a rate of 3,3% a year.

As the rate of rebleeding continued to be high in conservatively treated patients beyond six months after the first SAH, it became generally accepted that surgery was justifiable, as long as the operative mortality was lower than the natural rate.

Since the introduction of micro-neurosurgery in the early 1970's and with progress in neuroanaesthesia, intensive care and increasing surgical experience, results have improved dramatically and operative mortality has ranged between 3% and 15% (1,48,72,143,146).

A number of factors have been reported to influence operative results including pre-operative condition (24,49,50,60), vasospasm (9,10,49), timing of surgery (67), systemic hypertension (8,48,72,108), and site and

number of aneurysms (6,87,88,89). However, the relationship between these clinical factors and their combined effect on the patient's ultimate fate remains unclear and a detailed study of this subject has not been done in South Africa.

2. THE AIM OF THE THESIS

i) To analyse the management problems of aneurysmal SAH encountered in the Department of Neurosurgery of the Faculty of Medicine, University of Natal, at Wentworth Hospital during the years 1983-1986.

ii) To investigate possible factors influencing the outcome of patients admitted after SAH due to ruptured berry aneurysms.

iii) To evaluate calcium blocker Nimodipine (N ®) in the prevention and treatment of vasospasm.

iv) To establish the best possible management policy locally, in order to improve management results.

3.LITERATURE REVIEW

3.1. INCIDENCE OF BERRY ANEURYSMS

Age:

The incidence of aneurysm rupture is highest during the 4th, 5th and 6th decade of life (118). Aneurysms seem to be rare in children especially during the first decade (85,125). The co-operative aneurysm study (114) included one case of aneurysm in a child under 4 years of age. Patel & Richardson (104) found that among 3 000 cases of aneurysm, only 58 patients were under 20 years of age and none were under 2 years of age. Pakarinen (103) found no cases involving children among 511 patients. In his review of the literature the prevalence in each decade was as follows -

1st	-	1%
2nd	-	2%
3rd	-	6%
4th	-	15%
5th	-	26%
6th	-	28%
7th	-	16%
8th	-	6%

Therefore 85% of the aneurysms encountered fell between the 4th and 7th decade with decreasing incidence in younger and older patients.

Phillips et al (107) showed a steadily increasing incidence of aneurysms with increasing age level when correction was made for the smaller numbers of old people in the population.

Sex:

Weir (142) in his review, combined large series of cases of Sahs (114), Suzuki and Yoshimoto (129) and Pakarinen (103) with regard to sex/age distribution, and found a clear female predominance of 56% against 44% in males. There was, however, a tendency for males to predominate until about the 5th decade. There was definite predominance of females in a ratio 2 : 1 in internal carotid artery aneurysms. Middle cerebral artery aneurysms were only slightly more common in men.

Geographic & Racial Factors:

There are very few reports on this subject. Ramamurthi (109) indicated that aneurysms may be less common in India. The Japanese may have a higher incidence of aneurysm when compared with people in the Western hemisphere (128). These statistics are difficult to verify in the absence of population incidence figures and because the proportion of cases diagnosed may be low in developing countries.

Anatomical sites of aneurysm:

Ninety-five percent of aneurysms arise in close relation

to the Circle of Willis (114). The most common site of aneurysm is the region of the anterior communicating artery (ACoA) (30,3%) then posterior communicating artery (PCoA)(25%) and the middle cerebral artery bifurcation (MCA)(13,1%).

Giant aneurysms have a diameter larger than 25mm and have an incidence of 2% (129). Multiple aneurysms occur in 15% of aneurysm patients, according to angiographic evidence. However, in an autopsy series, the incidence of multiple aneurysms is much higher and reaches 22% and they are more common (74%) in females (114). The same study shows that in 47% multiple aneurysms occur on both sides, 21% are on the same side, 29% have one each in the midline and on one side and 3% have both in the midline.

3.2. INVESTIGATIONS

Lumbar puncture (LP):

For many years lumbar puncture has been the most important diagnostic procedure (31,147). Blood-stained cerebro-spinal fluid (CSF) should be centrifuged or left to stand to show xanthochromic supernatant although exceptionally, in less than 2% of cases, it may be clear.

Blood may be cleared from CSF from 24 hours to 24 days, while xanthochromia is usually present after 12 hours (31,142). More recently, however, there have been reports of the potential danger of LP in SAH (31,46) and

preference has been given to the CT for diagnosis of SAH, reserving LP for cases of suspected meningitis (56). Restricted availability of CT scan facilities however has made the omission of lumbar puncture impractical in many cases.

High resolution computed tomography (CT):

This has become the procedure of choice for the detection of SAH and the localisation of intracranial aneurysm (21). Subarachnoid haemorrhage in the presence of a bleeding aneurysm will be detected in more than 95% of patients in the first 24-hours, in almost 75% on day three, and in over 50% at the end of the first week from ictus. LP should be done only if the unenhanced CT does not demonstrate SAH, and in the absence of an intracranial mass.

In addition to SAH the unenhanced study should be evaluated for intraventricular or intracerebral haemorrhage, hydrocephalus and infarcts. Out of 1378 SAH patients included in a co-operative study, fewer than 10% of patients examined had a completely normal CT (67). Subdural haematomas occur in 1-8% of patients (42). The location of subarachnoid blood may frequently suggest the site of the bleeding aneurysm.

Enhanced CT studies should be performed for several

reasons. They will identify the cause of the SAH in most patients, confirm the localisation of the lesion, and aneurysms of a diameter above 5mm may be demonstrated (21,105,145).

In most of the cases then, CT can establish diagnosis and localisation so that definitive angiography can be deferred in seriously ill patients. The CT scan has proved to be a useful diagnostic tool in vasospasm because it can show evidence of cerebral ischaemia (3,73,144). Fisher(35) in a preliminary study in 1980 indicated that blood localised in the subarachnoid space in sufficient amounts (clot or thick layer) and at specific sites, is the only important aetiological factor in vasospasm, has a strong predictive value and identifies the patient in jeopardy from vasospasm requiring early preventive measures.

In a prospective study Kistler et al (70) were able to predict accurately the incidence of delayed vasospasm using similar criteria.

Cerebral angiography:

The ultimate diagnosis of berry aneurysms is achieved by complete transfemoral cerebral angiography (21). Angiography is essential to show the anatomical relation of the aneurysm to its parent vessel, also the presence of vasospasm and its extent. Angiography is usually done shortly before surgery and may be delayed in patients in serious neurological condition and/or at risk of

vasospasm.

Angiography is an invasive procedure carrying certain risks. Rupture of the aneurysm during angiography has been reported (38,98). Lilliequist (75) states that rapid injection of large amounts of contrast medium, during angiography, causes a dangerous rise in blood pressure which in turn may lead to aneurysmal rupture. This risk increases when there is already hypertension, raised intracranial pressure or vasospasm. Hyperosmolar contrast material might have a vasodilating effect that counteracts the acute vasoconstricting "sealing" effect of blood (71), and may damage the brain by passing through a fragile blood-brain barrier (12,116).

A review of the cases of aneurysmal rupture during angiography by Koenig et al (71) showed that these patients tended to be in poor condition with 18% being in serious and 32% moribund at the time of angiography. Fifty-three percent of the investigations were done within 12-hours of admission to the hospital and mortality of extravasation was 84%.

3.3. FACTORS INFLUENCING OUTCOME IN PATIENTS WITH SUBARACHNOID HAEMORRHAGE.

Definition of outcome:

Jennett and Bond (58) described a limited number of outcomes which can be recognised after brain damage. As SAH following ruptured aneurysm is a "brain disease"

causing brain damage of varying extent, it is widely accepted that the Glasgow Outcome Scale (GOS) be applied to the results of management of SAH.

The grades therefore are -

good recovery

mild disability

severe disability

persistent vegetative state

death

In most reviews dealing with assessment of outcome following SAH it is further simplified to -

favourable (good) outcome (i.e. good recovery and mild disability with patients capable of returning to their normal activities prior to SAH);

and

unfavourable (bad) outcome (i.e. severely disabled, persistently vegetative or death).

The more detailed statistics on outcome of SAH patients deal not only with physical and occupational aspects, but use sophisticated methods to assess multiple factors, including psychological and social, to define more precisely the so-called "favourable" outcome (9,10,124).

In 1974 Hunt & Kosnik (50) first alluded to the concept of

"overall mortality" in discussing the efficacy of management of SAH. This concept was expanded and re-emphasised by Hunt and Miller (51) and by Post et al (108) in 1977. Weir and Aronyk (138) called this "management morbidity and mortality".

Operative mortality:

Number of patients dying within 30-days of operation expressed as a percentage of those operated.

Management mortality:

The sum of operative deaths and non-operative deaths during the period of study expressed as a percentage of the total cases. It is more significant than operative mortality and morbidity, since these can be quite low after recovery from SAH (8,112).

3.3.1. PRE-OPERATIVE NEUROLOGICAL CONDITION

Neurosurgeons recognised very early that the initial condition of the patient is a strong prognostic factor. Various gradings have been adopted in the literature and similarities as well as discrepancies have been reported (76). Botterel (24) introduced, in 1956, a grading which was accepted and is used by some surgeons even today. Hunt & Hess (49) introduced in 1968, a system of grading (H & H) based mainly on recognition of vasospasm as the

main risk factor.

In a study by Jomin et al (60) of patients operated on without any disturbance of consciousness (grades I and II H&H) the cure rate was 90,3% and mortality rate 4,9%. On the other hand, when patients in groups III-V were operated upon, 38,6% were cured, 27,5% had poor results and 33,8% died. Clouding of consciousness therefore stands out as being the most significant risk factor in cases of intracranial aneurysm. The prognosis is always bad when the coma cannot be explained by compressive haemorrhage.

3.3.2. VASOSPASM

Focal ischaemic deficits (FID) due to vasospasm (VS) is considered, apart from rebleeding, to be one of the most severe complications in the clinical course of SAH due to a ruptured aneurysm. VS was found to be the single important factor in predicting both mortality and morbidity (7). VS was first demonstrated angiographically by Ecker and Riemenschneider (33) in 1951. They postulated that VS might be a major factor responsible for the high morbidity and mortality in patients with a ruptured aneurysm and that VS observed post-operatively was associated with a poor outcome even though surgery had been performed uneventfully.

VS can be divided into early and late phases (141). It has been possible to reproduce VS in animal models (74), but whether this is identical to that occurring in humans has not been proven. Early VS is believed to develop within minutes and to last up to 2 days and has been regarded as true VS i.e. contraction of the muscle wall of the vessels. Late VS develops usually from about 4 days after SAH and may last for approximately 2 weeks (36,67). It is characterised on histological examination by arterial intimal proliferation and myonecrosis (63). Both phases in involved arteries are demonstrated angiographically as narrowing of the contrast column in the lumen of the vessel. The nature and clinical consequences of the two processes are entirely different, necessitating different management approaches. Kapp (63) in 1982 proposed that the morphological changes seen in the arteries in delayed VS represented a repair process of a proliferative endarteriopathy following the initial muscular contraction and subsequent secondary injury to the artery. Microscopically it has been shown to consist of endothelial desquamation with adherence of platelets to the denuded internal elastic lamina and mural thrombus formation. Liszczak et al (77) demonstrated, in addition, that infiltration of blood elements into the arterial wall is a common morphological feature of angiographically demonstrated arterial spasm.

The aetiology and pathogenesis of VS remains obscure. Numerous endogenous agents have been reported to constrict

cerebral vessels and may thus play a role in the production of VS (133). The vasoactive degradation products from blood clot surrounding the cerebral vessels have been regarded as the most likely and potent causative agents (77,120). Fisher and co-workers (35) have demonstrated a close correlation between the amount and distribution of subarachnoid blood and severity of VS. Cerebral blood flow (CBF) and cerebral metabolism studies in patients with SAH show that CBF is greatly reduced in patients with VS (53) and that brain metabolism is even more impaired (136). The perfusion abnormality appears to correlate well with the clinical severity of the VS.
The literature concerning methods of preventing or treating VS is voluminous (146), indicating that at present there is no total solution to the problem. Beneficial effects of intravascular volume expansion and induced arterial hypertension in the treatment of VS have been reported (64).

Early surgery has been increasingly advocated by many authors to minimise the risk of rebleeding and to prevent the occurrence of FID by washing out the subarachnoid blood (13,14,16,18,79). However, the peak of rebleeding, according to Kassel et al in a co-operative study on 2 265 patients with SAH (65), was found to be actually on the same day as the initial bleed, followed by a decrease in the probability of a rebleed day by day. Even after early

surgery a considerable incidence of FID has been noted (79). According to Jomin et al (60) spasm and cerebral ischaemia represent an absolute contraindication to surgery for a ruptured cerebral aneurysm. There has also been evidence that the use of antifibrinolytic agents increases the subsequent development of FID (66).

Among the vast number of drugs used to counteract VS calcium channel blockers have attracted the attention of neurosurgeons looking for an effective method of combating VS. Calcium is required during muscle excitation to activate the adenosine triphosphate (ATP) dependant biochemical process for contraction of vascular smooth muscle (23). Although vasoactive agents act by many mechanisms, the final induction of contraction in all, is by increasing the free intracellular calcium concentration. Extracellular calcium is the primary source of calcium for the contraction of cerebral arteries in contradistinction to some systemic arteries which use intracellular calcium for contraction (25). Hence it would appear logical to counteract the influx of extracellular calcium into the muscle cell by using a specific antagonist to calcium. Nimodipine (Nimotop ®) is one of the most potent calcium channel blocking vasodilators with a preferential effect on cerebral vessels (68). Animal studies have suggested that nimodipine can reverse experimentally induced vasospasm (68,132,137) and improve CBF (90,94) without increasing the intracranial pressure

(ICP) (37).

A double-blind placebo controlled, multicentre trial using the oral form of nimodipine (4) has shown a statistically significant improvement in outcome of patients with SAH from a ruptured cerebral aneurysm. Since then there have been increasing numbers of reports in favour of using nimodipine in the prevention and therapy of FID following SAH (14,16,17,90,106,117).

3.3.3. HYPERTENSION AND AGE.

Andrews and Spregel (6) investigated the relationship between blood pressure and aneurysmal rupture. Systolic and diastolic pressure were not elevated to a statistically significant level in patients with aneurysms compared with the general population. A hypertensive patient under 55 years of age of either sex was found to be twice as likely to have multiple aneurysms as normotensive patients.

In a series of 250 aneurysm cases reported by McCormick and Schmalstieg (86) however, there was no evidence of association of hypertension with multiplicity of aneurysms, age at which aneurysms presented clinically, or age at rupture. The marked excess of hypertension among

Blacks was not associated with a corresponding excess of aneurysm (69).

These findings should not be confused with the fact that immediately following the onset of SAH the occurrence of hypertension has been found to be a very important prognostic factor (8). In these circumstances, it is probably partly a reflection of the Cushing response to intracranial hypertension and therefore the severity of the bleed.

Meyer and co-workers (93) in their study on CBF following SAH found that older patients had a much lower CBF following SAH and this in turn was proven to be associated with a high incidence of FID.

Artiola i Fortunny et al (8) looked at age, blood pressure on admission and neurological status in relation to mortality. Increasing age, hypertension and poor neurological state influenced surgical results dramatically.

3.3.4. SITE OF ANEURYSM

Sundt et al (126) in their study on results of surgical management of aneurysms found the highest rate of unfavourable outcome in vertebro-basilar aneurysms (26%),

followed by anterior communicating aneurysms (16%), middle cerebral artery aneurysms (14%) and internal carotid aneurysms (11%).

Jomin et al (60) found a much higher rate of unfavourable results in pericallosal artery aneurysms (35,4%)with a mortality of 17,7%. This he explains by associated haematomas. Hypothalamic damage was found in some cases, all of them with aneurysms in the region of the anterior communicating artery complex. This is related to damage to small perforating vessels arising from the posterior aspect of the anterior communicating artery and may result in diabetes insipidus (DI) or syndrome of inappropriate ADH secretion (SIADH) or Korsakoff syndrome (97,139).

Takaku (131) found these abnormalities occurring more often with aneurysms of the anterior communicating artery than all other sites combined. He found mortality with hypernatraemia to be 43%, with DI 25% and SIADH 15%. At autopsy hypothalamic haemorrhages were shown. The symptomotology of SIADH and its course is similar to that of delayed ischaemic deficit in vasospasm (149).

3.3.5. TIMING OF SURGERY

The primary purpose of surgery for ruptured aneurysms is

to prevent rebleeding, and secondly to facilitate the management of possible vasospasm. Knowledge of the daily risk of rebleeding and vasospasm is therefore essential. It has been reported that the highest risk of rebleeding occurs in the second part of the first week and in the beginning of the second week after the initial aneurysmal rupture (114,115)). However, in a report in 1983 from the co-operative aneurysm study by Kassel and Torner (65) including 2 265 patients, the rate of rebleeding was the highest (4,1%) within the first 24-hours and VS peaked between 4-9 days after ictus.

Inagawa (52) found the peak of rebleed within the first 6 hours after the first bleed. The rebleeding rate was not related to age, sex, BP on admission, size, shape or site of aneurysm, presence or absence of ICH or intraventricular haemorrhage. The more severe the initial bleed with resulting lower clinical grade and more extensive blood clot in the subarachnoid space on CT, the greater was the chance of rebleed.

The above information has provided a strong argument for early, or even ultra-early surgery. There are still, however, different reports concerning the peak of aneurysmal rupture (105). Recent data obtained from Denmark (113) found the peak of rebleed between 4-9 days. Significantly fewer rebleeds were reported in patients in good clinical grades (I-III) compared to those in poor

clinical grades (IV-V). Patients in a good clinical grade following rupture of a cerebral aneurysm may be candidates for urgent surgical occlusion of the aneurysm to prevent catastrophic rebleed.

What the optimum timing of surgical intervention in the recently ruptured intracranial aneurysm is, remains controversial. Surgical intervention between 4-10 days after SAH may be associated with high post-operative mortality and morbidity rates (67) due to progressive cerebral vasospasm for which there is no proven effective treatment to date. Consequently, it has been the policy in many surgical units to delay surgery for at least 10 days until this critical vasospastic period has passed (30,47,60). The post-operative mortality tends to decrease the longer the definitive operation is delayed, whereas the management mortality rate tends to increase over the same period as more patients die awaiting surgery (28). In a study by Weir (138) on management mortality and timing of surgery, patients in good condition (grades I and II H&H) and moribund (grade V) did not follow the trend. Timing of operation made no difference within these groups. The grade I and II patients did well and grade V patients died. The operative mortality was the same following early or late surgery in grade III and IV. However, the management mortality was significantly lower in those who had early aneurysm clipping.

An International co-operative study on the timing of aneurysm surgery (67) has shown a statistically significant difference in the outcome of patients with operations planned for different time intervals. The management mortality of patients in whom operation was planned on days 7-10 was 28%, significantly higher than the mortality for other intervals. The management mortality for the various intervals was -

0-3 days - 20%

4-6 days - 24%

7-10 days - 28%

11-14 days - 21%

15-32 days - 20%.

These were adjusted mortality rates which took into account the differences in risk factors. In examining the actual interval to operation, it was found that operative mortality rates were higher and favourable outcome was significantly reduced for intervals 0-3, 4-6 and 7-10 compared to 11-14 and 15-32 days ($p = 0,0013$). Mortality rates were as follows -

0-3 days - 17%

4-6 days - 19%

7-10 days - 18%

11-14 days - 7%

15-32 days - 8%

3.3.6. ANTIFIBRINOLYTIC THERAPY

The use of antifibrinolytic drugs, such as epsilon-amino-caproic-acid (EACA) and tranexamic acid has received mixed reviews (1,66). The effect of antifibrinolytic therapy post SAH was observed experimentally in dogs with scanning electron microscopy (SEM) (54). Twelve days treatment resulted in residual clot with thick fibrosis when examined 3 weeks after cisternal injection of blood. Three months after blood injection significant increase in subarachnoid fibrosis was shown which in turn was considered to be responsible for communicating hydrocephalus by disturbing epicortical CSF flow (55).

Kassel & Torner (66) in reporting observations of the co-operative aneurysm study, showed that while the rebleeding rate was markedly reduced after the first 48 hours, the incidence of focal ischemic neurological deficit was significantly increased (32,4% in treated patients -vs- 22,7% in untreated patients). Hydrocephalus was twice as frequent in those receiving antifibrinolytic agents as in those not receiving them. Thrombo-phlebitis and pulmonary embolus were not found to be significantly different.

4. CLINICAL MATERIAL AND METHODS

A retrospective review was made of the case records, angiograms and CT relating to a total of 263 patients admitted with subarachnoid haemorrhage to the neurosurgical unit of Wentworth Hospital, Durban, in 4 years between January 1983 and December 1986 (Table 1).

TABLE 1	MATERIAL	
	Total records 284	
Total patients 263		Remaining records 21
	Second Op 17	Re-admitted 4
	Initially refused 2	Initially unfit 2
	Total Records 284	
1 Op	2 Op	No Op
202	34	48
	Died without Op	Refused Unfit
	24	13 11

Seventeen patients had a second operation for which they

were re-admitted. Two patients were re-admitted and operated after initially refusing surgery. Two other patients were initially declared unfit for surgery. Therefore a total of 284 records were available. Two-hundred and two patients had one operation and 34 had 2 operations. Forty-eight patients did not have surgery, of these 24 died while awaiting surgery, 13 refused surgery and 11 were unfit for surgery and were discharged.

There were 106 (40,3%) males and 157 (59,7%) females. Sex, age and race distribution is shown in Table 2.

TABLE 2. SEX, RACE AND AGE DISTRIBUTION OF 263 PATIENTS

		n	%
SEX	Male	106	40,3
	Female	157	59,7
RACE	Black	204	77,6
	Asian	25	9,5
	Coloured	16	6,1
	White	17	6,5
AGE (Decades)	1	1	0,4
	2	6	2,3
	3	45	17,1
	4	73	27,8
	5	75	28,5
	6	37	14,1
	7	26	9,9

The diagnosis was confirmed by LP and/or CT. Severity of bleed seen on LP is divided into three distinct categories

(1) Clear CSF

(2) Xanthochromic CSF

(3) Heavily blood-stained (bloody) CSF,

severity of subarachnoid bleed on CT as described by Fisher et al(35) (Table 3).

TABLE 3. CT GRADING ACCORDING TO FISHER (CT-FISHER)(35)

GRADE	1	None
	2	Diffuse only
	3	Clot or thick layer
	4	Diffuse or none with ventricular blood.

SAH

In addition, the CT scans were evaluated for associated intracerebral/subdural haematomas, presence and degree of hydrocephalus and infarcts.

The definitive diagnosis of a berry aneurysm was made by four-vessel transfemoral angiography (21). The localisation of aneurysm, the degree and extent of vasospasm were evaluated from the films. Aneurysm locations were classified in the following manner -

- anterior communicating artery (ACoA)
- posterior communicating artery (PCoA)
- A1 segment of anterior cerebral artery (A1)

- internal carotid artery bifurcation (ICA)
- vertebral and basilar system (V-B)
- other.

Patients who had multiple aneurysms were classified separately.

Outcome is described according to the Glasgow Outcome Scale (GOS) (58). Patients with GOS 1 and 2 were considered as a favourable/good outcome, GOS of 3 (severely disabled), 4 (vegetative) and 5 (death) were together considered as an unfavourable/bad outcome. To simplify the outcome description in tables, only good outcome and mortality are specified. Operative and management mortality are as defined by Weir and Aronyk (138).

In addition to age, sex, site of aneurysm, multiplicity and CT appearance, certain other clinical variables were considered in the analysis of outcome.

Systemic blood pressure on admission: patients were subdivided into 2 categories (8) -

hypertensive (blood pressure >140/90mmHg); and

normotensive (blood pressure ≤140/90mmHg).

Serum glucose level on admission: patients were subdivided into 3 categories -

normoglycaemia (serum glucose below 6,2mmol/l)

mild hyperglycaemia (level 6,2-10mmol/l)

severe hyperglycaemia (level 10-20mmol/l)

There were no patients with serum glucose level above 20mmol/l on admission.

Clinical condition according to Hunt & Hess (H&H) classification (49) (Table 4) was noted on admission, at angiography and pre-operatively. Grade I and II was regarded as good clinical condition. Grade III constituted a separate grade as those patients proved to be at higher risk of VS (36,49). Grades IV-V patients were in a serious and/or moribund state.

TABLE 4. HUNT & HESS CLASSIFICATION (49)

GRADE	
I	Asymptomatic, minimal headache, slight neck stiffness
II	Moderate to severe headache, neck stiffness
III	Drowsiness, confusion, mild focal deficit
IV	Stupor, severe neurological deficit, vegetative disturbance
V	Deep coma, decerebrate rigidity, moribund appearance.

Timing of admission, angiography and operation

This was calculated in days considering day 0 as the day

of initial bleed. The patients were divided into three groups according to the following time intervals -

1. Early stage = 1-3 days;
2. Intermediate = 4-10 days;
3. Late stage = after 10 days.

Comparisons between and within groups (such as age and sex) and clinical variables were performed using chi-square analyses with the Yates corrections.

4.1. CALCIUM ANTAGONIST NIMODIPINE IN PREVENTION AND TREATMENT OF VASOSPASM.

This part of the thesis summarises two independent studies done by the author.
The studies had the approval of the Ethics Committee of the Faculty of Medicine, University of Natal.

4.1.1. OPEN PILOT STUDY

In view of the success of previous placebo-controlled oral administration trials(4,90,106), an open pilot study was instituted using both the parenteral and oral preparation of the drug in 46unselected patients (26 male and 20 female) with an age of 41,7 ± 8,5 years admitted to our

department 4,3 ± 4 days following SAH (Table 5).

TABLE 5 NIMODIPINE TREATED CASES

	x	SD	n	%
Age	41,7	8,5	46	
Female			20	
Male			26	
Time SAH Admission	4,3	4,0	45*	-
24-Hours			13	28
1-3 Days			14	31
>4 Days			18	40
Time SAH (N ®)	8,9	5,5	45	
24-Hours			2	4,4
1-3 Days			6	13,3
>4 Days			37	82,3
Time SAH-Operation	11,3	6	42	
Duration of IVI (N®)	10,7	3,4		
Oral	5,8	3,4	46	
Start of Post-Op (N®)			17	45
Pre-Op			29	63

* In 1 case time was unknown

After the formal consent had been obtained, nimodipine treatment was commenced 8,9 ± 5,5 days and operation performed 11,4 ± 6,0 days after the day of bleeding. Initially nimodipine was given immediately post-operatively only, but in the last 29 cases treatment was

commenced after cerebral angiography had shown the presence and site of the aneurysm and the degree of angiographic vasospasm.

Nimodipine treatment was started as a continuous intravenous infusion in an initial dose of 1mg/hour (15µg/kg/hour) for 2 hours. During this time the vital parameters, especially blood pressure, pulse and level of consciousness were observed. Provided these were stable, the dosage was then increased to 2mg/hour (30µg/kg/hour). The infusion was continued during surgery and for at least 5 days post-operatively. (The constant intravenous infusion of nimodipine was carried out concurrently with an infusion solution in an amount not less than 1000ml/day). The treatment was later changed to an oral dose of 360mg/day in 6 divided doses. The mean time for intravenous treatment was 10,7 ± 3,4 days and the subsequent oral treatment for 5,8 ± 3,4 days for the total group. Pulse, blood pressure and temperature were closely observed and laboratory investigations of haematological parameters, blood gases and urine-analysis were done prior to treatment and on several occasions during treatment, and finally on completion of treatment. Final assessment of the patients neurological condition was carried out using the Glasgow Outcome Scale (58) on discharge.

The patients were divided into four treatment groups -

1. Therapeutic - when angiographic vasospasm was associated with a clinical deficit (12 cases).
2. Prophylactic - when the patients had no neurological deficits (34 cases).
3. Topical - during operation, after clipping of the aneurysm, topical intracisternal administration of nimodipine was carried out (38 cases). Two-hundred micrograms (1ml) of nimodipine was diluted in 19ml of Ringer's solution and left in situ for 10 minutes. Macroscopic assessment was made of relief of the observed vasospasm at the operative site.
4. Intra-arterial. In 6 patients from the therapeutic group nimodipine was injected into the internal carotid artery during angiography. The first two cases received 200 micrograms of nimodipine and the remaining four cases received 500 micrograms. This was diluted with Ringer's solution to create a volume of 10ml and given as a slow injection over 10 minutes. Angiography was repeated after the intra-arterial injection. Blood pressure and pulse rates were assessed before the injection, immediately after the injection and at 10-minute intervals during the procedure. The arterial $PaCO_2$ was also measured to ensure that comparisons of radiological arterial calibre took

place with similar arterial carbon dioxide levels.

Glucose & Calcium levels:

Among the multiple laboratory tests carried out including full blood count with differential count, ESR, liver function tests, urea, creatinine and electrolytes, cholesterol and triglycerides, blood gases and urine analysis, only the glucose and calcium levels showed changes during nimodipine treatment and these were analysed with regard to the statistical significance of the changes. The Hotelling t-test and paired t-test were used to differentiate between the glucose and calcium levels before and after commencement of treatment. This is a multivariate procedure and was employed since both glucose and calcium levels were observed on the same individuals. (Institute of Biostatistics, Johannesburg, Dr. P.J. Becker)

4.1.2. CONTROLLED COMPARATIVE STUDY

During the period 1983 to 1985, 61 patients received parenteral nimodipine treatment commencing immediately after angiography.

A group of 60 patients, matched only for aneurysm location, did not receive nimodipine treatment and formed the concurrent control group. The only reason for these patients not receiving nimodipine was the non-availability

of an infusion pump for continuous intravenous calibrated administration of the drug. Therefore, the two groups were randomly allocated. The two groups appeared well matched with regard to age and sex, as well as the Hunt & Hess grading on admission (Table 6). Nimodipine treatment was instituted in the same manner as described in the previous chapter. During surgery, after clipping of the aneurysm, nimodipine was also administered topically into the subarachnoid space at the site of manipulation. In the control group no specific prophylactic therapy against vasospasm was instituted. The two groups were then compared statistically for outcome, the incidence of VS and other complications. Blood glucose levels were specifically analysed.

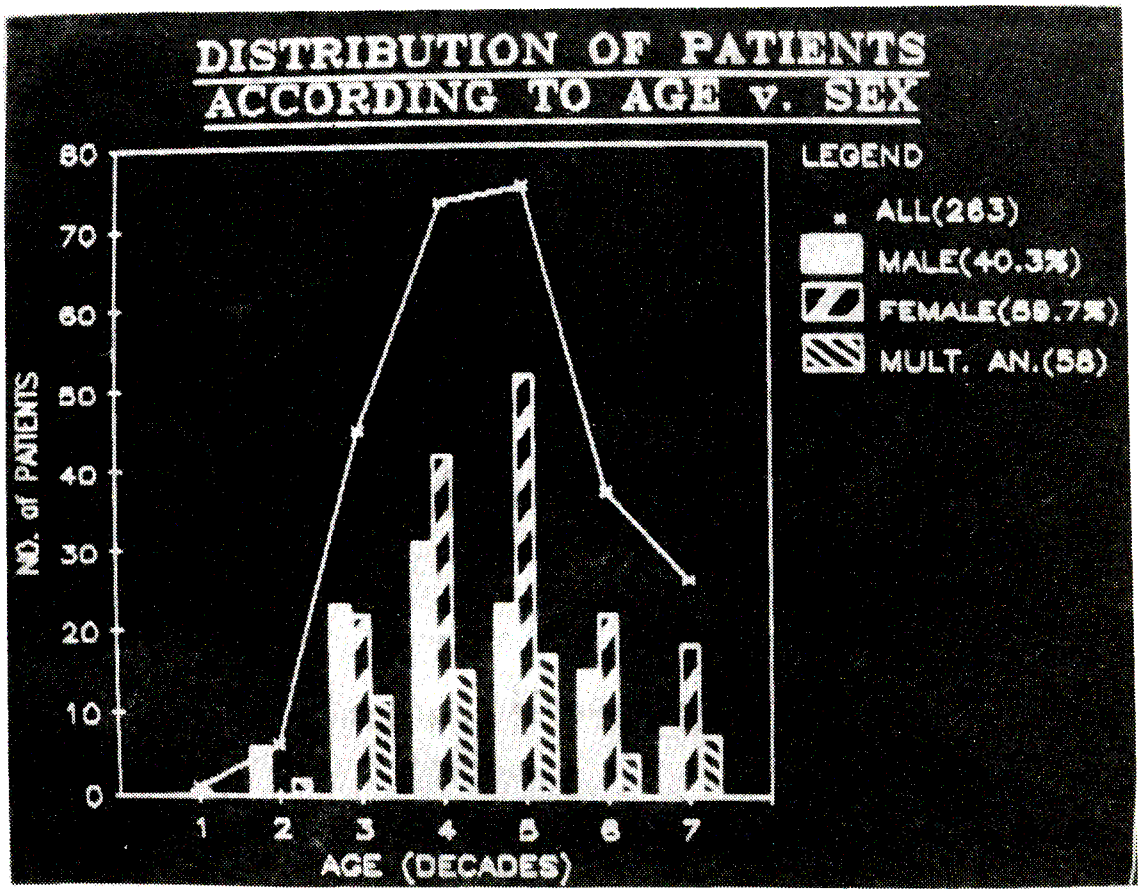
TABLE 6. PATIENTS IN COMPARATIVE STUDY			
		Nimodipine	Control
	Total	61	60
	Male	29	23
	Female	32	37
	Age (Years)	41,5 ± 10,0	42,5 ± 14
H & H ON ADMISSION	I	35	36
	II	18	17
	III	5	6
	IV	3	1
			NS

5. RESULTS

5.1. INCIDENCE OF ANEURYSM.

Age and sex distribution in 263 patients is shown in Fig 1. The peak of aneurysm incidence was in the 4th and 5th decades. There was a predominance of 59,7% female patients. However, in relation to age in decades, males predominated up to the third decade with a peak in the fourth decade. Females predominated from the fourth decade with a peak in the fifth decade.

FIG 1.



Racial distribution is shown in Table 7. This shows an overwhelming predominance of Black patients in 77,6% and correlates with the same predominance of Black patients in the region of Natal and Kwa-Zulu. There is an increased percentage of Coloured patients when compared with their distribution in the total population, but this is similar to their distribution in all patients admitted to Wentworth Hospital. There is a slightly lower number of White and Asian patients admitted with SAH compared to their distribution in the population.

TABLE 7. RACE DISTRIBUTION (1983-1986)

	SAH (n=263)		TOTAL ADMISSIONS WENTWORTH (n=28920)	POPULATION NATAL/ KWA ZULU (n=5.892033)
	n	(%)	(%)	(%)
BLACK	204	(77,6)	59,8	77,5
COLOURED	16	(6,1)	5,2	1,7
ASIAN	25	(9,5)	17,5	11,2
WHITE	17	(6,5)	17,5	9,5

The incidence of aneurysm sites is based on 268 angiographies in 263 patients and is shown in Table 8 and Fig 2. Five patients had repeat angiography in which the result was different from the previous one.

TABLE 8	LOCALISATION OF ANEURYSMS		
	n= 286	ALL (%)	BLACK (%)
PCoA	93	(32,5)	(34,5)
ACoA	47	(16,8)	(13,9)
MCA	34	(11,9)	(12,6)
ICA	22	(7,7)	(7,6)
Al	13	(4,5)	(5,8)
V-B	4	(1,4)	(0,5)
Other	15	(5,2)	(4,9)
Multiple	58	(20,3)	(20,2)
Bilateral	39		
Mirror*	(18)	(PCoA=10, MCA=4, Other 4)	
Unilateral	19		
(L)	(8)		
(R)	(11)		
Giant (>25mm)	6	(2,1)	

*Mirror aneurysm included as single site.

The most common site of aneurysm is PCoA (32,5%), then ACoA (16,8%) and MCA (11,9%). There were only 6 giant aneurysms, all of them at the ICA bifurcation.

When only Black patients were analysed, the predominant site of aneurysm on PCoA became more obvious (34,5%) when compared with ACoA (13,9%).

FIG. 2

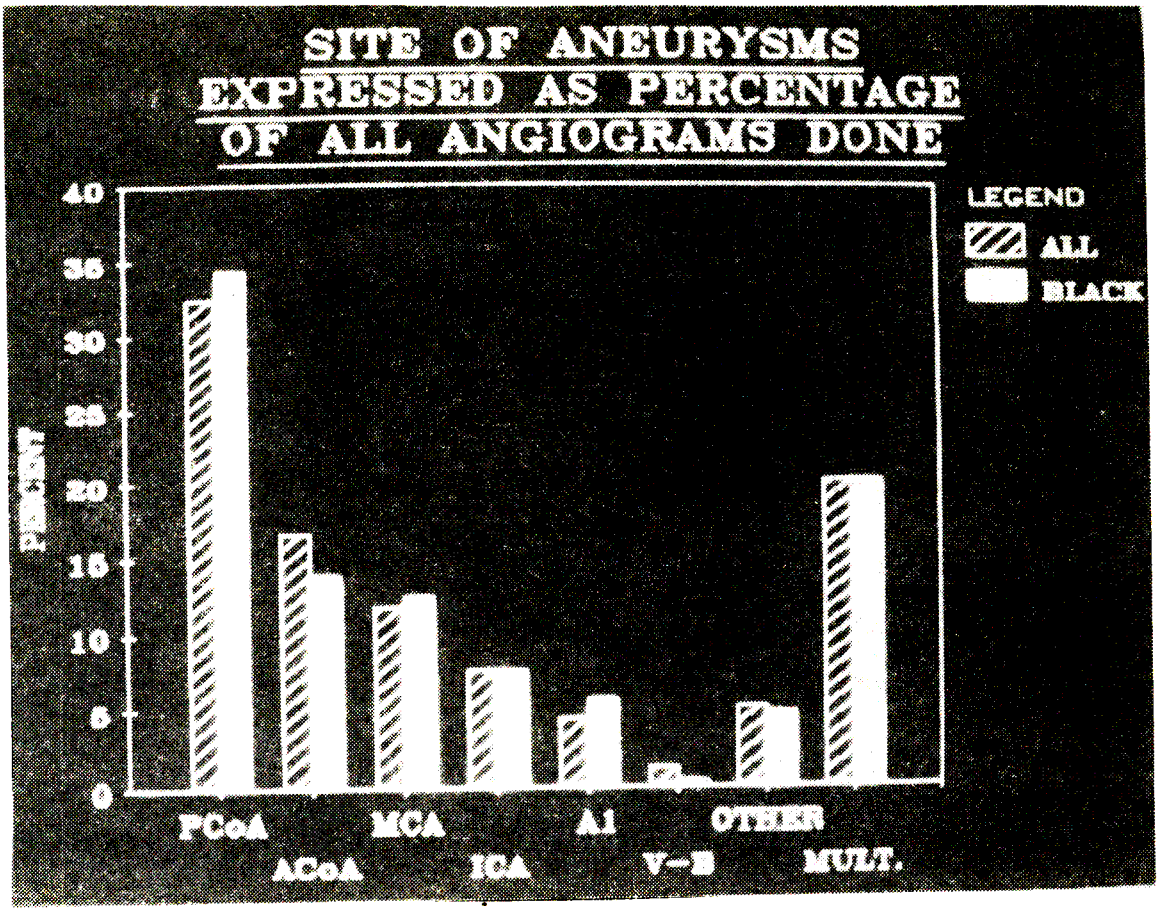
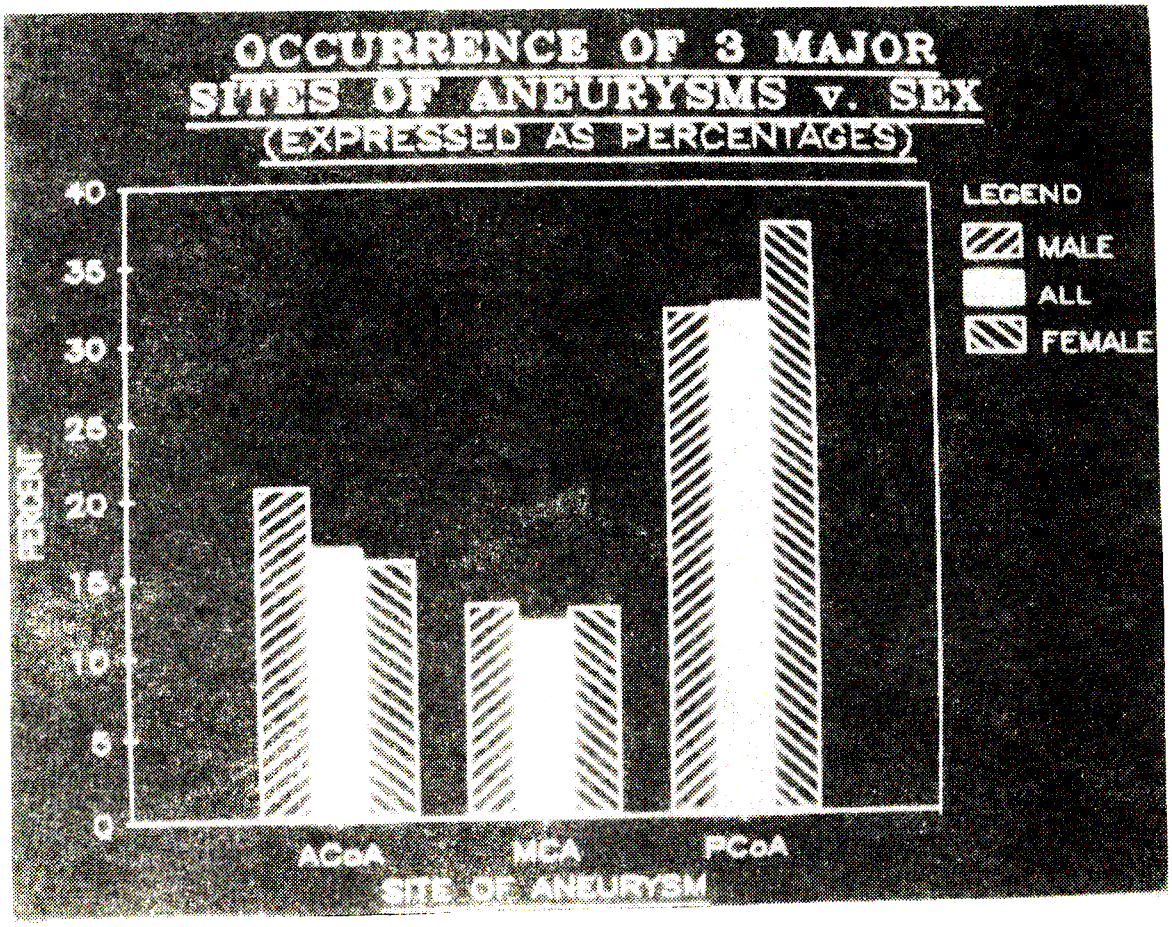

SITE OF ANEURYSMS
EXPRESSED AS PERCENTAGE
OF ALL ANGIOGRAMS DONE
LEGEND
ALL
BLACK
PERCENT
40
35
30
25
20
15
10
5
0
PCoA
ACoA
MCA
ICA
A1
V-B
OTHER
MULT.

FIG. 3


OCCURRENCE OF 3 MAJOR
SITES OF ANEURYSMS v. SEX
(EXPRESSED AS PERCENTAGES)
LEGEND
MALE
ALL
FEMALE
PERCENT
40
35
30
25
20
15
10
5
0
ACoA
MCA
PCoA
SITE OF ANEURYSM

The three main aneurysm sites were PCoA, ACoA and MCA were compared with the sex of the patients (Fig 3).

When compared with their overall incidence, ACoA aneurysms were slightly more often found in males, PCoA aneurysms in females while MCA aneurysms had an equal sex distribution. There were 58 (20,3%) multiple aneurysms (more than one) and within this group 18 mirror aneurysms (same site bilaterally). Ten of the mirror aneurysms were on the PCoA. Their relation to age (in decades) is shown in FIG 1. There was no difference in incidence of multiple aneurysms in Black patients. Hypertensive patients showed an increase in the incidence of multiple aneurysms (26%) especially below the age of 40 (31%) (Table 9). However, it failed to show any statistical significance.

TABLE 9 MULTIPLE ANEURYSMS -vs- HYPERTENSION (HT)

	HYPERTENSION		
	On Treatment	On admission	
	All n=62	Blacks n=108	Young (<40 yrs) Blacks n=49
n	16	25	15
%	26%	23%	31%
	N.S.		N.S.

5.2. TIMING OF ADMISSION

One-hundred and fourteen patients were admitted within 3 days following initial bleed, 99 patients within 4-10 days and 58 patients later than 10 days. The relation between time of admission and outcome is shown in Table 10.

TABLE 10. TIME FROM SAH TO ADMISSION -vs- OUTCOME

	SAH - ADMISSION (Days) 0-3	4-10	>10
n=271*	114 (42%)	99 (36%)	58 (21%)
GOOD OUTCOME	65 (57%)	70 (71%)	47 (81%)
DEATH	35 (31%)	18 (18%)	9 (15%)
		p <0,05	p <0,05
H&H I/II	64 (56%)	64 (65%)	41 (71%)
III	41 (36%)	23 (23%)	10 (17%)
IV/V	9 (8%)	12 (12%)	7 (12%)

* 8 Patients were re-admitted with a new SAH.

Patients admitted in the acute stage within 72-hours of onset had good results of 57% and a mortality of 31%. The later patients were admitted after SAH the better was their condition on admission (H&H) and the better was their outcome. This carried a statistical significance of p <0,05.

5.3. CLINICAL CONDITION

The relation of clinical condition on admission to outcome is shown in Table 11.

TABLE 11. CLINICAL CONDITION (H&H) ON ADMISSION AND BEFORE OPERATION -VS- OUTCOME.

	H&H	I/II	III	IV/V
	n=271*	169	74	28
GOOD OUTCOME		132 (78%)	27 (36%)	17 (61%)
		p < 0,001		N.S.
		BEFORE OPERATION		
	n=236	168 (71%)	60 (25%)	8 (3,4%)
GOOD OUTCOME		139 (83%)	35 (58%)	2
DEATH		21 (12%)	15 (25%)	2
		p < 0,01		N.S.

* 8 patients re-admitted with new SAH

Patients admitted in a good clinical condition (grades I/II H&H) had a good outcome in 78%. Patients admitted in grade III (H&H) had a significantly worse outcome p<0,001) with only 36% favourable results. Serious and moribund patients on admission (grades IV/V H&H) showed a surprising 61% good overall management result. The latter group, however, included only 28 cases.

One-hundred and sixty-eight patients who were in a good clinical condition at operation (I/II H&H) had a much higher good post-operative result (83%) and lower mortality (12%) than patients in grades III/IV or IV/V p<0,01). Operative mortality in both latter groups was 25%.

5.4. CEREBROSPINAL FLUID (CSF) EXAMINATION.

Information regarding the above was available in 176 cases. One-hundred and twenty-nine cases showed bloody CSF on LP, 47 xanthochromic and 7 clear fluid. (Table 12)

TABLE 12 . CSF AT LUMBAR PUNCTURE -vs- OUTCOME

CSF	BLOODY	XANTHOCHROMIC	CLEAR
n=176	129 (73%)	40 (23%)	7 (4%)
GOOD OUTCOME	86 (67%)	30 (75%)	5
DEATH	29 (22%)	6 (15%)	2
	N.S.		

Bloody CSF showed a trend towards a worse overall prognosis with 67% of good results and mortality 22% when compared with clear/xanthochromic CSF (good results in 75% and mortality 15%). This, however, did not show a statistical significance.

Forty-six per-cent of patients with bloody CSF showed, on CT, a thick clot/layer of blood in the subarachnoid cisterns (CT-Fisher grade 3) and was associated with vasospasm in exactly the same percentage (45,7%) (Table 13).

TABLE 13. BLOODY CSF -vs- CT-FISHER GRADE AND VASOSPASM

	CT-FISHER GRADE				
	1	2	3	4	VASOSPASM
n=	48	15	59	5	
129	37%	12%	46%	4%	46%

5.5. HYPERTENSION AND HYPERGLYCAEMIA

Patients hypertensive on admission showed a generally worse ($p < 0,01$) outcome with 59% good results and 27% mortality when compared with normotensive patients (good results 76% and mortality 17%) ($p < 0,01$)(Table 14). Older (>50 years) hypertensive patients had a 54% overall good outcome and younger patients 64%. This failed to show any statistical significance. (Table 15)

TABLE 14. BLOOD PRESSURE ON ADMISSION -vs- OUTCOME			
		>140/90	≤140/90
	n=270	148	122
GOOD OUTCOME		82 (59%)	93 (76%)
DEATH		38 (27%)	21 (17%)
		p< 0,01	

TABLE 15. AGE OF HYPERTENSIVE PATIENTS -VS- OUTCOME.			
		<50 YEARS	>50 YEARS
	n=148	102	46
GOOD OUTCOME		65 (64%)	25 (54%)
DEATH		27 (26%)	13 (28%)
		N.S.	

There were 164 cases with normal plasma glucose levels on admission (3,2 - 6,2mmol/l). Those patients showed significantly better overall (p< 0,001) results with good outcome in 83% and 19% mortality when compared with 102 cases with elevated plasma glucose levels above 6,2mmol/l (good outcome 57% and mortality 30%). The degree of hyperglycaemia tended to influence mortality. Patients

with moderate hyperglycaemia (84 cases) with levels 6,2 to 10mmol/l had a mortality of 29%, whereas patients with severe hyperglycaemia (18 cases) with levels 10-20mmol/l had 39% mortality. This difference however was not statistically significant. There were no patients admitted with plasma glucose levels above 20mmol/l.

TABLE 16. SERUM GLUCOSE LEVEL (mmol/l) ON ADMISSION -vs- OUTCOME

		NORMAL (<6,2)	HYPERGLYCAEMIA (>6,2)	(6,2-10)	(10-20)
	n=266	164	102	84	18
OUTCOME	GOOD	137 (83%)	58 (57%)	48 (57%)	10 (56%)
			p <0,001	N.S.	
	DEATH	31 (19%)	31 (30%)	24 (29%)	7 (39%)
			p < 0,05	N.S.	

There were 55 cases in which hypertension on admission co-existed with hyperglycaemia (Table 17). These patients had a statistically significant (p <0,001) worse outcome overall (good results 47% with mortality 36%) than patients with neither or only one of these abnormalities (good results 79%, mortality 19%).

TABLE 17. HYPERTENSION/HYPERGLYCAEMIA -VS- OUTCOME		
	BOTH	NONE/EITHER
n= 270	55	215
GOOD OUTCOME	26 (47%)	169 (79%)
	p < 0,001	
DEATH	20 (36%)	42 (19%)
	p < 0,02	

5.6. COMPUTERIZED TOMOGRAPHY (CT) FINDINGS.

All patients had CT done on admission and these were analysed. Severity of SAH was graded according to Fisher (35). The relation of particular grades to outcome is shown in Table 18.

TABLE 18 CT-FISHER GRADE -VS- OUTCOME				
	CT-FISHER			
	1	2	3	4
n= 266	112	38	108	8
GOOD OUTCOME	91(81%)	30(79%)	53(49%)	5
	p < 0,001			
DEATH	13(12%)	5(13%)	40(37%)	3
	p < 0,01			

Two-hundred and sixty-six scan pictures were evaluated in 263 patients (3 patients were re-admitted and had new and different CT results). CT-Fisher grade 3 (thick blood layer/clot) has distinctly shown a much poorer overall prognosis with only 49% of good results and a high mortality rate of 37% when compared with normal CT ($p < 0,001$) or diffuse SAH ($p<0,01$).

Even intraventricular bleeds in isolation or in addition to diffuse SAH (CT-Fisher 4) seemed to have a better outcome, although the small numbers (8 cases) preclude statistical analysis.

CT-Fisher grade 3 had a higher association rate with vasospasm diagnosed pre-operatively (47%) when compared with grades 1 ($p<0,01$) and 2 ($p<0,02$) (Table 19). Every second patient therefore, with CT-Fisher grade 3 had vasospasm on angiography.

Hydrocephalus was seen in 35 cases (13,1%) but only in 4 cases was this associated with signs of acute rise in intracranial pressure (ICP) necessitating shunt procedures (Table 20).

TABLE 19	CT-FISHER GRADE -vs- VASOSPASM (VS)			
	CT-FISHER			
	1	2	3	4
n= 266	112	38	108	8
VS (ANGIO) 93(23%)			Mild 7 Moderate 20 Severe 24	
	29(26%)	9(24%)	51(47%)	4
	p < 0,01	p<0,02		

TABLE 20.	OCCURRENCE OF HYDROCEPHALUS (CT)	
	n	35
RAISED ICP	4	11%
BLOODY CSF	18	51%
CT-FISHER 3	24	69%

Severe SAH as seen on CT and LP seemed to influence the development of hydrocephalus. In 18 out of 35 cases (51%) of hydrocephalus there was bloody CSF on initial LP and in 24 (69%) there was a thick layer/clot in the basal cisterns on initial CT (CT-Fisher grade 3).

Intracerebral haematoma (ICH) was found in 68 (26%) of the cases. This was associated with a less favourable outcome

(56%) and mortality 28%. (Table 21)

TABLE 21. INTRACEREBRAL HAEMATOMA ON CT.		
	n	68
GOOD OUTCOME	38	56%
DEATH	19	28%

5.7. FOUR-VESSEL ANGIOGRAPHY

Two-hundred and seventy initial angiographic studies were done to visualise and localise an aneurysm, as well as assess the degree and extent of vasospasm.

Localisation of aneurysms in relation to overall outcome is shown in Table 22.

Results of note are the statistically significant $p < 0,05$) lower incidence of overall favourable results (53,2%) in anterior communicating artery (ACoA) aneurysms

TABLE 22. SITE OF ANEURYSM -vs- OUTCOME

	ACoA	ICA	MCA	A1	PCoA	V-B	MULTIPLE
n= 271	47	22	34	13	73	4	58
GOOD OUTCOME	25 (53%) p<0,05	17 (77%)	25 (73%)	10 (77%)	66 (71%)	2	41 (71%)
DEATH	14 (30%)	4 (18%)	4 (12%) N.S.	3 (23%)	19 (20%)	1	15 (26%) N.S.

and lower overall mortality rate in middle cerebral artery bifurcation (MCA) aneurysms (11,8%). Poor overall results in ACoA aneurysms were associated with a higher incidence of the lower clinical grades on admission ($p < 0,001$) (Table 23).

TABLE 23. OUTCOME OF ACoA -vs- H&H ON ADMISSION

	I/II	III	IV/V
n= 47	28	16	3
GOOD OUTCOME	20 (71%)	4 (25%)	1
DEATH	3 (11%)	9 (56%)	2
	$p < 0,001$		

Multiple aneurysms (58 cases) had a similar favourable outcome to single aneurysms (71%) and morbidity rate (26%).

Angiographically diagnosed vasospasm occurred in 94 patients (34,8%), with statistically lower ($p < 0,02$) incidence of vasospasm in patients who had angiography early (20%) when compared with angiography done after 4 days post-SAH (39%) (Table 24).

TABLE 24. VASOSPASM -vs- TIME TO ANGIOGRAPHY			
	SAH-ANGIOGRAPHY (DAYS)		
	1-3	4-10	>10
n = 270	60	128	82
VASOSPASM n=94 (35%)	20%	39%	39%
Mild	1,7%	7,8%	9,8%
Moderate	11,7%	9,3%	13,4%
Severe	6,7%	21,9%	15,8%
	p < 0,02		

Diffuse, severe vasospasm was seen most often (21,9%) in patients with angiography done between days 4-10 post-SAH. Vasospasm on angiography was associated in 26,6% with post-angiographic deterioration and carried an overall rate of good results in (63%) and a mortality of 27,7%, and in 54,3% was associated with CT findings of thick blood layer/clot in subarachnoid cisterns (CT-Fisher grade 3) (Table 25).

TABLE 25.	VASOSPASM ON ANGIOGRAPHY -vs- OUTCOME n = 94 (35%)
POST-ANGIO DETERIORATION	25 (27%)
GOOD OUTCOME	59 (63%)
DEATH	26 (28%)
CT-FISHER GRADE 3	51 (54%)

Forty-five cases or 16,7% of the cases deteriorated at angiography or within 12-hours thereafter. The cause for deterioration was almost equally (5-6%) distributed between vasospasm, rebleed and metabolic disturbance (Table 26).

TABLE 26. TIMING OF ANGIOGRAPHY -VS- POST-ANGIOGRAPHY DETERIORATION.				
	SAH-ANGIOGRAPHY (DAYS)			
	1-3	4-10	>10	
n= 270	60	128	82	%
Vasospasm 14	3 (5%)	9 (7%)	2 (2%)	5%
Rebleed 17	4 (7%)	10 (8%)	3 (4%)	6%
Metabolic 14	3 (5%)	8 (6%)	3 (4%)	5%
TOTAL 45	10 (16%)	27 (21%)	8 (10%)	16,7%
	N.S.		p<0,05	

Early angiography carried a slightly lower deterioration rate to angiographies done on day 4-10 post-SAH, but with no statistical significance. Delayed angiography cases (done after day 10 post-SAH) showed an overall lower ($p < 0,05$) rate of post-angiography deterioration of (10%).

Clinical condition at the time of angiography (H&H) influences deterioration rate (Table 27). Patients in good clinical condition (grades I/II H&H) had a significantly lower ($p < 0,001$) incidence of deterioration when compared with patients in grades III/IV.

TABLE 27. POST-ANGIOGRAPHY DETERIORATION -vs- CLINICAL CONDITION (H&H)

	H&H AT ANGIOGRAPHY		
	I/II	III	IV/V
n= 270	185	77	8
45 (16,7%)	19 (10%)	27 (35%)	3
	p <0,001		

5.8. SURGICAL INTERVENTION

There were 236 operations on 222 patients. Twenty-four patients died without operation. Good operative outcome was obtained in 75% of patients and the mortality rate was

16%. Operative results in relation to timing of surgery is shown in Table 28.

There were only 11 cases operated in the early stages (1-3 days post-SAH). There was a good outcome in 5 cases and the same number of patients died. The good results improved from 71% for operations between 4-10 days post-SAH (mortality 21%) to 80% in delayed surgery beyond 10 days post-SAH (mortality 10%).

Patients in good clinical condition without altered level of consciousness (grades I/II H&H) generally did well regardless of the timing of their surgery. Good results were obtained in 5 out of 7 cases in early surgery; 78% in day 4-10 post-SAH and 88,2% in delayed surgery.

Patients operated on in a serious to moribund condition (grade IV-V H&H) generally did badly regardless of time of surgery although the small number (8 cases) does not allow statistical analysis. Only two cases had a favourable outcome after delayed surgery.

TABLE 28 OPERATIVE RESULTS IN RELATION TO TIMING OF SURGERY.

Time SAH-Op. (Days)	1-3				4-10				>10 DAYS			
H&H at Op.	I/II	III	IV/V	All	I/II	III	IV/V	All	I/II	III	IV/V	All
n=236	7	1	3	11	76	23	1	100	85	36	4	125
GOOD OUTCOME 176 (75%)	5	0	0	5	59 (78%)	12 (52%)	0	71 (71%)	75 (88%)	23 (64%)	2	100 (80%)
DEATH 38 (16%)	2	1	2	5	11 (14%)	10 (43%)	0	21 (21%)	8 (9%)	4 (11%)	0	12 (10%)

$p<0,05$

Patients in grade III H&H can be analysed only for surgery 4-10 days post-SAH and delayed surgery, since there was only 1 case in grade III H&H operated on early. Those patients operated in the period 4-10 days post-SAH showed a significantly higher ($p < 0,05$) mortality rate (43%) compared to delayed surgery (11%).

Out of 236 patients operated upon 162 were in grade I/II H&H, 50 in grade III and 24 in grades IV/V H&H on admission (Table 29).

One-hundred and fifty-one patients remained in grade I/II when operated on and this resulted in 82% good outcome and mortality 13%. However, 11 patients deteriorated by the time of operation to grade III. Eight of these patients had a good outcome and 2 died. Four patients died awaiting surgery.

Operative cases admitted in grade III H&H (50 cases) remained so in 45 cases when operated (53% had good outcome, 27% died). While awaiting surgery 3 patients improved to grade I and had good results, but 2 deteriorated to grade IV/V and had a bad outcome. Seventeen patients died pre-operatively.

TABLE 29. CLINICAL CONDITION (H&H) ON ADMISSION AND BEFORE OPERATION -VS- OUTCOME

H&H on admission	n	H&H AT OPERATION (Outcome: Good / Death) I/II	III	IV/V	Operative results	Died before Op.	Management results
	n	168	60	8	236	24	260
I/II	162	151 (82% 13)	11 (8 2)	0	(81% 13)	4	(80% 16)
III	50	3 (3 0)	45 (53% 27)	2 (0 0)	(54% 24)	17	(40% 43)
IV/V	24	14 (12 2)	4 (3 1)	6 (2 2)	(71% 21)	3	(63% 30)
Total	236	168 (82% 12)	60 (58% 25)	8 (2 2)	(75% 16)	24	(68% 24)
		p < 0,01	N.S.				

Out of 24 operative cases admitted with grade IV/V, 14 improved to grade I before operation (12 had a good outcome and 2 died), 4 improved to grade III (3 with a good outcome post-operatively and 1 died). Of the remaining 6 who were operated in the same grade IV as on admission, 2 had a good outcome and 2 died. Three patients died without operation.
Taking into account that 24 cases died pre-operatively, the overall management results were - good results 68% and mortality 24%.

In addition to the 24 pre-operative deaths, 11 cases were not operated on since they were in a moribund condition, and of these only 1 was grade V H&H on admission. Three cases admitted in grade I and 7 in grade III deteriorated to grade V and were declared by the surgeons to be unfit for surgical intervention. Time and cause of deterioration or death in all non-operated cases, are shown in Table 30. Out of 114 patients admitted in an acute stage (1-3 days after SAH), 5 (4%) deteriorated, 4 due to rebleed (RB)(3,5%) and only 1 patient deteriorated on day 3 due to vasospasm (VS)(0,9%).

After day 4, rebleeding and vasospasm were equally responsible for patients deterioration or death (8-10%).

TABLE 30. NON-OPERATED CASES: PRE-OPERATIVE DEATH/ MORIBUND CONDITION.

		TIME SAH-ADMISSION (DAYS)					
		1-3		4-10		>10	
	n	114		99		58	
DEATH/ DETERIORATION	35	5		19		11	
		RB	VS	RB	VS	RB	VS
H&H on admission I/II	7 (4%)	1		1	3	1	1
III	24 (32%)	3		7	5	5	4
IV/V	4 (14%)		1	2	1		
n		4	1	10	9	6	5
%		3,5%	0,9%	10%	8%	10%	9%

The vasospasm was diagnosed angiographically more often in patients undergoing delayed surgery (Table 31). However, the operative results in those patients with pre-operative vasospasm significantly improved ($p < 0,05$) for operations performed later than 10 days (good results in 89% and mortality 2%) when compared with operations performed between 4-10 days post-SAH (good results 48%, mortality 40%). Post-operative vasospasm occurred in 12% of cases operated on between day 4-10 post-SAH, and in only 1,6% after delayed surgery.

TABLE 31. PRE-OPERATIVE VASOSPASM -vs- TIMING OF SURGERY AND OUTCOME.

	VASOSPASM PRE-OP (ANGIOGRAPHY) n= 73 (31%)		
	TIME SAH-OP (DAYS)		
	0-3	4-10	>10
n	11	100	125
73	1 (9%)	25 (25%)	47 (38%)
GOOD 54 (77%) OUTCOME	0	12 (48%)	42 (89%)
DEATH 12 (16%)	1	10 (40%)	1 (2%)
		p <0,05	
	VASOSPASM POST-OP		
	1	12 (12%)	2 (1,6%)

SURGERY IN OLDER PATIENTS

There were 51 patients above 50 years of age who underwent surgery (Table 32). The comparison of their outcome to younger patients showed a higher mortality rate (20% -vs- 15%) and a less favourable outcome (63% -vs- 78%) in the older patient (p <0,05). Patients in the sixth decade carried distinctly worse operative results with good outcome in only 54,8% and mortality 29%. This co-incided with the highest incidence of hypertension on admission in this age group (64%).

TABLE 32. SURGICAL OUTCOME -vs- AGE

	n =236	OUTCOME GOOD (75%)	OUTCOME MORTALITY (16%)	BP >140/90 ON ADMISSION %
1	1	1		0
2	6	5	1	33%
3	38	32 (84%)	4 (10%)	39%
4	68	50 (74%)	13 (19%)	46%
5	72	56 (78%)	10 (14%)	47%
		p <0,05		N.S.
6	31	17 (55%)	9 (29%)	64%
7	20	15 (75%)	1 (5%)	59%

5.8.1. INTRAOPERATIVE COMPLICATIONS

Intraoperative complications in relation to outcome are listed in Table 33.

TABLE 33. INTRA-OPERATIVE COMPLICATIONS

n=75	PREMATURE RUPTURE 49	MASSIVE BLEEDING 40	OCCLUSION MAJOR VESSEL 4	BRAIN SWELLING 18
GOOD OUTCOME	56%	57%	1	7
DEATH	(22%)	(25%)	2	8

Premature rupture of aneurysms occurred during 49 operations and a good outcome was achieved in 56% of these cases (mortality 22%). This did not change when premature rupture was associated with massive bleeding (good outcome 57% and mortality 25%). Major vessels had to be occluded in 4 cases. Half of these patients died subsequently and only 1 had a good outcome (occlusion of A1 segment of anterior cerebral artery). Brain swelling was encountered during 18 operations and this was associated with a high mortality (8 cases) and a lower rate of good results (7 cases).

Incidence of premature rupture and brain swelling in relation to timing of surgery and outcome is shown in Table 34.

TABLE 34. PREMATURE RUPTURE -vs- TIMING OF SURGERY			
	TIME SAH - OP (DAYS)		
	1-3	4-10	>10
n	11	100	125
49(21%)	5	23 (23%)	21 (17%)
GOOD (57%)	2	11 (48%)	15 (71%)
OUTCOME			
DEATH (31%)	2	8 (35%)	3 (14%)
SEVERE BRAIN SWELLING			
8(18%)	4	10 (10%)	4 (3%)
GOOD (39%)	1	3	3
OUTCOME			
DEATH (44%)	3	4	1

The aneurysm ruptured prematurely in 5 out of 11 cases operated in the early stage (1-3 days); 2 of these patients died and 1 remained severely disabled. Twenty-three percent of 100 aneurysms operated on between 4-10 days post SAH ruptured prematurely and this was associated with a 52% bad operative result (mortality 35%). Seventeen percent of 125 aneurysms ruptured at delayed surgery with a 29% unfavourable outcome (14% mortality). In 4 out of 11 cases operated on in the acute stage, severe brain swelling was encountered and 3 cases died post-operatively.

Brain swelling complicated operations less frequently when they were done between 4-10 days post SAH (10%) but this

was associated with bad results as well, i.e. 4 out of 10 patients died, 3 remained severely disabled. Only in 3% of delayed operations was brain swelling found (4 cases). One patient subsequently died.

Temporary clips were applied to occlude main vessels in 38 (16%) operations (Table 35). In 55% this had to be done to isolate the ACoA complex. In 32% ICA was temporarily clipped and in 26% MCA. Occlusion was maintained in 58% of patients for less than 5 minutes; in 29% 5-10 minutes and only in 5 cases (13%) was it prolonged more than 10 minutes. The application of temporary clips was associated with 37% bad post-operative results and 21% mortality, slightly worse results than overall operative results, but not of statistical significance.

TABLE 35. TEMPORARY CLIPS AT OPERATION (n=38) (16%)		
SITE	ACoA	21 (55%)
	ICA	12 (32%)
	MCA	10 (26%)
	OTHER	5 (13%)
TIME(Min)	0-5'	22 (58%)
	5-10'	11 (29%)
	>10'	5 (13%)
	GOOD OUTCOME	24 (63%)
	DEATH	8 (21%)

5.8.2. INTRACRANIAL PRESSURE MONITORING (ICPM) -VS- CSF SEPSIS.

ICPM was inserted in 71% of the operated cases (168 cases).

In 147 cases (62%) intraoperative ventricular drainage to minimise retraction and facilitate dissection was converted into intraventricular ICPM. A subdural cup catheter was left as ICPM in 21 cases (9%) (Table 36). Post-operative CSF infection developed in 19 (11%) of those patients who had ICPM, all of them with intraventricular catheters (13%). One of these patients subsequently died as a result of the CSF infection.

TABLE 36. INFLUENCE OF INTRACRANIAL PRESSURE MONITORING (ICPM) ON POST-OPERATIVE CSF INFECTION

		NO ICPM	ICPM VENTRICULAR	ICPM SUBDURAL
	n(%)	68 (29%)	147 (62%)	21 (9%)
CSF INFECTION	19(11%)	0	19 (13%)	0
DEATH (RELATED)	1	0	1	0

5.9. ANTIFIBRINOLYTIC THERAPY

Antifibrinolytic therapy with Tranexamic Acid (Cyclocapron) was started on admission in 158 cases, to prevent rebleeding (Table 37).

This was associated in 9% of cases with development of hydrocephalus, more often than in patients not on treatment with Cyclocapron (6%). Cyclocapron was associated with vasospasm more often and not only on initial angiogram (37% -vs- 28%) but significantly $p<0,05$) in post-operative period (9% -vs- 0,8%).

TABLE 37. ANTIFIBRINOLYTIC THERAPY -vs- HYDROCEPHALUS AND VASOSPASM.

		HYDROCEPHALUS	VASOSPASM	
			ANGIO	POST-OP
	n(%)	21 (7%)	94 (33%)	15 (5%)
TREATED	158	14 (9%)	59 (37%)	14 (9%)
UNTREATED	126	7 (6%)	35 (28%)	1 (0,8%)
		N.S.	N.S.	$p < 0,05$

5.10. CALCIUM BLOCKER NIMODIPINE IN TREATMENT AND PREVENTION OF VASOSPASM.

5.10.1. OPEN PILOT STUDY.

Therapeutic Group (Angiographic spasm with FID):

The outcome for this group of patients is shown in Table 38. Out of 12 patients an overall good result was obtained in 3 cases in this group and 7 patients died. There were 4 deaths which were thought unlikely to be related to vasospasm or nimodipine therapy (Table 39). One was directly related to operative factors, one patient died from a rebleed prior to surgery and 2 died from septic complications after surgery. Two patients had severe vasospasm resulting in death from massive infarction as

shown on CT scan, despite nimodipine administration, and one patient died from extreme refractory hyperglycaemia which was thought to be nimodipine related. Therefore 25% (3/12) of the cases were failures, or a complication of nimodipine treatment.

TABLE 38. FINAL OUTCOME OF PATIENTS TREATED WITH NIMODIPINE.

	OUTCOME	
	GOOD	DEATH
Therapeutic Group(n=12)	3 (25%)	7 (58%)
Prophylactic Group(n=34)	21 (61%)	4 (12%)
Total (n=46)	24 (52%)	11 (24%)

Prophylactic Group (Patients without neurological deficits):

The outcome in this group is shown in Table 38. This sub-group comprised 34 patients. The overall mortality was 12% (4/34) and 61% (21/34) had a good outcome. In this group there were no deaths due to operative complications (Table 39).

TABLE 39. CAUSE OF MORTALITY/MORBIDITY

CAUSE:	DEATH	SEVERE DISABILITY	RELATED TO N®
	THERAPEUTIC GROUP:		
Operation related complications	1	0	No
Meningitis	2	0	No
Rebleeding (before operation)	1	0	No
Vasospasm - Infarct	2	0	? Yes
Severe Hyper-glycaemia	1	0	? Yes
	PROPHYLACTIC GROUP:		
Operation related complications	0	4	No
Pneumonia	1	0	No
Meningitis	1	0	No
Vasospasm-Infarct	2	1	? Yes

Two patients died from septic complications after surgery and 2 from vasospasm confirmed by CT scan and angiography. One patient remained severely disabled as a result of vasospasm. Therefore only the latter 3 (9%) cases were regarded as failures of nimodipine treatment.

Topical Group:

Definite macroscopic vasodilatation of arteries previously seen to be in spasm was seen in 26 of the 38 cases (68%) after topical nimodipine application. In the remainder it

was thought by the surgeon and his assistant that there had been no change in the diameter of arteries.

Intra-arterial group:

In none of these patients (6) was there any angiographic evidence of relief of spasm of the visible major intracranial arteries and, in addition, two of the patients died subsequently of severe FID.

SIDE EFFECTS AND COMPLICATIONS OF NIMODIPINE TREATMENT.

There was a statistically significant increase ($p < 0,001$) in blood glucose and a statistically significant decrease ($p < 0,001$) in calcium levels in patients on nimodipine treatment when compared with pre-treatment values (Table 40).

The glucose and calcium levels obtained before and during treatment were compared to those in a control group consisting of 54 cases admitted to the hospital for reasons other than subarachnoid haemorrhage (mainly head injury) (Table 41). The glucose and calcium levels in patients before nimodipine treatment and those in the control group were not statistically different. In contradistinction the calcium levels for patients on nimodipine treatment were significantly lower ($p > 0,001$)

than in the control group and the glucose levels in the treated group were significantly higher ($p > 0,002$) than in the control group.

Hyperglycaemia (normal value 3,82-6,16mmol/l) occurred in virtually all the treated patients, but did not require any alteration in the treatment dosage and returned spontaneously to normal values in 42 cases. In four cases only it needed the use of insulin. In one patient, however, nimodipine therapy had to be stopped since the patient developed a severe insulin resistant hyperglycaemia which directly contributed to his death (Case 4, page 97).

In our series significant hypotensive episodes were found in 8 of 46 cases (17,3%) necessitating dosage alteration in 3 (6,5%) and cessation of nimodipine treatment in 1 case (2%).

TABLE 40. CALCIUM AND GLUCOSE LEVELS BEFORE -VS- DURING NIMODIPINE TREATMENT

		Before N® Treatment	During N® Treatment	Control Group	p-Values associated with Hotelling's t-test	p-Values associated with Students paired t-test
	n	38	39	54		
Calcium	$\bar{x}$	2,233	1,976	2,273		0,0001
	SD	0,283	0,345	0,171	< 0,001	
	n	40	40	51		
Glucose	$\bar{x}$	7,138	9,530	7,467		
	SD	2,190	3,255	2,596		0,0002

$\bar{x}$ = Mean (level)

SD = Standard deviation

TABLE 41. CALCIUM AND GLUCOSE LEVELS COMPARED WITH CONTROL GROUP

	Before N® treatment p - value	After N® treatment p - value
Calcium	0,45 (N.S.)	< 0,001
Glucose	0,51 (N.S.)	< 0,002

ILLUSTRATIVE CASE REPORTS

Four cases are presented as examples of failure of the nimodipine therapy.

Case 1:

A 33 year old male was admitted 3 days following a subarachnoid haemorrhage. He had a right hemiparesis, a left III cranial nerve palsy and a H&H grade III. A CT on admission was graded as CT-Fisher 3 (Fig.4). Angiography showed a large internal carotid bifurcation aneurysm on the left with angiographic spasm in the internal carotid artery and its branches proximal and distal to the aneurysm for a short distance (Fig.5). Intracarotid injection of nimodipine was carried out but there was no evidence of reduction of spasm on a repeat angiogram 10 minutes later. Nimodipine was started intravenously immediately after angiography. On day 4 of

CASE 1

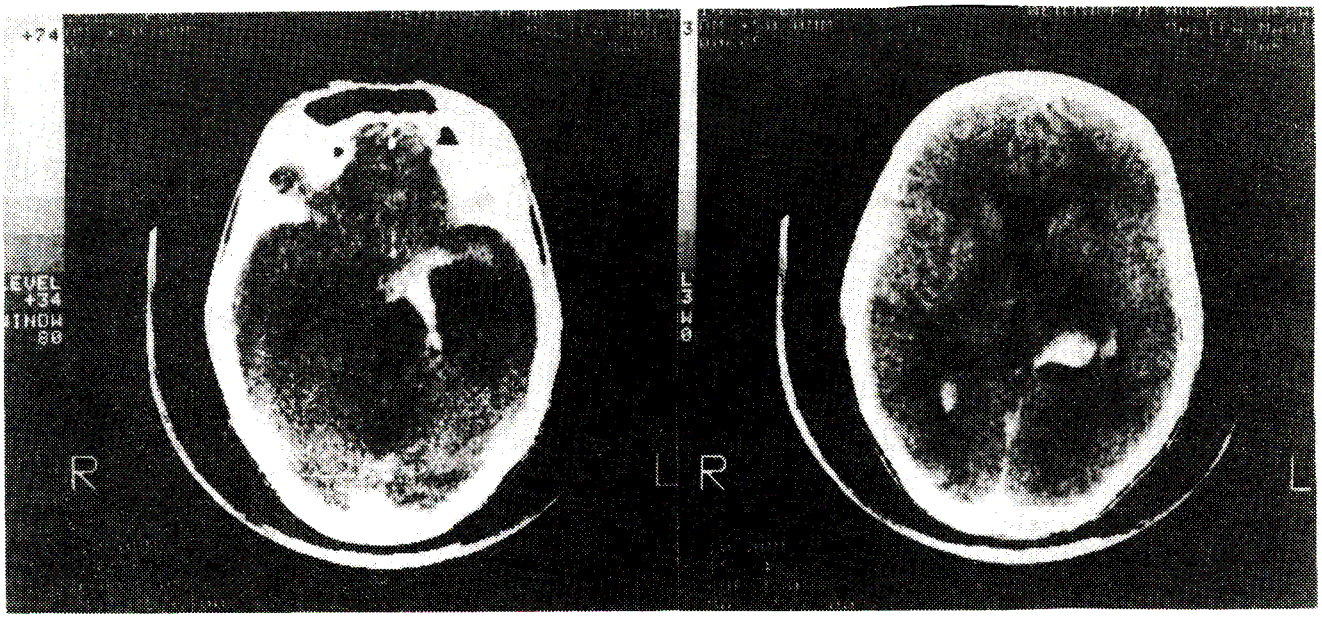


Fig. 4 (a.b) CT on admission (CT-Fisher 3).

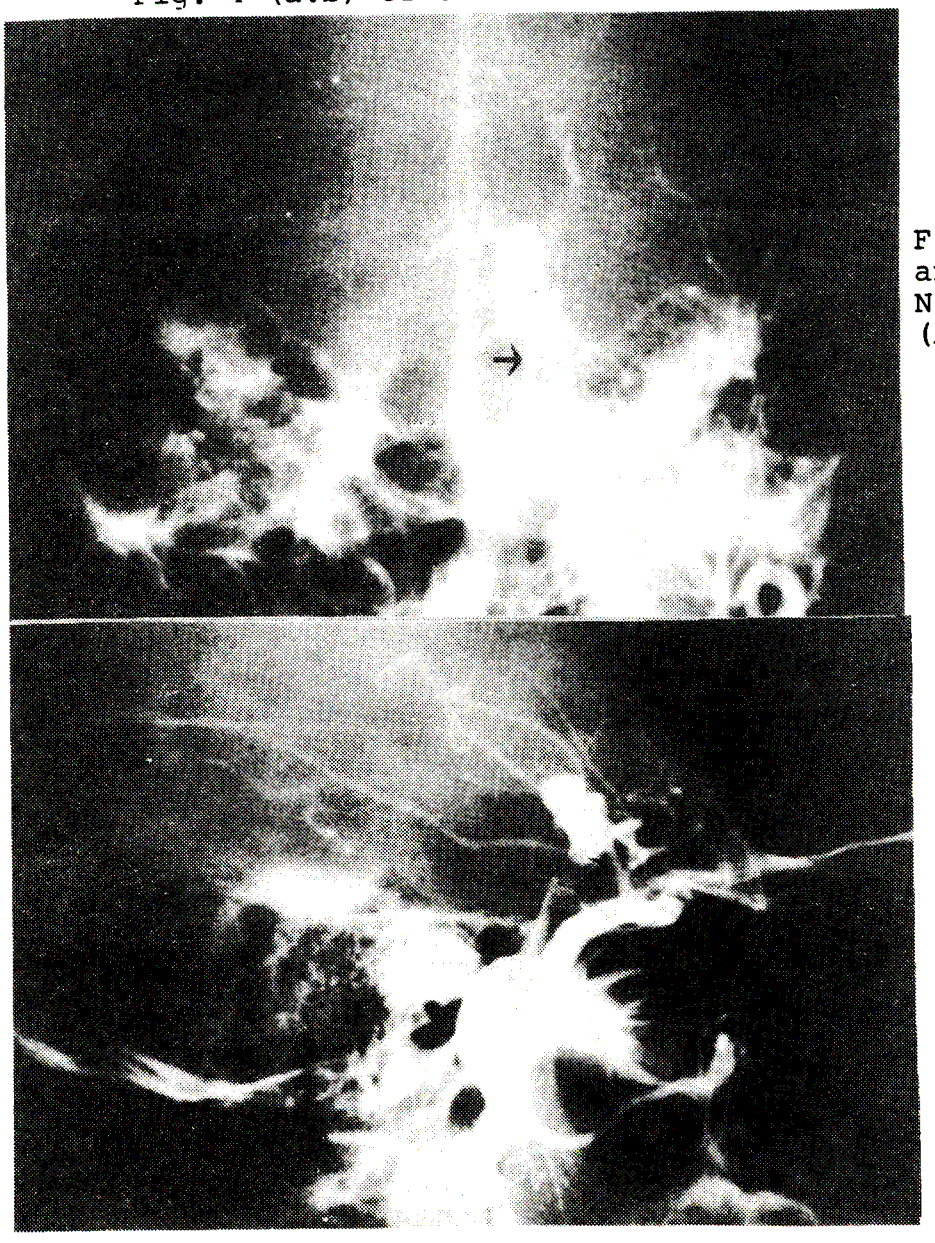


Fig. 5 (a,b) Carotid angiography before Nimodipine treatment. (Arrow - vasospasm)

CASE 1

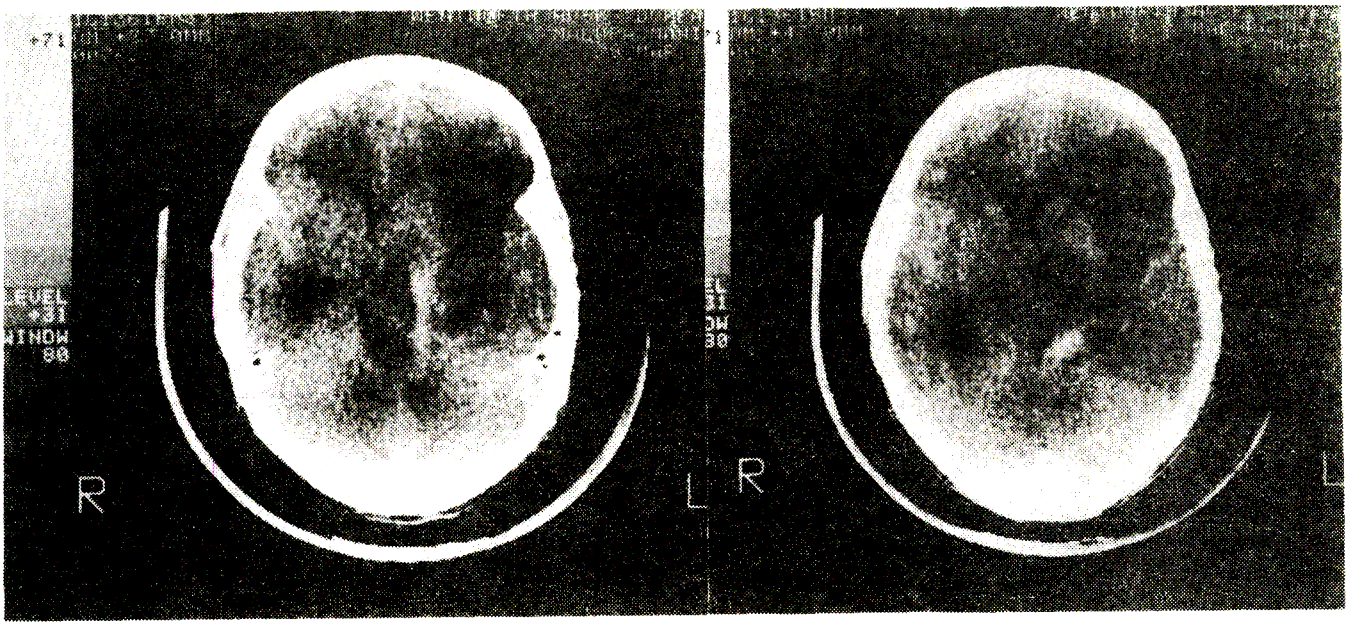


Fig. 6 (a,b). CT on day 4 of Nimodipine treatment.

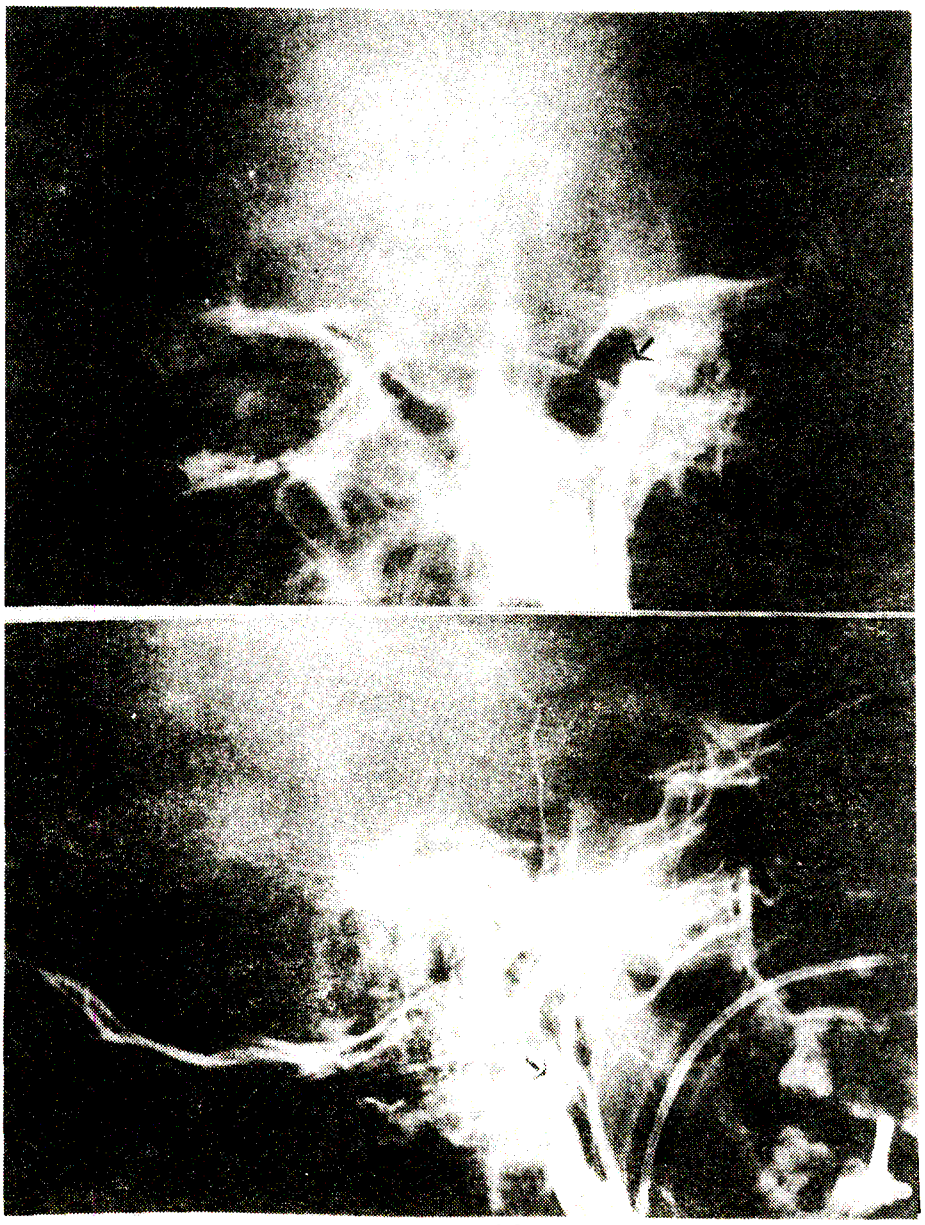


Fig. 7 (a,b,)
Angiography on day 5 of Nimodipine treatment.

intravenous nimodipine treatment there was a sudden fall in blood pressure and a deterioration in the level of consciousness. The previous right hemiparesis became a complete hemiplegia. A CT was repeated on the same day and showed a massive infarction in the middle cerebral artery territory on the left side (Fig. 6). Angiography was repeated the next day and this showed complete occlusion of the left internal carotid artery (Fig. 7). The patient died the following day. The postmortem examination showed a macroscopically intact internal carotid artery with no thrombus nor embolus. Therefore the complete angiographic occlusion of the internal carotid artery must be considered to be the result of vasospasm.

Case 2:

A 50 year old male was admitted one day after SAH in H&H grade III. A CT done on admission was graded as CT-Fisher 3. There was blood in the basal cisterns as well as in the ventricles (Fig. 8). Angiography was carried out 3 days later and demonstrated an anterior communicating aneurysm and localized angiographic spasm (Fig. 9). The patient was operated on the same day and the aneurysm was clipped uneventfully. Intracisternal nimodipine was applied with an obvious macroscopic vasodilatory effect. Intravenous nimodipine was commenced immediately post-operatively. Two hours later the patient had developed a

CASE 2

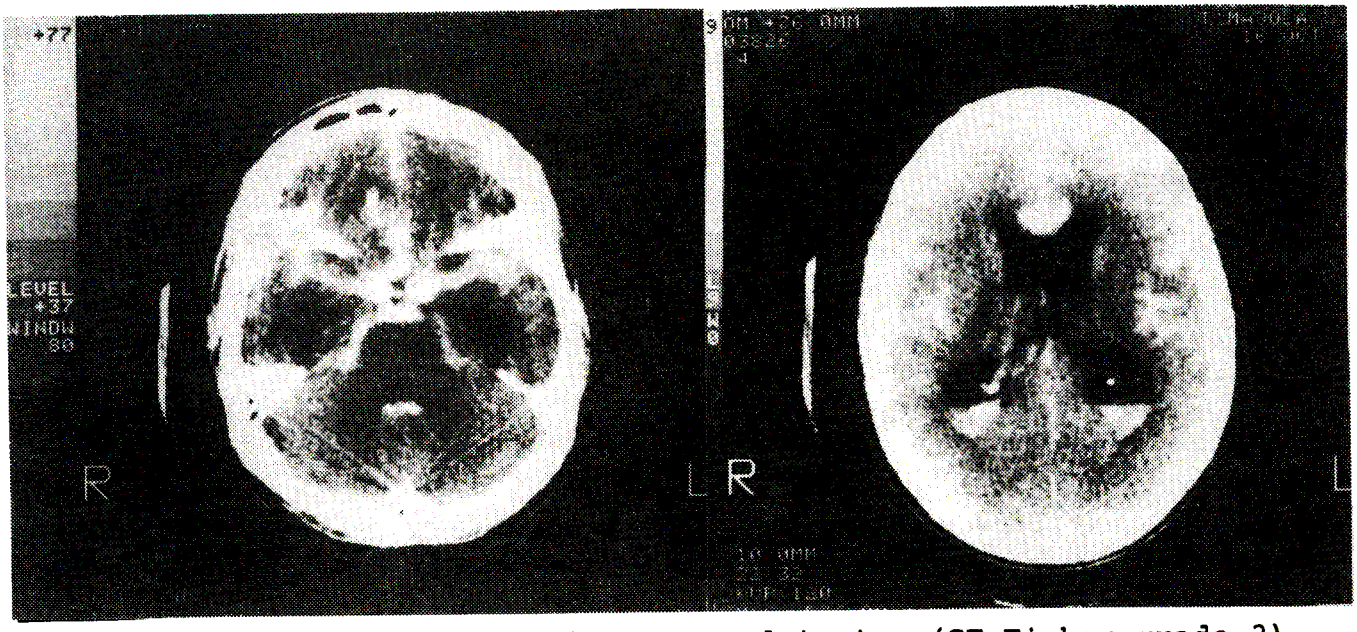


Fig. 8 (a,b). CT on admission (CT-Fisher grade 3)

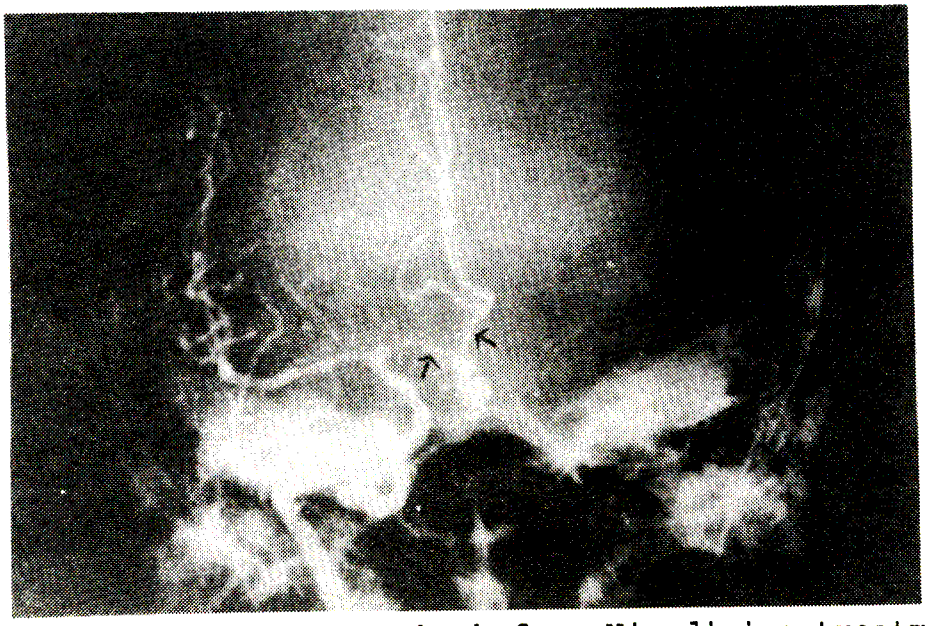


Fig. 9. Angiography before Nimodipine treatment. (Arrows - vasospasm)

CASE 2

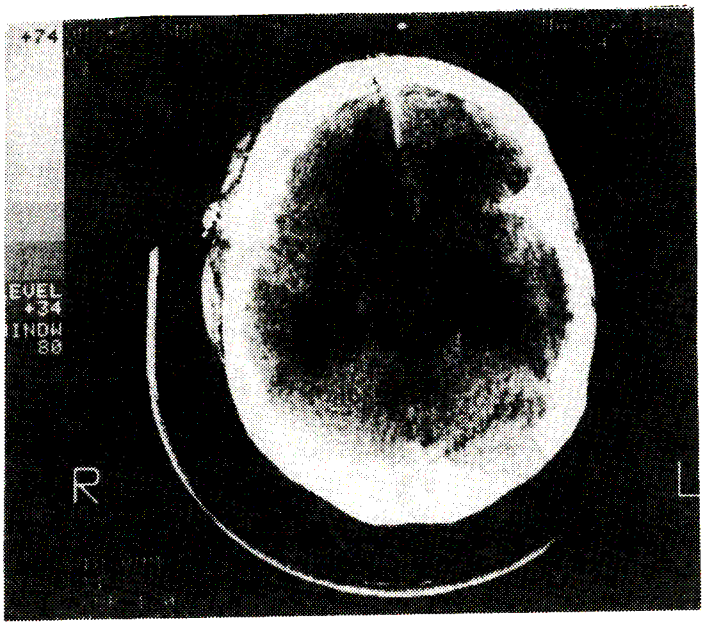


Fig. 10. Post-operative CT.

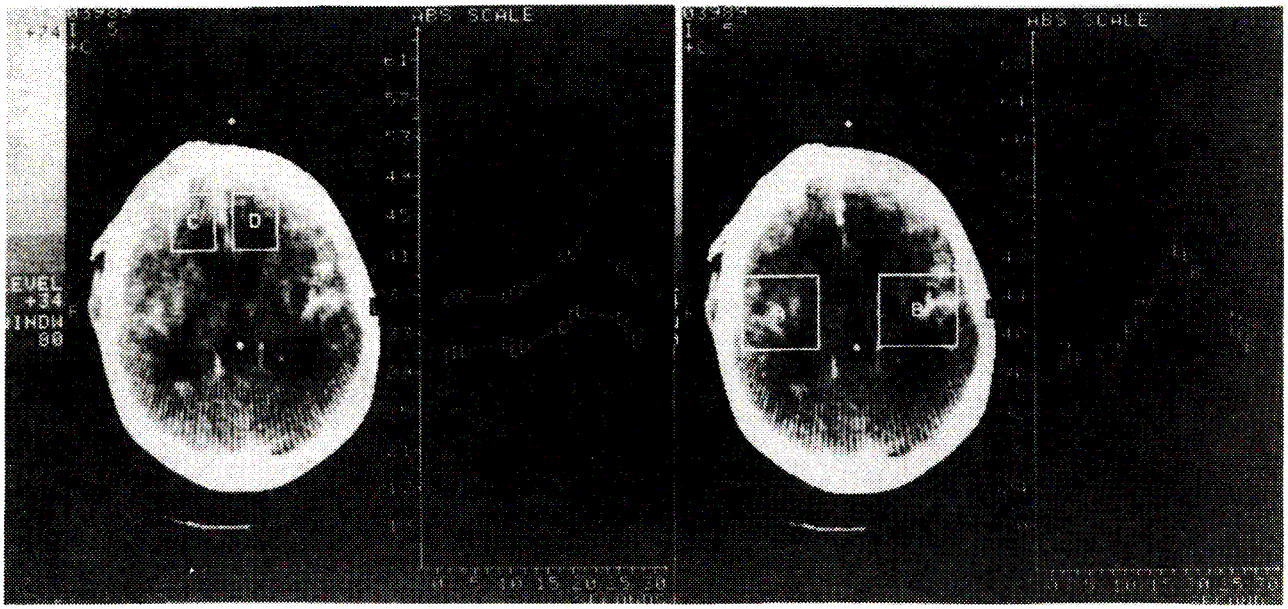


Fig. 11 (a,b). Dynamic CT post-operatively.

right hemiparesis. The following day the patient had a hypotensive episode and dopamine was necessary to restore blood pressure to previous levels. A CT was done on the same day and showed bifrontal low density areas more pronounced on the right (Fig. 10). A dynamic CT was then done and clearly demonstrated relatively low blood flow in both frontal regions when compared to other areas (Fig. 11), the flow in the left frontal area being the lowest. The patient died on the 18th post-operative day without significant change in his clinical condition.

Case 3:

A 48-year old female was admitted one day following SAH, in good general condition and H&H grade I. A CT done on admission showed SAH and CT-Fisher 2 (Fig. 12). Angiography was carried out the next day and this showed an aneurysm of the right middle cerebral artery (Fig.13). There was adjacent localised angiographic spasm and of the A1 segment on the same side. Nimodipine was started intravenously immediately after angiography. The patient was operated on 5 days after the commencement of nimodipine treatment and the aneurysm was clipped. Nimodipine was applied and produced an obvious macroscopic vasodilatation. Two days later the patient developed a dense left hemiplegia and decreased level of consciousness. A dynamic CT showed equal flow in both frontal and occipital regions (Fig. 14), but the right

CASE 3

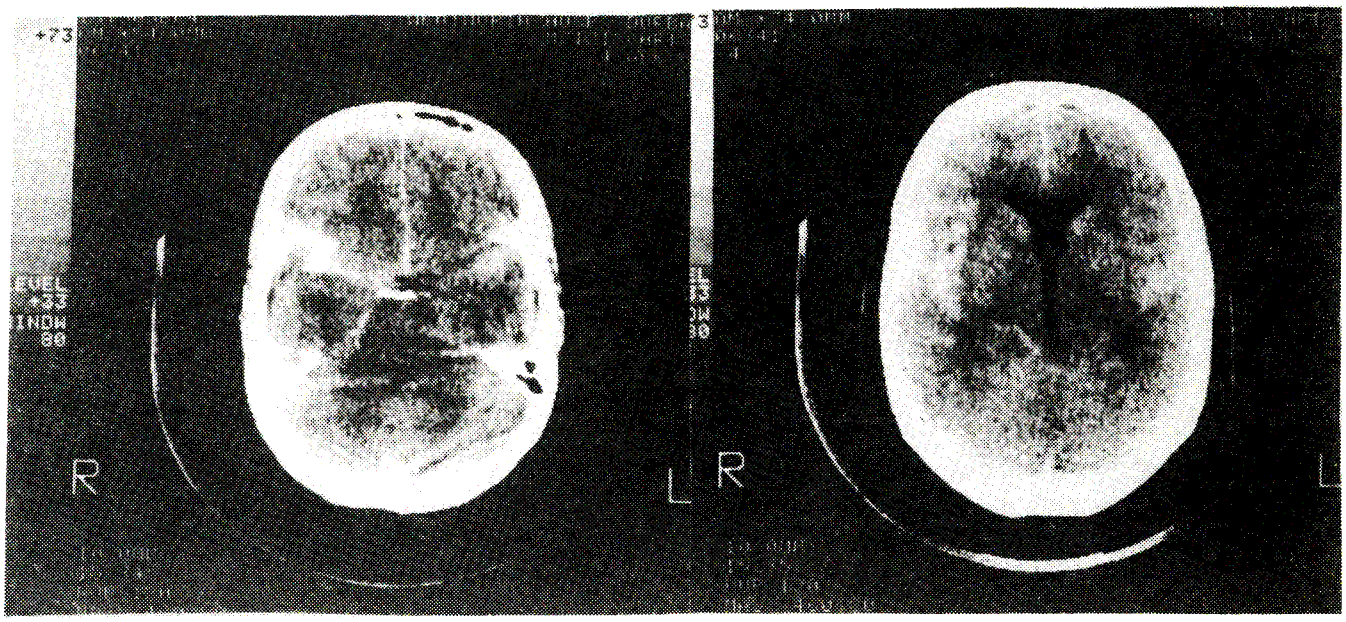


Fig. 12 (a,b). CT on admission (CT-Fisher 2)

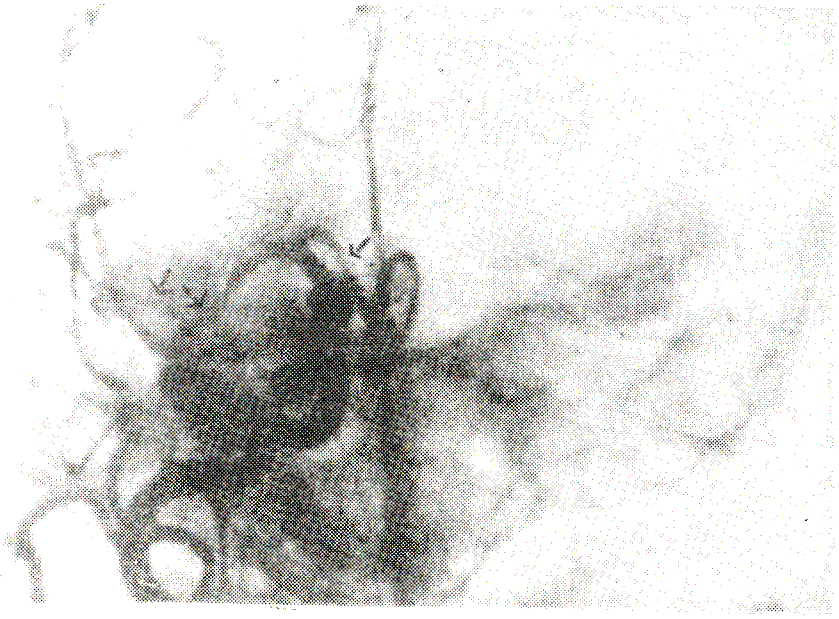


Fig. 13. Angiography before Nimodipine treatment.
(Arrows - vasospasm)

CASE 3

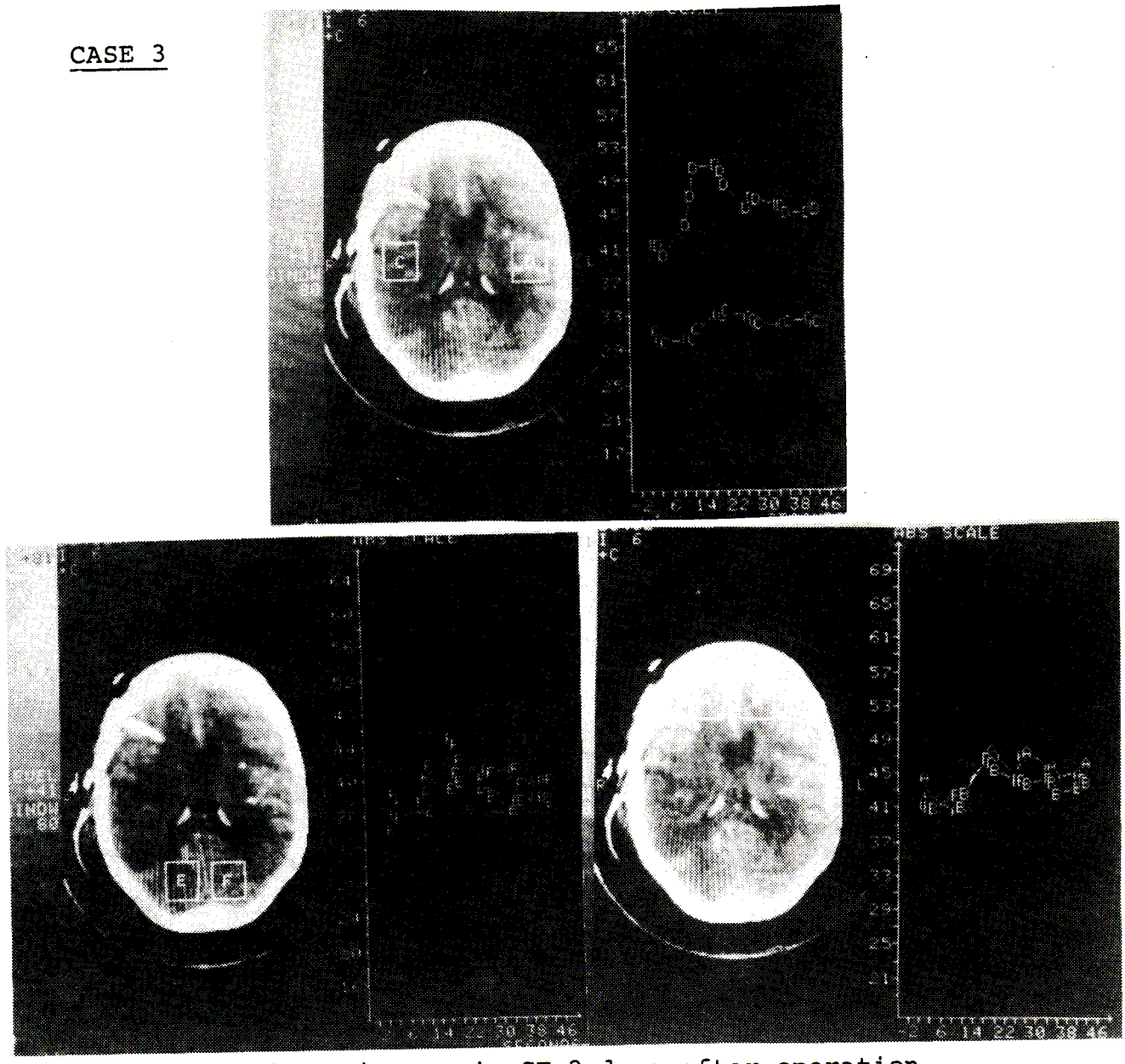


Fig. 14 (a,b,c) Dynamic CT 2 days after operation.

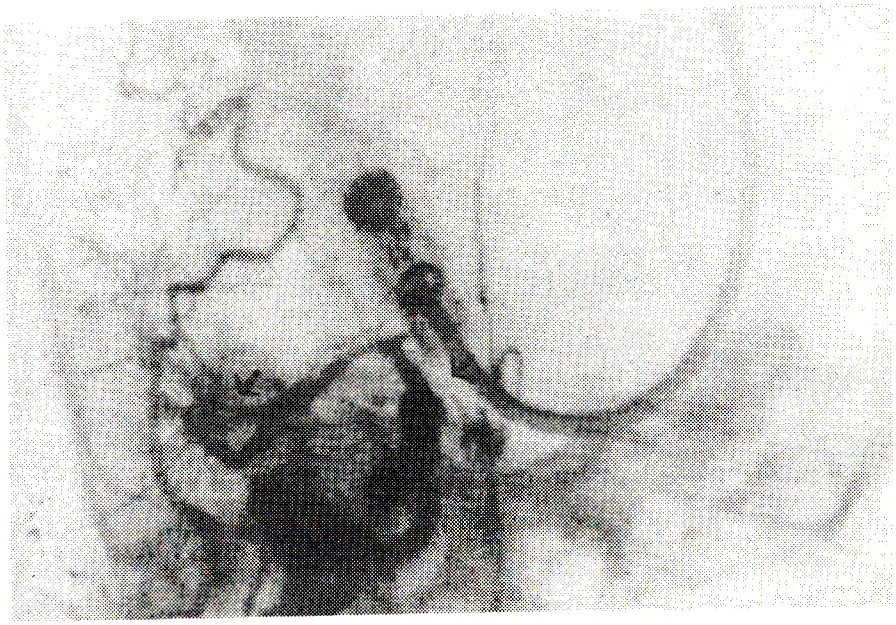


Fig. 15. Post-operative angiography. (Arrow shows vasospasm)

middle cerebral territory blood flow was much lower. Carotid angiography was then carried out and showed the vessels to be patent and in considerable spasm, particularly the middle cerebral artery and the A1 segment on the right side (Fig. 15). In spite of the treatment, the patient gradually deteriorated and subsequently died on day 25 post-operatively.

Case 4:

A 45-year old female was admitted 3 days following SAH. The patient had no previous history of diabetes mellitus nor hypertension. On admission the patient was in H&H grade I. The blood glucose level on admission was 8,9mmol/l. The CT on admission was normal (CT-Fisher grade 1) and cerebral angiography demonstrated a left posterior communicating aneurysm with no angiographic spasm. At operation, due to technical problems, the internal carotid artery had to be temporarily clipped and the anterior choroidal artery permanently clipped. In order to minimise a potential neurological deficit as a result of the intraoperative complications, nimodipine was started immediately. Post-operatively the patient was noted to be dysphasic and had a right hemiparesis. However, 2 days later she was able to speak and the right hemiparesis showed signs of improvement. At that stage a random blood glucose level was 16,7mmol/l. Improvement continued until the 15th post-operatively day and of nimodipine treatment,

when a marked deterioration in the level of consciousness occurred. The patient was found to be hypotensive and the blood glucose level had risen to 43,7mmol/l. The CT was repeated and showed only a small residual haematoma at the operative site. Treatment with insulin continued but the glucose level was so unstable that it was decided to stop nimodipine treatment. Subsequently the blood sugar was gradually controlled but the patient remained in a poor condition and died 4 days later.

5.10.2. CONTROLLED COMPARATIVE STUDY ON NIMODIPINE

Overall mortality rate in the 61 nimodipine treated patients was 23% compared to 15% for the control group of 60 (Table 42). There was no statistical significance in this comparison. The difference appeared greatest in the grade I H&H patients, 26% compared to 8% in the control group. Evaluation of outcome appeared to show slightly better results in the control group, but the difference was again of no statistical significance. Nimodipine appeared also not to decrease the incidence of vasospasm which was 29,5% compared to 18% for the control group. The blood glucose levels in both groups were compared and it was demonstrated that hyperglycaemia occurred more frequently in nimodipine treated patients ($p < 0,02$). In addition it was found that hypotensive episodes occurred in 18% of the nimodipine treated cases necessitating

dosage alterations in 11 cases (5%) and in one case (1,6%) the nimodipine infusion had to be discontinued (Table 43).

TABLE 42. RESULTS OF COMPARATIVE STUDY

		NIMODIPINE ® n=61	CONTROL n=60
GOOD OUTCOME		41 (67%)	49 (81%)
DEATH		14 (23%)	9 (15%)
			N.S.
MANAGEMENT MORTALITY:			
H&H ON ADMISSION	I	9/35 (26%)	3/36 (8%)
	II	2/18 (11%)	3/17 (18%)
	III	2/5	2/6
	IV	1/3	1/1
VASOSPASM		18/61 (29,5%)	11/60 (18%)
			N.S.
HYPERGLYCAEMIA		54/61 (88,5%)	43/60 (72%)
			$p < 0,05$

TABLE 43. HYPOTENSION WITH NIMODIPINE THERAPY
n = 11 (18%)

Dosage alteration	3 (5%)
Nimodipine stopped	1 (1,6%)

6. DISCUSSION

6.1. INCIDENCE OF ANEURYSMS

The age and sex distribution within the SAH patients admitted to Wentworth Hospital during the years 1983-1986 does not differ significantly for that obtained in literature (85,103,114,118,125) although generally younger patients were dealt with (Fig.1, Table 2). The peak of aneurysm incidence fell into the 4th and 5th decades compared with the 5th and 6th decades quoted in the literature (103). Female patients predominated even more in our present series (59,7%) than in Pakerinen (103), Suzuki (129) and Sahs (114) study (56%) but similarly male patients predominated in the earlier decades (present series until the third decade, and Pakerinen's study until the fifth decade).

We have to take into account the fact that the age of the patients in this study is in the majority only estimated (often given by the patient) and the finding of younger aged patients might simply be the result of under-estimation or miscalculation.

The racial distribution of the patients (Table 7) correlates generally with racial representation of the region (Natal and KwaZulu). A slightly smaller percentage of White (6,5% -vs- 9,5%) and Asian (11,2%-vs-9,5%)

patients admitted is probably caused by the fact that some of those patients are treated by the private sector. There was a higher percentage of Coloured patients (6,1%) compared with their representation in the population (1,7%). However, when compared with the overall number of admissions to the hospital, the percentage is similar (5,9%).

Localisation of aneurysms when compared with those from the co-operative study of Sahs et al (114) showed the statistically significant different incidence of posterior communicating artery aneurysms (PCoA) ($p < 0,01$) and anterior communicating artery (ACoA) aneurysms $p<0,001$)in our series which was even more evident in Black patients (Fig. 2 Table 8). Other studies give the anterior communicating artery (ACoA) as the most common site (114,142) while this study shows a definite predominance of PCoA aneurysms.

Multiple aneurysms were encountered more often (20,3%)(Fig.1, Table 8) than quoted by Suzuki (15%)(127,129) but the incidence was similar to the figure reported by Sahs (18,5%)(114). Present findings confirm that there is no increase in the incidence of multiple aneurysms in Black patients (20,2%) (69) and that hypertension increases the incidence of multiple aneurysms (Table 9) (23%) especially in younger patients (31%)(6).

Anterior-communicating artery aneurysms were found more often in males (Fig. 3) as was found in the study by Pakarinen (103), and PCoA aneurysms more often in females, but the differences were not as obvious.

6.2. FACTORS INFLUENCING OUTCOME

Timing of admission (after SAH) influenced significantly the overall outcome (Table 10). Patients admitted in the acute stage (0-3 days post SAH) had a worse prognosis than those admitted between days 4-10 post SAH ($p < 0,05$) and the latter group did worse than patients admitted later than 10 days post SAH ($p < 0,05$). Our findings are in agreement with those of the co-operative study (67) and show that the more serious patients are admitted earlier, the percentage of good condition patients (I/II) gradually increases as the time interval to admission increases (56% in the early stage, 65% in days 4-10 and 71% after day 10).

The clinical condition of the patients, both on admission and before operation, has been found to be the most important factor influencing outcome (8,24,49,60,102). This study confirms this finding as patients in a good clinical condition (grade I H&H) did well regardless of timing of surgery (Table 11,28) when compared with grades III/V H&H ($p < 0,01$).

Several investigation results seem to be a reflection of severity of SAH and therefore clinical condition of the patient:

1) Heavily blood stained CSF showed a tendency towards less favourable prognosis (Table 12) since in 46% it is associated with a thick layer of blood or clot in the subarachnoid cisterns (CT-Fisher grade 3) and vasospasm (Table 13).

2) High blood pressure and hyperglycaemia on admission reflects the severity of initial bleed by Cushing response (hypertension)(8) or stress response (hyperglycaemia)(136) and therefore are associated with a statistically significant worse prognosis especially when they occur in combination (Table 17). Hyperglycaemia is, especially dangerous in SAH, due to lowered CBF (53,83) and even its degree influenced the mortality rate (Table 16), i.e. 29% and 39% in mild hyperglycaemia, (below 10mmol/l) and 10-20mmol/l respectively, while in normoglycaemic patients 19%. There were no patients admitted with serum glucose levels above 20mmol/l presumably taking the above into account, unfit for any form of neurosurgical intervention.
Detailed discussion on influence of hyperglycaemia in SAH is continued in chapter

6.5 on page 116 and proves that high serum glucose should be avoided and possibly mild hypoglycaemia induced (111).

The highest incidence of hypertension found in the sixth decade coincided with the worst prognosis, indicating that hypertension at least partly contributes, in conjunction perhaps with other associated diseases, in older patients (119), towards their worse ($p < 0,05$) overall prognosis (Table 32).

3) The finding of a thick layer of subarachnoid blood or clot on CT (CT-Fisher grade 3) proved to be associated with a statistically significant worse prognosis (Table 18) and was associated with moderate to severe vasospasm proved angiographically (Table 19) and hydrocephalus (Table 20). This finding proves the prognostic value of CT (3,35,70).

Intracerebral haematomas carried a less favourable outcome (Table 21) but this was of no statistical significance.

Site of Aneurysm and angiographic vasospasm

The most often quoted unfavourable site of anterior circulation berry aneurysms is the anterior communicating artery (ACoA)(126). In the present study this proves to

be statistically significant ($p < 0,05$) and good management results in ACoA aneurysms were obtained in only 53% (Table 22). This figure is much worse than those quoted by other authors (60,126). However, the other authors give only operative results. Poor results in ACoA aneurysms are explained by damage to nearby vital structures (especially the hypothalamus) either by associated haemorrhage or by interruption of their blood supply via perforating arteries originating in the ACoA complex (60). Surgical manipulation especially dissecting in the close vicinity of multiple perforating arteries may contribute to poor overall results. In our study, the initial bleed and poor clinical condition were responsible for a less favourable outcome in ACoA berry aneurysms since half of those patients were in grades III-V (H&H) and those were the cases with poor outcome (Table 23). When patients in good clinical condition were looked at, they had a similar outcome to those with aneurysms in other locations. Diffuse, severe, vasospasm was seen most often ($p < 0,02$) on angiography between days 4-10 post SAH (Table 24) and carried a poor overall prognosis (Table 25).

6.3. POST-ANGIOGRAPHY DETERIORATION

The alarming figure of 16,7% (45 cases) was found as the percentage of our patients who deteriorated at angiography or within 12 hours thereafter (Table 26). Even if the

natural rebleeding rate of the disease is taken into account, the figure is much higher than that quoted by other authors (75,98). The causes of deterioration were found to be equally distributed (5-6%) among rebleeding, vasospasm and metabolic causes (Table 26).

Inagawa (52) found that ultra-early angiography within 6 hours post SAH is associated with a high rate of rebleeding during angiography, i.e. two-fold (32%) when compared with the rate of overall rebleeding (15%). Early angiography done within 3 days post-SAH did not carry a higher risk of deterioration (Table 26), and in fact carried a slightly lower rate (16% -vs- 21%) of post-angiography deterioration (N.S.). Significantly fewer ($p < 0,05$) deteriorations were found after delayed angiography done later than 10 days post SAH. Patients in good clinical condition (grades I/II H&H) had a much lower ($p < 0,001$) rate of deterioration post angiography (Table 29). Careful preparation of the patients for angiography, the experience of the Radiologist, and time and technique of the procedure are the other factors quoted which contribute to the risk (98).

6.4. TIMING OF SURGICAL INTERVENTION

Good surgical results of 75% and 16% mortality are comparable with the results of other authors (2,67,72). However, different surgical outcomes quoted by different

authors are merely the result of different management policies rather than surgical techniques. Obviously surgeons who decide to operate on all patients with SAH regardless of their clinical condition and time post SAH, will have the worst surgical results. Delayed surgery on grade I and II patients will carry the best ($p < 0,05$) results (Table 30). In our series we had an 88% good result and 9% mortality in this group.

An international co-operative study (67) on the timing of aneurysm surgery demonstrated that the overall outcome from early operation is equivalent to, or better than, (especially alert patients) that from delayed operation in a large number of neurosurgical centers throughout the world.

Early operation in units with well organized, experienced, committed teams is practical and perhaps produces results that are at least as good as, and together with an effective therapy for vasospasm superior to the results of delayed surgery (14,18,28,79). Whether those outstanding results achieved with early surgery can be replicated by other centres with more limited experience and resources, remains of serious concern.

Our surgical results with regard to timing of surgery and pre-operative clinical condition (Table 28) show that operating on patients in grades I/II (H&H) carries a

similar and good outcome regardless of the timing of the operation (5/7 cases in early surgery, 78% between 4-10 days and 88% delayed surgery). However, the longer definitive surgery is postponed the more patients are lost awaiting surgery (Table 29,30). Four patients initially in grade I/II died and a further 3 deteriorated to a moribund condition and were not operated on. The results favour early surgery, or surgery as soon as is possible, in all grade I/II patients regardless of timing of admission.

The main concern appears to be in patients admitted in grade III (H&H). They had a much worse surgical result (good outcome 54%). While delaying surgery, only 3 patients improved to grade I and were successfully operated, 2 deteriorated to grade IV and were operated upon with bad results. A further 17 patients died before operation and 7 deteriorated to a moribund condition and were not operated on. Therefore the overall management results of patients admitted in grade III were extremely poor (36% of good results).
In an attempt to improve these results, patients in grade III should be operated earlier to prevent rebleeding, to prevent or decrease severity of vasospasm and to permit more aggressive treatment of cerebral vasospasm.

Patients in serious condition (H&H grade IV/V) had no

favourable surgical results when operated on up to 10th day post SAH, but 2 out of 4 patients in grade IV who underwent delayed surgery had a favourable outcome. The small number of operated cases in this group does not allow further comment. However, out of 24 patients admitted in serious condition, 14 improved to grade I and were operated with similar favourable results, while 4 cases improved to grade III and were operated upon, 3 of them with good results (Table 29).

The results are in favour of admitting those patients as soon as possible and aggressive, conservative management in the early stage and operation on improvement of their condition. Some selected, stable cases may be managed by delayed surgery.

Operating on cases with proven vasospasm, between 4-10 days post SAH, has proved to have a significantly worse outcome ($p < 0,05$). A delay in surgery in these cases improved the outcome dramatically (48% -vs- 89%) (Table 31) and reduced the incidence of post-operative vasospasm (12% -vs- 1,6%) (Table 31).

Vasospasm has a diffuse effect on the Circle of Willis adjacent to the aneurysm and can be intensified by dissection of the vessels and operative trauma. It constitutes a contraindication to any form of immediate surgical intervention in grades III-V, other than those rare cases in which there is an associated haematoma.

As far as operative technique is concerned, there are two aspects worth commenting on:

Firstly, the use of temporary clipping for a short time, or intermittently (in our series up to 10 minutes) carries a better outcome than premature rupture (good results 63,2% -vs- 56%, mortality 21% -vs- 27% respectively) (Tables 33-35). It fails, however, to show statistical significance. Taking into account that the group of temporary clipping includes the cases where premature rupture necessitated temporary clipping, the difference is even more in favour of this procedure in difficult surgery (e.g. early surgery).

Secondly, intraoperative ventricular drainage to facilitate retraction, with conversion to post-operative ICPM, became almost a routine in our department. Aucoin (11) compared different methods of ICPM with post-operative infection and found that intraventricular ICPM (especially in vascular operations) carried a significantly higher sepsis rate in the form of ventriculo-meningitis (i.e. 21,9% -vs- 4,1% for subdural catheters).

In the present study, our rate of CSF sepsis after aneurysm surgery, with post-operative ICPM, was 11%, all in cases with intraventricular ICPM (13%) and none with subdural cup catheters (Table 36). Although this rate is substantially lower than that quoted earlier, our ventricular ICPM's were removed much sooner (not later

than the 4th post-operative day). Only 30% of ventricular drains were removed by that day in Aucoin's study (11). Additionally, we had 1 death definitely caused by ventriculitis. Still favouring post-operative ICPM in SAH cases, subdural cup catheters should be, as often as possible, the method of choice.

Pre-operative antifibrinolytic therapy resulted in a higher ($p < 0,05$) incidence of hydrocephalus and angiographically proven vasospasm postoperatively (Table 37). This makes the use of antifibrinolytic therapy not worthwhile despite it's effect in decreasing the rebleeding rate (66).

6.5. CALCIUM BLOCKER NIMODIPINE IN PREVENTION AND TREATMENT OF VASOSPASM.

In 1983, Allen et al (4) reported fewer neurological deficits in patients with subarachnoid haemorrhage due to ruptured aneurysms and angiographically verified vasospasm when treated with oral nimodipine than with a placebo. Death or severe neurological deficit from vasospasm also ocurred less frequently in nimodipine treated patients. However, if all the morbidity attributed to spasm were included, there was no statistically significant difference demonstrated. Subsequently other controlled

studies (90,106) with the oral form of nimodipine also supported it's effectiveness in reducing the occurrence of neurological deficits due to vasospasm. None of these trials however proved unequivocally that the clinical benefit had been the result of direct inhibition of cerebral arterial spasm.

Experimental reports documenting the effect of nimodipine have involved the reversal of only the acute or subacute (0-2 day) phases of cerebral arterial spasm in animals receiving small quantities of subarachnoid blood and producing a reduction in arterial diameter of only 20-30% (123). This degree of arterial spasm is relatively mild when compared with that seen in human clinical conditions. A recently developed model(101,134), to induce severe chronic arterial spasm closely resembling that found in human cases of SAH, may provide a more accurate experimental method of testing the efficacy of calcium blockers in preventing or reversing arterial vasospasm.

There is also at present, other clinical and laboratory evidence suggesting that systemic therapy with nimodipine may not significantly affect the degree of angiographically visualised arterial spasm (34,101,143,148). The reported beneficial effect of nimodipine observed in clinical trials may result from an improvement in the collateral blood flow produced by the dilatation of small vessels (15,25)

An intracarotid bolus injection of nimodipine to reverse angiographic vasospasm of major cerebral arteries in 6 cases from the therapeutic group was not successful and this form of administration was therefore abandoned as being ineffective. The observation is in keeping with the preliminary report of Grotenhuis (41) using an identical method. Boker and co-workers (22) have reported 3 cases where angiographic vasospasm was reversed by intracarotid nimodipine. The dose used, however, was higher and the time of injection much longer. In addition, they noticed a 'dangerous' increase in the angiographic size of the aneurysm.

Topical application of a nimodipine solution at the time of surgery, after clipping of the aneurysm, was in the study macroscopically effective in dilating spastic arteries predominantly of small calibre in 2/3 of the cases. This observation is supported by others (14,15,17,19,26). This method of administration would be of value if it could be continued post-operatively by an intraventricular(39,137) or intracisternal(17,19) infusion. This would provide a minimal dose for maximal potency and minimal associated side effects. One problem using this method would be that the treatment might need to be prolonged more than 4-5 days which would be inadvisable in view of the increased risk of cerebro-

spinal-fluid infection (11).

In an open pilot study on nimodipine, better results were obtained in the prophylactic group (Table 38), but severe FID due to vasospasm caused unfavourable outcome in 9% of the nimodipine treated cases (Table 39). The comparative study (Table 42), although not double-blind but randomized, compared the overall results of 2 groups of patients treated in one department over an identical period of time with the same referral criteria and management protocols and operated upon by the same surgeons. We could find no beneficial effect of nimodipine on either the overall results or the incidence of vasospasm.

The patients were prophylactically treated with nimodipine as soon as diagnosis was confirmed after arrival at the neurosurgical department, but this was, in the vast majority of cases, well beyond the third day following SAH.

Delayed vasospasm after the third day post-SAH has been reported to be a complex and multi-factorial process and according to some investigators represents possible structural arterial narrowing comprising a proliferative vasculopathy or vasculitis (63,141). Treatment then commenced after 3 days post-SAH would be ineffective when this delayed, structural vasospasm was already present. However, more recent studies have returned to the original

concept of chronic vasospasm being a reversible condition of prolonged vascular smooth-muscle contraction (39,132).

Several adverse effects of initial parenteral nimodipine treatment were encountered, which might have negated any beneficial effect of calcium blocking. These have not been previously reported in other clinical studies.

1. Hypotensive episodes: In primates, Harris & Symon (43) found a significant drop in blood pressure with parenteral infusion of nimodipine. It was also found that nimodipine did not increase blood flow in the experimental animals with closed skulls. It also severely compromised cerebral autoregulation to alterations of PaC02 and systemic hypotension. This view is supported by the observations of Nosko (100) and Zabramski(148) that nimodipine can have significant, dose-related systemic haemodynamic effects including a reduction of mean arterial blood pressure and an increase in cardiac output. These findings would suggest that careful monitoring of the blood pressure of patients on parenteral nimodipine is essential. Gioia (39) in canine models noted a drop in blood pressure when giving nimodipine sublingually (17%) or intravenously (41%) without reversal of vasospasm.

The hypotensive episodes observed with parenteral nimodipine therapy might therefore produce a dangerous adverse reaction, as the brain would lose its capability of autoregulation and this may lead to hypoperfusion

aggravating ischaemia and resulting in the development of vasospasm.

2. Hyperglycaemia: Hyperglycaemia which was observed in nimodipine treated patients is obviously dangerous in view of the large number of recent studies and reports (40,83,92,121,122,130). The initial acidosis observed during ischaemia is due to lactic acid production from anaerobic metabolism, whereas the later acidosis is due to an accumulation of free-fatty acids (FFA) as a reflection of energy failure. Ljunggren (78) in an experimental study found that the intracellular pH in hyperglycaemic animals after 5 minutes of total ischaemia decreases to levels close to 6,0 and a pronounced difference was found in the lactate content being 20,7 $\pm$ 0,3µmol/g in hyperglycaemic, 12,1 $\pm$0,5 µmol/l in normoglycaemic and 4,8 $\pm$ 0,7µmol/l in hypoglycaemic animals. However, in spite of these observed pH differences, the energy charge (EC) did not alter. Furthermore, when the tissue was perfused for 15 minutes following a 5 minute total ischaemic period there was an identical degree of restoration of the energy state in all three groups. A state of incomplete ischaemia (as would occur in arterial vasospasm) with maintenance of less than 10% of the normal CBF is far more detrimental to neuronal tissue than complete ischaemia, whether measured by the energy state, metabolic parameters, electrophysiological phenomena or neurological outcome (61,62,110,123). Two main hypotheses have been

proposed to explain these observation (121) -

a) Firstly, during incomplete ischaemia, FFA, especially arachidonic acid, may be oxidised with the resultant accumulation of prostaglandins, thromboxanes, leukotrienes and free radicals - all potent factors in the aetiology of arterial vasospasm and cellular damage;

b) Secondly, an excessive supply of substrate for anaerobic glycolysis may lead to excessive tissue acidosis which enhances tissue damage.

In Marsh's study (83) the brain pH in glucose-treated monkeys with an incomplete ischaemic state fell to around 6,0 at 3 hours compared to a placebo group in which the pH declined but stabilised at a plateau of 6,7. At death, in both groups, the pH fell to near 6,0. During complete ischaemia the normal glycogen and glucose stores are sufficient to increase tissue lactate levels to about 15µgmol/gm of brain. If there is residual flow (e.g. arterial vasospasm), and coincidental hyperglycaemia, the lactate rises to about 20µgmol/gm and may even attain a level of 35-40µgmol/gm. The result of the tissue lactate rise, to about 20µgmol/gm tissue water, is an increase of ischaemic cell damage (62).
Hypotension in combination with hyperglycaemia would have a similar effect even if moderate vasospasm were present. In more prolonged ischaemia with associated

hyperglycaemia, astrocytic swelling becomes evident and oedema develops, further compromising the decreased nutrient delivery. This often progresses further after re-perfusion and results in tissue infarction (122). Intracellular acidosis can also directly cause neuronal death by the denaturing of proteins and therefore loss of metabolic function (110).

Nimodipine has been proven to block voltage-dependent calcium channels (68). It is possible, however, for extracellular calcium also to enter cells via channels not specifically controlled by slow-channel blockers (91). Brandt (25) suggests, for example, that prostaglandin PGI can open membrane calcium channels that cannot be blocked by Ca-blockers directly. This was confirmed by Nosko et al (99) who found, in addition, that nimodipine was ineffective in vasospasm induced by haemoglobin.

It has been suggested that calcium blockers do not seem to affect the intracellular calcium(20). Hass (44) proposed a hypothesis for the molecular mechanisms of cellular damage due to raised intracellular calcium. Raised intracellular calcium would stimulate the release of sequestrated intracellular calcium and various transmitter substances which would, in turn, enhance further calcium influx. Increased intracellular calcium would also stimulate phospholipase A2 and/or C activity, resulting in an increased permeability of neuronal and mitochondrial

membranes, releasing FFA, the precursor of prostaglandins and other related substances. The influx of calcium is enhanced in ischaemia by failure of the ATP dependent sodium - calcium antiport system and sequestration by the endoplasmic reticulum. The electrophoretic accumulation of calcium by the mitochrondria would then uncouple oxidative phosphorylation. Cerebral ischaemia due to vasospasm triggers a cascade of events which might not be reversed by slow-channel blockers, especially if the cascade is already well advanced. In clinical terms this would mean that treatment had commenced too late. A decrease of extracellular calcium and hypocalcaemia may be the result or an indicator of these events.

Decreased serum calcium levels were observed in nimodipine treated patients (Table 40), when compared with pre-treatment levels. Harris and Symon (43) found that parenteral infusion of nimodipine increased the blood flow threshold at which oedema formation and disturbances in ion homeostasis began. Therefore, in areas where blood flow is critical, the cells would then be more susceptible to ischaemic damage. They also showed that even preloading with nimodipine did not stop the movement of calcium into ischaemic cells, and, did not prevent a tendency to a decreased serum calcium level associated with a significantly lower extracellular calcium when compared to a placebo group. This, they suggested, indicated that the blood flow level at which calcium-ion homeostasis was

disrupted was higher in the nimodipine treated animals.

The side effects observed in this study may be either dosage dependent or related to the method of administration or both. Studies on effective brain tissue nimodipine levels (45) could contribute to the determination of the appropriate dose of the drug, to provide an adequate concentration and maximal pharmacological effect with reduced risk of significant systemic side effects. The intrathecal administration of nimodipine promptly reversed cerebral arterial vasospasm in several canine models of SAH which systemic administration failed to do (39). Auer (16,17) has also reported on the intracisternal application of nimodipine immediately following aneurysm surgery which in his experience consistently resolved any intraoperative observed spasm and improved outcome.

Early surgery with topical application of nimodipine (16) and subsequent intracisternal or intrathecal administration of the drug might provide evidence for the use of a lower concentration of nimodipine in the CSF to prevent or reverse vasospasm, and prevent delayed FID, without systemic side-effects.

7. CONCLUSION

1. The incidence of aneurysms is similar with regard to age and sex distribution, to data obtained from the literature. There is no racial predominance in aneurysm incidence.

Statistically significant differences were found in location of aneurysms - PCoA being the commonest site in patients referred to Wentworth Hospital.

2. The main factors influencing outcome were :
clinical condition of the patient and timing of admission, hypertension and hyperglycaemia, presence of vasospasm and CT appearance of a thick layer of blood or clot in the subarachnoid space.

All these factors seemed to determine the severity of the initial bleed and are to be considered in management policy.

3. The high rate of post-angiography deterioration (16,7%) was noted, the reasons being equally distributed between rebleeds, vasospasm and metabolic causes.
The highest risk of deterioration was in grade III (H&H) patients after angiography done between 4-10 days post-SAH.

4. Surgical results were improved by delayed surgery, but increased the overall management mortality and morbidity.

5. The systemic administration of the calcium blocker nimodipine did not reverse, or prevent, vasospasm (used later than day 3 post SAH).

Additionally parenteral nimodipine caused serious adverse effects, i.e. hypotension and hyperglycaemia which, in turn, might have negated beneficial effects of calcium blocking.

6. After taking the above into consideration, the timing of surgery for aneurysmal SAH is suggested depending on the clinical condition of the patient on admission.

I/II grade (H&H) patients should be operated on as early as possible regardless of timing of admission and results of radiological investigations (CT, angiography). Early surgery (1-3 days) should be the aim of the effort including referral, transport and hospital organization.

III grade (H&H) patients should be operated on as early as possible, provided radiological investigations do not carry high risk factors i.e. CT-Fisher grade 3, severe angiographic vasospasm. When the latter is present, surgery should be performed soon after day 10 post-SAH.

preparation and selection of patients for angiography.

IV/V grade (H&H) patients should be treated conservatively in specialised units as soon as possible, preferably neurological or neurosurgical wards, and operated on as soon as their grade improves or, in selected (by surgeon, radiologist and anaesthetist) cases by delayed surgery (after day 10 post SAH).

The above is presented as the proposed management policy for aneurysmal SAH in patients admitted to the Department of Neurosurgery, University of Natal Faculty of Medicine and Wentworth Hospital.

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