BARBITURATE TREATMENT

IN EXPERIMENTAL

TRANSIENT FOCAL CEREBRAL ISCHAEMIA

by

CHARLES FREDERICK KIECK

M.B., Ch.B., (Stell.), F.C.S., (S.A.)

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CHAPTER 1

INTRODUCTION

Cerebro-vascular disease, stroke, is a major cause of morbidity and death in South Africa. Wyndham (1981), reported that it ranked first as a cause of death in the Coloured, second in the Asian, third in the White and fourth in the Black population and as such is responsible for 10%, 12%, 7% and 8% respectively of all deaths in the economically active population of these groups.

Because the consequences of a cerebro-vascular accident are profoundly damaging, any new therapy that may suggest a preventative or protective effect, stimulates tremendous interest both in the medical profession and amongst the lay public. Many "dramatic" and "rational" therapies for cerebral ischaemia such as hypothermia, hypocapnia, hypercapnia and hyperbaric oxygen have all been discarded as they were regarded as either impractical or because promising laboratory results could not be reproduced clinically.

Following the synthesis of barbituric acid by Von Bayer in 1864, it was reported that barbiturates depressed the cerebral metabolic rate for O_2 ($CMRO_2$) and the cerebral bloodflow. There followed other reports suggesting a possible protective effect against cerebral anoxia and ischaemia in sub-primate experiments. The report by Smith et al (1973) initiated an extensive investigation of barbiturate treatment for permanent focal cerebral ischaemia simulating a stroke, with other workers investigating global cerebral ischaemia to reproduce the event of a cardiac arrest.

THE THESIS

When the research, which forms the basis of this thesis was started in 1979, the theoretically attractive situation of transient focal cerebral ischaemia simulating a cerebral vessel occlusion followed by re-vascularization, had not been specifically investigated with barbiturate treatment.

Cerebral infarction is progressive and evolves over hours, proceeding from ischaemia and functional loss to cell death. Sundt et al (1969), Crowell et al (1970), Hayakawa and Waltz (1975). Complete recovery is possible if re-vascularization is instituted in time. This time interval depends on the regional cerebral bloodflow during the period of the vessel occlusion and this bloodflow is provided by the collateral circulation. Thus whether infarction results and the extent of it, becomes a factor of the period of ischaemia and the collateral circulation present. Dujovny et al (1976), Morawetz et al (1978), Ojeman et al (1979), Kieck and Crowell (1979), Jones et al (1981). This ischaemic period may vary tremendously from less than an hour to as much as 5 hours and occlusion times of up to an hour can be tolerated without infarction at very low regional cerebral bloodflow levels. Morawetz et al (1978), Kieck and Crowell (1979), Jones et al (1981).

In the clinical situation there would be an obligatory delay from the onset of ischaemia to the institution of barbiturate treatment and completion of re-vascularization. Treatment during this period would thus be a major contribution if it could afford protection so as to allow restitution of cerebral bloodflow before irreversible infarction took place.

The South African Vervet monkey was chosen for the investigation of the effect of barbiturate treatment on transient focal cerebral ischaemia in a model simulating the clinical event. In this experiment pentobarbital therapy would be delayed for 1 hour to provide for the expected delay that would occur from the onset of ischaemia to the institution of treatment. Similarly, ischaemia was to last 4 hours to allow for a minimum time interval necessary to complete the re-vascularization. It was also borne in mind that many stroke patients would be older people; the barbiturate dose of 30mg/kg would be such as to induce prolonged coma but not major cardiovascular disturbances with a fall in blood pressure and/or cardiac arrest.

Much of the technique and background knowledge was acquired during the year 1977-1978, when I was a microsurgical fellow with Drs. R.M. Crowell and R. Ojeman at the Massachusetts General Hospital in Boston.

CHAPTER II

REVIEW OF THE LITERATURE

(A) HISTORICAL AND EARLY OBSERVATIONS AND STUDIES

HISTORICAL

Barbituric acid was first synthesized from the condensation of malonic acid and urea by Adolph von Bayer, working in Ghent in 1864. Goodman and Gilman (1970). Barbituric acid is not itself a central depressant but the derivatives, the barbiturates, are. The first hypnotic barbiturate, diethylbarbituric acid, or barbital, was introduced into clinical medicine by Fischer and Von Mering in 1903 as "Veronal" and phenobarbital was introduced in 1912 as "Luminal". Over the years more than 2500 barbiturates were synthesized and 50 were marketed for clinical use. Goodman and Gilman (1970). The intermediate acting pentobarbital and the ultrashort acting thiopental became the most widely investigated barbiturates for the treatment of cerebral anoxia and ischaemia.

METABOLIC AND CEREBRAL BLOODFLOW STUDIES

In 1932 Quastel and Wheatley reported that cerebral metabolic studies in vitro showed the oxygen consumption during glucose, lactate and pyruvate oxidation could be reversibly reduced from 840ul O_2 to 492ul O_2 by adding thiopental.

This was followed by a report by Dameshek et al in 1934 who, in human studies, observed a decrease in the arterio-venous oxygen difference across the brain during anaesthesia with sodium amytal;

this suggested suppression of oxygen utilization. This observation was confirmed by Schmidt et al in 1945 who showed a definite decrease in oxygen consumption in Rhesus monkeys during deep thiopental anaesthesia.

The introduction of the nitrous oxide method for estimating cerebral bloodflow (CBF) by Kety and Schmidt in 1945, permitted the more accurate calculation of cerebral oxygen consumption under a variety of conditions. Using this method, Himwich et al (1947) showed a decrease of the cerebral metabolic rate for oxygen ($CMRO_2$) of 37% in humans during pentobarbital anaesthesia. Wechsler et al (1951) also showed the decrease in $CMRO_2$ but in addition demonstrated a drop in mean arterial blood pressure (MABP) and an increased CBF in 6 of the 12 patients during thiopental anaesthesia. They postulated that some interference with the intracellular mechanism was responsible for the decreased $CMRO_2$.

However, in a major study Pierce et al (1962), showed that anaesthetic doses of thiopental decreased $CMRO_2$ by 52% and CBF by 48% in man. They argued that this seemed to be secondary to the depressive effect of barbiturates on neuronal activity.

ANOXIA AND BARBITURATES

During this time, other workers investigated the effect of various anaesthetic agents on experimental anoxia.

Emerson et al (1942), reported for the first time on the possible protective effect of barbiturates in cerebral anoxia. The study was mainly investigating the effect of 10% ethanol on adult mice exposed to lethal anoxia in a decompressive chamber, but other

animals were also pre-treated with amytal and pentobarbital. Whereas ethanol-treated animals showed a significantly improved survival, pentobarbital also reduced mortality but to a lesser extent. Similarly Snyder (1946), reported prolongation of respiratory effort in rabbits who had their tracheas ligated. This was less dramatic in the mature animals as compared to the premature new-born.

Following these pioneering reports of barbiturate action on CBF, $CMRO_2$ and its possible protective effect, Arnfred and Secher (1962) argued that having established that oxygen consumption of cerebral cells is reduced by barbiturate, it is natural to assume that individuals exposed to a considerable degree of anoxia might be protected by this drug and able to resist this insult. They presented what was described by them as the first work on the protective effect of barbiturates against anoxia and they obviously missed or ignored the reports by Emerson et al (1942) and Snyder (1946).

In a series of reports by Arnfred and Secher (1962), Wilhjelm and Arnfred (1965), Wilhjelm (1965) and Secher and Wilhjelm (1968), a longer survival time for mice exposed to 2,5% and 5% oxygen and pre-treated with thiopental to induce quiet sleep, was shown when compared to an untreated awake group. Repeating the study, similar results were not only shown for thiopental but also for the anaesthetic agents halothane, cyclopropane, urethane, hydroxydione and detrovel. On the addition of CO_2, survival times similar to thiopental were achieved and when they combined these two agents, survival times were prolonged by 300-400%.

They speculated that the protective effect was related to the sedative and anti-convulsant action of these drugs because control animals died agitated and convulsing, suggesting that their increased metabolic rate reduced their tolerance to anoxia. They also thought that the cerebral vasodilation brought about by adding CO_2 with the resultant increase in CBF, may have played a rôle.

This apparent protective effect lead them to suggest a possible rôle for barbiturates in clinical practice. In an uncontrolled clinical study, using thiopental anaesthesia in caesarian section, they concluded that it "did not jeopardize the prognosis of the baby although it did make them sleepy."

ANOXIA AND BARBITURATES IN THE NEW-BORN

The danger of anoxia during delivery and immediately post partum, lead other workers also to investigate a possible protective rôle for barbiturates during this period.

Snyder (1946), reported prolongation of respiratory effort in rabbits following ligation of their tracheas. This was more dramatic in the premature new-born rabbit. Campbell et al (1968), studied the effect of pre-treatment with pethidine (Meperidine) and pentobarbital on the resuscitation of new-born rabbits exposed to nitrogen. Whereas both drugs increased the interval to the last gasp, the barbiturate group had a higher survival rate as well.

Cockburn et al (1969), expanded their experiment to include metabolic and pathological studies. Rhesus featuses, delivered by caesarian section had the umbilical cord clamped and their heads covered with a bag. The 14 mothers received either local anaesthesia or 16-43 mg/kg pentobarbital anaesthesia. The pentobarbital reduced

the rise of H^+ and pCO_2 during the period of anoxia, in the blood. These monkeys only showed brain damage in 3, whereas all 7 control monkeys showed extensive damage in the inferior colliculus and brain stem, but cortical sparing.

However, in contrast to Secher and Wilhjelm (1968), who suggested a possible rôle for barbiturates during delivery, they expressed doubt whether it could be used as a safe and effective therapeutic agent in man.

ISCHAEMIA AND BARBITURATES

The earlier work on cerebral anoxia was performed by exposing small animals to gas mixtures of no oxygen or low concentrations, or by asphyxiating the animal. However, experimental models to produce total cerebral ischaemia were being developed and the effect of barbiturates tested on them.

Wright and Ames (1964), described a two-stage procedure in the cat, with the carotids temporarily occluded a week after operative ligation of all other arteries to the brain. Cats pre-treated with 12 mg/kg pentobarbital or urea, showed increased survival times when compared to controls or ethanol and mannitol treated animals.

In contrast, Goldstein et al (1966), reported on a dog model based on work by Brockman and Jude (1960), where global ischaemia was produced by occluding the ascending aorta and superior and inferior venae cavae. Dogs pre-treated with pentobarbital needed 13 minutes of ischaemia to produce severe neurological damage compared to 8-10 minutes in morphine anaesthetized dogs. However, when compared to a group under ether anaesthesia in Brockman's report, results were

very similar. Also the detrimental effect of morphine on cerebral ischaemia could have influenced the outcome. Baskin and Hosobuchi (1981) and Baskin et al (1982).

COMBINED ANOXIA AND ISCHAEMIA WITH BARBITURATES

Whereas the earlier experimental models used either anoxia or ischaemia, Yatsu et al (1972), produced both global ischaemia and anoxia in a rabbit model by exposing it to 4% oxygen and dropping the blood pressure (MABP) to 30 mmHg with trimethapam. A period of 5 minutes was timed from the moment an iso-electric electro encephalogram (EEG) appeared, at which time the 5 test animals received 5 mg/kg of the rapid acting barbiturate, methohexital.

There was a significant difference in favour of the treated animals, with all 5 making a full recovery but 3 of the controls dying and the other 2 suffering neurological damage.

The 2 groups were well matched but the authors noted that the time to an iso-electric EEG was 2 minutes in the treated group but 4 minutes in the control group. They expressed concern about this, especially when it is stated that ischaemic periods of 3 minutes usually lead to full recovery but 5 minutes will result in severe neurological damage. The authors speculated on the possible protective mechanism but their work offered no explanation for it.

Thus by 1972 it had been well documentated that barbiturates would decrease CBF and $CMRO_2$. In addition, an apparent protective effect against global anoxia and ischaemia was shown in mice, rabbits and dogs. However, protective effects were also shown for other anaesthetic agents and many discrepancies were apparent in the various experimental models.

(B) PERMANENT FOCAL ISCHAEMIA

PERMANENT FOCAL ISCHAEMIA AND BARBITURATES WITH POSITIVE RESULTS

Following these earlier reports which were directed at the investigations of pre-treated sub-primates in global anoxia and ischaemia, Smith's report, Smith et al (1973), on the barbiturate management in focal cerebral ischaemia, introduced a new dimension to this field of study. From then on research during the remainder of the decade would be directed at either focal cerebral ischaemia, simulating a clinical stroke or global ischaemia to reproduce the event of a cardiac arrest.

Smith, Hoff, Hankinson and co-workers, Smith et al (1973, 1974), Smith (1977), Hoff et al (1973, 1975), Hoff and Smith (1977), Hoff and Marshall (1979) and Hankinson et al (1974), produced focal cerebral ischaemia by clipping the internal carotid and middle cerebral arteries in dogs and the middle cerebral artery in baboons through a small temporal craniectomy using microsurgical techniques.

Forty-two dogs were divided into groups of 6 each. Four groups received halothane anaesthesia as 0,8% ("light"), 1,9% ("deep"), 1,9% plus hypotension and a group with halothane discontinued prior to vessel ligation, "awake group". The barbiturate groups received pentobarbital 56 mg/kg and thiopental 40 mg/kg prior to vessel ligation and 40 mg/kg thiopental 15 minutes following vessel ligation.

The treated animals fared much better with only 1 dog developing a neurological deficit and infarction sizes ranging from 0,1% to 2,7%. In contrast, the halothane animals all developed neurological defi-

cits and the infarction sizes ranged from 10% in the "light" group to 28% and 34% in the "deep" groups. These results were certainly dramatic, especially when compared to the "deep" halothane groups and contradicted a protective effect for halothane shown by Wilhjelm and Arnfred (1965).

They speculated on the possible mechanism for this apparent protective effect and reviewed the literature on some aspects of the "steal" and inverse "steal" phenomenon, $CMRO_2$ and intracranial pressure alterations. However, they did not present any data from their study to support this.

These workers repeated the study using baboons. Hoff et al (1975). Four groups of animals were either anaesthetized with halothane (1,16%) or pre-treated with 60 mg/kg, 90 mg/kg and 120 mg/kg of pentobarbital: the neurological and pathological results were not dramatically different. One animal of the 4 control animals and 4 out of 11 of the barbiturate animals died with the infarction sizes ranging from 2% to 27% in the control group and 0,5% to 34% in the treated groups with an averaged mean of 14,9% and 2,9% respectively.

However, 2 of the very early deaths in the barbiturate groups showed no frank infarction and were regarded as having normal brains. This could conceivably have influenced the statistical analyses favourably. Even so, they concluded that there was a significantly favourable outcome for the high dose barbiturate groups (90 and 120 mg/kg) but not for the 60 mg/kg group. They pointed out that major cardio-respiratory difficulties were common in the high dose group, requiring prolonged ventilation and phenylephrine to maintain the blood pressure.

Other groups of workers also reported a protective effect for barbiturates in primates. Moseley and Molinari and co-workers, Moseley et al (1975), Molinari et al (1976, 1977), produced middle cerebral artery occlusion in Rhesus monkeys by embolizing them with silicone cylinders through the carotid artery. Treated monkeys received 4 mg/kg/hr pentobarbital for 12 hours starting within 30 minutes of the vessel occlusion. Although no significant difference in mortality and infarction sizes were shown, they concluded that their results suggested a better outcome in the treated groups because the infarcts were confined to the deep structures and the general recovery was better.

Similarly, Michenfelder and associates, Michenfelder and Milde (1975) and Michenfelder et al (1976), having shown some degree of protection in squirrel monkeys but not in cats or dogs, reported on an experiment using Java monkeys with middle cerebral artery occlusion. Treated monkeys received 14 mg/kg pentobarbital, delayed for 30 minutes followed by 7 mg/kg every 2 hours for 48 hours. Although all parameters monitored were similar in the 2 groups, the individual monkey weight is not given but only the range as 0,8 to 1,9 Kg, which is important because lighter and younger monkeys may tolerate ischaemia better.

The 9 barbiturate monkeys fared much better, all animals surviving with 4 showing neurological deficits and infarction in contrast to 3 of the control animals that died with 8 showing neurological deficits and infarction. Even so, they cautioned against a hasty clinical application and pointed out that many promising laboratory regimes, including hypercapnia, hypocapnia, Dextran 40, steroids, glycerol and serum albumin, had all fallen by the wayside.

PERMANENT FOCAL ISCHAEMIA WITH EQUIVOCAL OR NEGATIVE RESULTS

In contrast to the apparent protective effect shown by the previously reviewed work, a number of reports appeared showing equivocal or negative results.

Michenfelder and Milde (1975), reported on a series of multiple experiments involving gerbils, cats, dogs and squirrel monkeys. They showed no protection in the gerbils, cats or dogs treated with pentobarbital and concluded that it does provide a degree of protection but it is only consistently demonstrated in the primates. Lightfoote et al (1977), reported a lower yield of infarcted hemispheres in pentobarbital treated gerbils but this incidence of 37% was the same as that reported by Berry et al (1975) with the use of Ketamine. Unusual was the report by Black et al (1978), where 7 of 10 cats pre-treated with 50 mg/kg pentobarbital, died within 50 hours of ischaemia, although the infarction size was only 1,49% compared to the control group with 17,2% infarction and only 1 death.

On the other hand, Dujovny et al (1976) and Yonas et al (1980a), showed no protection in dogs with middle cerebral artery ischaemia and pre-treated with 25 mg/kg pentobarbital. Similarly, Selman and Spetzler (1980) and Selman et al (1981b), showed no protection in baboons with pentobarbital therapy delayed for 30 minutes and maintained for 96 hours. In fact, 4 of the 5 animals died with massive infarction and oedema; in contrast, all 5 controls survived.

PERMANENT ISCHAEMIA AND DELAYED BARBITURATE TREATMENT

Whereas in most of the earlier work animals were pre-treated with barbiturates, other workers did delay the treatment for a short period of up to half an hour. Smith et al (1973), Moseley et al (1975), Michenfelder et al (1976). Although these experimenters tried to simulate the clinical event of a stroke, they agreed that it was unlikely that a physician would be able to institute therapy within this time interval. A number of workers specifically investigated the interval that therapy could be delayed for and still provide protection against ischaemia.

McGraw (1977) and Levy and Brierley (1979), presented work on gerbils made ischaemic by carotid artery ligation. McGraw delayed treatment for 1 hour but these animals did not show any protection when compared to animals anaesthetized with ether and treated with saline. In contrast, Levy and Brierley delayed therapy for 2 hours and concluded that the treated animals showed less shift of the brain and ischaemic neuronal changes and that delayed treatment does protect against ischaemia. However, a major criticism of their work is that the untreated animals showed significantly more motor activity and seizures with a resultant increased metabolic state. Disburbing also is the work by Black et al (1978), where all 10 cats treated with 50 mg/kg pentobarbital after a delay of 2 hours died, compared to only 1 in the control group.

Whereas the results in these smaller animals yielded rather unconvincing evidence, Corkill et al (1976) and Yonas et al (1980a), expanded the experiment in dogs and investigated various intervals of delayed therapy. Corkill et al concluded that a 1 hour delay

could still provide protection but not if therapy was given at 3 or 6 hours following the onset of ischaemia. Similarly, Yonas et al investigated pre-treatment with pentobarbital and 15 minutes, 2 hours and 4 hours of delayed treatment with thiopental. Although no untreated controls were investigated, they showed, rather surprisingly, an apparent protective effect in the delayed thiopental groups compared to the pre-treated pentobarbital group.

These authors having shown an apparent protective effect for treatment delayed as long as 4 hours, speculated on why this should provide some protection. Levy and Brierley admitted that the sedative and anti-convulsant action might have played a rôle but suggested that suppression of the hypermetabolic state at 3-4 hours post ischaemia, would allow limited energy stores to be available for maintaining cell integrity. Both Corkill et al (1976) and Yonas et al (1980a), suggested that the micro-collateral circulation was protected. It was shown to begin to fall at 3 hours post ischaemia with peri-vascular oedema or intravascular thrombogeneses amongst the possible responsible factors.

BARBITURATE DOSAGE STUDIES

In the earlier reported work, a variety of dosage regimes were used. Arnfred and Secher (1962), endeavoured to induce quiet sleep whereas Smith et al (1973) and Hoff et al (1975), used a wide range of dosages without stating the reason for this. Michenfelder et al (1976), stated that their dosage regime was an empiric one to obtain moderate anaesthesia compatible with adequate haemodynamics. They pointed out, however, that a more rational approach would have been an EEG burst suppression end-point, indicating a relatively

deep anaesthesia and adequate haemodynamics. Several investigators directed themselves to this problem experimentally.

Hankinson et al (1974) and Steen and Michenfelder (1979), showed in dogs and mice respectively that optimum barbiturate effect was related to a dose of 60 mg/kg. Whereas Hankinson demonstrated considerable variability with lower dosage regimes, Steen showed a linear relationship up to the optimum dose of 60 mg/kg after which further increases lead to a decline in survival time.

In contrast, Corkill et al (1978), investigating doses of 10, 15, 20, 40, 50 and 80 mg/kg pentobarbital, demonstrated significant reduction of infarct sizes in dogs receiving 15-20 mg/kg. Increased doses did not alter the outcome and in fact, 2 animals in the 50-80 mg/kg group died. On the other hand, Yonas et al (1979), found that 40 mg/kg as well as 80 mg/kg thiopental protected in dogs compared to the animals that received 25 mg/kg pentobarbital. Thus it was shown that not only would a considerable variation of dosage regimes seem to afford protection against ischaemia, but also differences between thiopental and pentobarbital became apparent.

BARBITURATE PLASMA LEVELS

Miller (1979) and Bruce et al (1978), questioned the usefulness of barbiturate plasma levels as an index of therapeutic efficacy. A number of the other workers though, thought that it may be useful to determine dosage regimes. Whereas Yonas et al (1979) showed that plasma levels of 0,93 to 1,65 as well as levels of 1,95 to 4,97 ug/ml afforded protection in 2 groups of dogs, Weidler et al (1979), reported different results. In cats with middle cerebral artery ischaemia, blood levels of more than 30 ug/ml were

associated with death while the survivors had levels less than 30 ug/ml. They speculated that the combined effect of cerebral ischaemia and barbiturates may be detrimental to the heart, accounting for some of the delayed deaths.

In an attempt to overcome the major cardio-vascular problems associated with high dose barbiturates, Selman et al (1981a), titrated the administration to the EEG and blood pressure response. A loading dose of 30 mg/kg, followed by a continuous infusion of 0,75-12,5 mg hourly, resulted in a consistent iso-electric EEG with few adverse cardio-vascular problems and an average barbiturate plasma level of 27,3 ug/ml. Using this dosage regime, they showed an apparent protective effect in baboons with transient middle cerebral artery ischaemia but not with permanent occlusion of this vessel.

(C) GLOBAL ISCHAEMIA AND ANOXIA

The earlier experimental workers on global anoxia and ischaemia, Emerson et al (1942), Snyder (1946), Arnfred and Secher (1962), Wilhjelm and Arnfred (1965), Wright and Ames (1964) and Goldstein et al (1966), used mice and dogs to study the effect of pre-treatment with barbiturates on the survival times of these animals. Following this, Bleyaert et al (1977, 1978), developed a monkey model and initiated a series of investigations to study the effect of high dose barbiturate treatment for global ischaemia simulating the clinical event of a cardiac arrest.

Global ischaemia was produced for 16 minutes in Rhesus monkeys by applying a high pressure neck tourniquet with simultaneous trimethaphan induced hypotension. Animals treated with 90 mg/kg thiopental at 5 and 15 minutes and 120 mg/kg at 60 minutes, showed a significantly improved outcome compared to untreated animals and those with treatment delayed for 30 minutes in the 120 mg/kg group, all of which showed no protection. These results, they thought, suggested that treatment should be instituted early, although they could not explain the paradoxical outcome of treatment at 30 and 60 minutes in those who received 120 mg/kg barbiturate.

However, a number of unresolved questions and discrepancies were present in their work. Although the 5-minute treated group is given a zero (no deficit) neurological score, they stated that some of the animals were ataxic, a sign that merits a score according to their model. It is also strange that 120 mg/kg at 60 minutes should afford protection but not at 30 minutes. They also referred to unpublished data where controlled ventilation in monkeys paralysed

with pancuronium reduced neurological damage significantly. This raised the question of how much the barbiturate effect was due to sedation and immobilization.

In contrast to the above study, Steen et al (1979) and Jackson et al (1979), could not show any protective effect in dogs with 8-12 minutes of global ischaemia produced by ligating the ascending aorta and both venae cavae. Dogs were treated either prior to ischaemia or at 10-12 minutes post ischaemia. Major cardiovascular and respiratory difficulties were encountered necessitating dopamine infusion in the Jackson study. Steen et al (1979), stated that this supported their contention that the most likely mechanism of barbiturate protection in focal ischaemia is related to the reduction of the cerebral metabolic rate and such a reduction would not be expected in total global ischaemia. Similarly, Snyder et al (1979), in a different dog model, where global anoxia was produced by plugging the endo-tracheal tube, showed no benefit with barbiturate treatment.

Even so, Breivik et al (1978), as a direct result of their Rhesus monkey studies, devised a protocol for an uncontrolled feasibility trial of barbiturate therapy during cardiac resuscitation following an arrest in humans. This was issued to 20 centres around the world and Safar et al (1979) and Safar (1980), reported that the proportion of severely damaged patients was no higher compared to the standard method of resuscitation. This was followed by the introduction of an international pilot study and Detre et al (1981), reported that the attempt proved feasible and that a prospective randomized clinical trial was to be undertaken.

(D) TRANSIENT FOCAL ISCHAEMIA

Whereas global anoxia and ischaemia and permanent focal ischaemia became quite extensively investigated, the theoretically attractive situation of transient focal ischaemia with barbiturates was not. At the time I started my research in 1979, there was no reported work which specifically investigated this event. However, two reports were published in 1981, where this was specifically investigated in dogs and baboons.

Yonas et al (1981), investigated the "grace" period in transiently focal ischaemic dogs after which revascularization will result in improved neurological outcome. Treated animals that received 20 mg/kg thiopental followed by 10 or 20 mg/kg for 2 to 3 hours, commencing 15 minutes after middle cerebral artery embolisation, were compared to dogs pre-treated with 25 mg/kg pentobarbital and to a group of dogs reported on previously by them. Dujovny et al (1976). A middle cerebral artery embolectomy was performed after 6 hours and the outcome in the thiopental group was significantly better compared to the pentobarbital group. This group, in fact, did very poorly with all animals showing neurological deficit and infarction. They then concluded that the "grace" period had been extended from 5 to 6 hours by thiopental, based on their previous work, Dujovny et al (1976), which showed that an embolectomy done after 5 hours would result in haemorrhagic infarction.

However, these results and conclusion do raise a number of questions. Although the pentobarbital dose was less than the thiopental regime, it did not provide protection. They claimed that the "grace" period had been extended from 5 to 6 hours but in their previous

report, Dujovny et al (1976), only embolectomies at 3, 4, 5 and 7 hours are mentioned and discussed in the text, though a 6 hour period did appear in one of the tables, showing infarction. Also, no group of dogs without any barbiturate anaesthesia was available to serve as controls. Lastly, similar extensions of the "grace" period for dimethyl sulfoxide (DMSO) and methyl-prednisolone were shown by them. Dujovny et al (1979).

Similarly, Selman et al (1981b), reported apparent protection in a baboon model with 6 hours of middle cerebral artery occlusion. However, whereas the treated group was in barbiturate coma for 96 hours and ventilated, the control animals were awake and breathing spontaneously. The control animals developed severely raised intracranial pressures and infarcts compared to normal pressure and minor pathological changes in the treated group. However, the ventilated animals showed much better oxygenation, with the arterial pO_2 being 115-160 mmHg, compared to 70-110 mmHg in the control animals. One can thus only speculate as to how much the mechanical ventilation played a rôle in the better outcome of the treated animals.

(E) BARBITURATES COMPARED TO OTHER DRUGS

In the earlier work, protective effects were shown for other drugs during cerebral anoxia and ischaemia. Emerson et al (1942), investigated 10% ethanol as the major agent and to a lesser degree, barbiturates. Similarly, Wilhjelm and Arnfred (1965), showed increased survival times for anoxic mice treated with halothane, cyclopropane, urethane, hydroxydione, detrovel and also for CO_2. While Wright and Ames (1964), showed some benefit with urea treatment in global ischaemia.

Recently, a number of agents were investigated in conjunction with barbiturates. Whereas Steen et al (1978), found that diazepam (7,5 mg/kg) did increase survival times in hypoxic mice, it was not as good as mephobarbital. In contrast, Siemkowicz (1980), showed as good an outcome for diazepam compared to pentobarbital in hyperglycaemic ischaemic rats. In contrast to Steen et al (1978), who suggested that the effect is related to the anaesthetic action, Siemkowicz maintained that the anti-convulsant action which thus prevents a hypermetabolic state, plays a rôle. On the other hand, Aldrete et al (1979), showed that phenytoin treated ischaemic rabbits had an improved outcome compared to a placebo and thiopental treated group, but thought that this anti-convulsant acted by reducing CBF, $CMRO_2$ and prevented K^+ leakage from the cell. Tamura et al (1979), also compared pentobarbital to a new imidazole derivative and as good an outcome with the imidazole agent and much less depressant action, was shown.

(F) MODE OF ACTION OF BARBITURATES

The apparent protective effect of barbiturates had many workers investigating the possible mechanism for this. Following the original observation and studies on cerebral metabolic rate and cerebral bloodflow by Quastel and Wheatley (1932), Kety and Schmidt (1945), Himwich et al (1947) and Pierce et al (1962), numerous other reports attempted to explain this action.

ANAESTHETIC EFFECT

Steen and Michenfelder (1978, 1979), concluded after showing a protective effect for only the anaesthetically active isomer and racemic form of mephobarbital, that the effect was related to the anaesthetic action of barbiturates and not to the anti-convulsant action. However, Siemcowicz (1980), showed a significant protective effect for diazepam and thought it was related to the anti-convulsant properties. In contrast, Aldrete et al (1979), thought that the anti-convulsant drug, phenytoin, protected by decreasing CBF, cerebral metabolic rate and K^+ leakage from the cell.

METABOLIC STUDIES

Following cerebral anoxia or ischaemia, the energy stores of ATP and phosphocreatine become rapidly depleted with accumulation of lactic acid and a fall in pH.

The earlier work by Quastel and Wheatley (1932), Pierce et al (1962) and others, showed that barbiturates decrease $CMRO_2$ significantly. In a series of experiments by Gatfield et al (1966), Michenfelder and Theye (1970, 1973), Michenfelder (1974), Michenfelder and Milde (1975, 1977), Sundt et al (1979), Nilsson and Siesjö (1975) and

Kofke et al (1979), it was further shown that this metabolic depression was dose dependent and occurred only until the EEG became isoelectric. Also the rate of ATP and phosphocreatine depletion and lactate accumulation,was clearly lower in barbiturate treated animals. It was also shown that there was no alteration in the cerebral metabolic pathways or of the intracellular redox state, with the brain concentrations of ATP, lactate, pyruvate and phosphocreatine unchanged but with an increase in glucose. Thus it was speculated that barbiturates cause neuronal depression and thus reduced metabolic activity and energy requirements, rather than altering metabolic pathways, to make the brain more tolerant to anoxia and ischaemia.

In contrast, Nilsson (1971) and Nordström et al (1977), showed that barbiturates did not affect ATP depletion, lactate accumulation, $CMRO_2$ or CBF during anoxia or ischaemia. Similarly, Nemoto and Frinak (1979), found no improvement in the brain oxygenation and pH in ischaemic rats. Nordström concluded that the protective effect does not seem to be a consequence of reduced energy requirement.

Whereas Michenfelder and associates and Gatfield et al (1966), showed that the metabolic depression is related to the anaesthetic dose with no change in the metabolic pathways, Crane et al (1978) and Hakim and Moss (1976), reported different results. Crane showed that a major decrease in the CMR for glucose occurred with only 10-20% of the usual anaesthetic dose and argued that small subanaesthetic doses should theoretically also be protective. Hakim found 25% increase in the pentose phosphate pathway induced by barbiturates at the expense of the Krebs-cycle and suggested that this alteration may be a protective measure facilitated by barbiturates.

MEMBRANE AND CELLULAR STABILIZATION

It has been speculated further that barbiturates protect by stabilizing membranes and thus prevent the secondary events that may follow on cellular failure and the release of substrates.

Whereas Nemoto et al (1977), showed that barbiturates reduced the cyclic AMP (adenosine monophosphate), Akiguchi et al (1980), reported that the dopamine and nor-epinephrine depletion of the cerebral vessel during ischaemia was reduced. These authors suggested that prevention of a cyclic AMP-catecholamine induced change will be beneficial during ischaemia. Similarly, Astrup et al (1977), showed that the K^+, Na^+, Ca^{++} and Mg^{++} loss from the cells were reduced or prevented by barbiturates during ischaemia and suggested that this maintains the cellular metabolic machine.

In contrast, Wade and Sorenson (1978), reported a marked increase in the CSF K^+ during ischaemia which was not influenced by barbiturates. They concluded that the barbiturate action was different to that of hypothermia, which will delay this K^+ rise.

FREE RADICAL SCAVENGING

The reduction of the cerebral metabolic rate could not explain the apparent protective effect of barbiturates in transient total global ischaemia. Demopoulos et al (1977a, 1977b) and Flamm et al (1977, 1979), advanced a hypothesis that barbiturate protection may be linked to the ability to scavenge or neutralize free radicals. These substances which are molecules with an unpaired electron in an outer orbit and present in a high energy state, can cause the alteration and fragmentation of the molecular membrane. This is

reflected in the alterations of components such as cholesterol and free fatty acids (FFA) with consumption of the normally occurring anti-oxidant, ascorbic acid.

Demopoulos (1977a, 1977b), Flamm (1977, 1979), Majewska et al (1978) and Yoshida et al (1980), showed that methohexital and pentobarbital reduced and controlled these free radical reactions and improved the anti-oxidant ability of the brain.

However, Smith et al (1980) and Nemoto et al (1981), reported no inhibition of these free radical reactions with phenobarbital and pentobarbital but some with thiopental and methohexital. However, whereas Smith et al (1980), concluded that barbiturate protection is unrelated to free radical scavenging, Nemoto et al (1981), thought differently. They stated that in terms of the major FFA, pentobarbital did show a significant reduction in the release of arachidonic acid and postulated a protective effect which is exhibited by this action.

OEDEMA FORMATION AND INTRACRANIAL PRESSURE

Earlier observation by Horsley (1937) and Shapiro et al (1973), indicated that barbiturate anaesthesia will reduce intracranial pressure in humans. Smith et al (1973) and Corkill et al (1976), suggested that barbiturates prevented peri-vascular oedema and elevation of intracranial pressure following cerebral ischaemia as a possible mechanism to explain their reported barbiturate protection.

Smith and Marque (1976), Simeone et al (1979) and Lawner et al (1979), investigated the effect of barbiturates. Experimentally produced cerebral oedema was significantly reduced by barbiturates and Innovar when compared to control or hypothermic animals.

On the other hand, Harbaugh et al (1979), showed a prompt decrease in intracranial pressure associated with a simultaneous drop in arterial blood pressure but found no alteration in the water and Na^+ content of the oedema fluid.

In contrast, Selman et al (1980), found that barbiturate treated baboons with permanent occlusion of the middle cerebral artery, developed marked elevation of intracranial pressure. Thus a wide variation had been reported on the effect of barbiturates on cerebral oedema and intracranial pressure.

Whereas Smith and Marque (1976), concluded that the protective effect of barbiturates is related to reducing the peri-vascular oedema, Harbaugh et al (1979), thought the action was more related to decreasing cerebral blood volume and brain capillary pressure.

HYPOTHERMIA

Since barbiturates interfere with temperature control regulation, a degree of accidental hypothermia may have contributed to the beneficial effect. Hypothermia as such, has been widely investigated as a protective adjunct for cerebral ischaemia with contradictory experimental and clinical results. Pontius et al (1954), McMurrey et al (1956), Rosomoff (1959) and McDowall (1971).

Lafferty et al (1978) and Nordström and Rehncrona (1978), reported synergistic effects for combined hypothermia and barbiturates, achieving $CMRO_2$ depression at 30°C that usually occurs at 22°C. However, Hägerdal et al (1978), failed to show this synergism.

Whereas Hägerdal showed better results with hypothermia compared to barbiturates, Steen and Michenfelder (1979), reported similar survival times for 29°C and barbiturates in hypoxic mice.

CEREBRAL BLOODFLOW AND THE "STEAL" PHENOMENA

Lassen (1959) and Lassen and Palvalgyi (1968), showed that bloodflow may be diverted from the maximally vasodilated ischaemic areas by vasodilation in the non-ischaemic brain regions, the "steal" phenomenon. The converse may also happen and flow may be increased by vasoconstriction in the non-ischaemic regions, the "inverse-steal" phenomenon. Barbiturates were thought to be cerebral vasoconstrictors, Pierce et al (1962) and Marsh et al (1977), and as such would increase bloodflow in the ischaemic area through the "inverse-steal" mechanism.

Hanson et al (1975), found no evidence of an "inverse-steal" effect for barbiturate. In contrast, Branston et al (1979), reported that in ischaemic regions which showed an iso-electric EEG and CBF below 20cc/100gm/minute, methohexital increased CBF. This did not occur if the CBF was more than 25cc/100gm/minute and the EEG showed electrical activity. They concluded that this was due to an "inverse-steal" phenomenon.

However, Marin et al (1981), found pentobarbital to inhibit spontaneous mechanical activity and tone in the isolated human artery in vitro. The relaxation was dose dependent and linked to Ca^{++}. They concluded that these observations disagree with the hypothesis that barbiturates directly constrict cerebral arteries although they agreed it may constrict the arterioles.

(G) CLINICAL APPLICATION

The apparent protective effect of barbiturates on hypoxic mice, Arnfred and Secher (1962), lead these workers, Secher and Wilhjelm (1968), to suggest a possible róle for it in clinical practice. They concluded from an uncontrolled study, where mothers were induced with thiopental anaesthesia for caesarian section, that this "did not jeopardize the prognosis" of the baby. Similarly, Smith et al (1974), stated that they believed barbiturates deserved a clinical trial as an anaesthetic or anaesthetic supplement. Others, Cockburn et al (1969) and Michenfelder et al (1976), cautioned against the premature use and Smith (1977), pointed out that even though it seemed "rational" to use it, there was no clinical data to support this.

However, Breivik et al (1978) and Safar (1980), developed a protocol for a feasibility trial of barbiturate therapy in resuscitation following cardiac arrest. This was followed with the introduction of a 3 year (1979-1982) international multicentre, randomized clinical study. Detre et al (1981), reported on the preliminary analysis of the first 85 cases and concluded that the attempt at a prospective randomized clinical study, was feasible.

On the other hand, no controlled prospective trial for barbiturate use in focal cerebral ischaemia or raised intracranial pressure in clinical practice had been introduced. A number of case reports and uncontrolled patient series had appeared in the literature with Geevarghese et al (1977), Hoff et al (1977), Lawner and Simeone (1979), Woodhurst et al (1980), Bennet (1980), Kassel et al (1980), Belopavlovic and Buchtal (1980b) and Rose et al (1981), reporting

on the use in cerebral ischaemia, while Marshall et al (1978, 1979), used barbiturate coma in raised intracranial pressure following trauma or during metabolic coma (Reye's syndrome).

It was shown that humans could tolerate high dose barbiturate therapy although Belopavlovic and Buchtal (1980b), had to use dopamine to maintain the blood pressure in one of their patients. Yonas et al (1980b), introduced a regime of a series of decreasing doses of thiopental after the CVP and/or wedge pressure was elevated to achieve a rapid high barbiturate blood level without causing cardiovascular and respiratory depression. Stanski et al (1980), further showed that the pharmacokinetics of barbiturates altered during high dose treatment. The barbiturate elimination changes from the first order or linear to non-linear with an apparent increase in the half-life.

However, Kassel et al (1980), reported on 12 patients with subarachnoid haemorrhage and spasm treated with barbiturate coma with 11 deaths. They concluded that although these discouraging results were most probably a reflection of the patient's condition, barbiturate therapy should be limited to patients with life threatening conditions until such time that further evidence of its usefulness becomes manifest.

CHAPTER III

MATERIALS AND METHODS

(A) ANIMALS

Thirty South African Vervet monkeys of both sexes, weighing on the average 5,8 kg, were used. The animals were obtained from the Cape Provincial Animal Centre, Delft, at Kuilsriver where they had been quarantined and acclimatized. The week prior to the experiment, they were transferred to the University of Cape Town Animal House which is a fully equipped facility attended by trained technical staff. Monkeys were alternately assigned to either the Barbiturate or Control group.

(B) ANAESTHESIA

The animals were starved overnight and after induction of anaesthesia with 7 mg/kg of Ketalar intramuscularly at 7.30 a.m., they were taken to the Jan S. Marais Surgical Laboratory. The monkeys were intubated with the appropriate size endotracheal tube and mechanically ventilated with a 40% O_2 and 60% N_2O mixture. Anaesthesia was maintained by adding 0,5% to 1% Halothane intermittently so as to have the monkey as close to being awake as possible and thus minimize the drug effect on the experiment. It was not necessary to paralyse the monkeys as they tolerated the ventilation easily which was set at a rate of between 14 and 16 breaths per minute and adjusted if necessary.

(C) SURGERY/MONITORING

This was performed under normal sterile surgical technique. The left upper thigh was shaved and prepared with Betadine. The femoral artery and vein were exposed below the inguinal ligament and medium size catheters introduced with permanent ligation of the vessels. The arterial line was connected to a pressure transducer for continuous blood pressure monitoring. The venous line was used for intravenous fluid and drug administration. Ringers Lactate was given at a rate of 30% blood volume during the first hour and 10% per hour for the rest of the experiment. Ampicillin 250 mg was given at this time. The first blood gas analysis was also done at this stage and the necessary respiratory adjustments made. Further blood gas determinations were made at 1 to 2 hourly intervals or more often when indicated. Continuous rectal temperatures were measured and intermittent warming with a heating fan applied to keep the temperature at 37°C.

The monkey was then placed in an Animal Stereotaxic frame so as to have the right orbit accessible. This area was shaved, prepared and draped with sterile surgical drapes. The operating microscope was then introduced for a transorbital microsurgical exposure of the anterior circle of Willis as first suggested by Sundt. O'Brien and Waltz (1973) (Fig. I, II and III). The skin was incised along the supra-orbital ridge from the lateral to the medial canthus, using a bipolar diathermy to control bleeding. The periosteum was stripped down, staying outside the periorbita in an attempt to keep this intact and to prevent the bulging orbital fat from making surgery unnecessarily difficult.

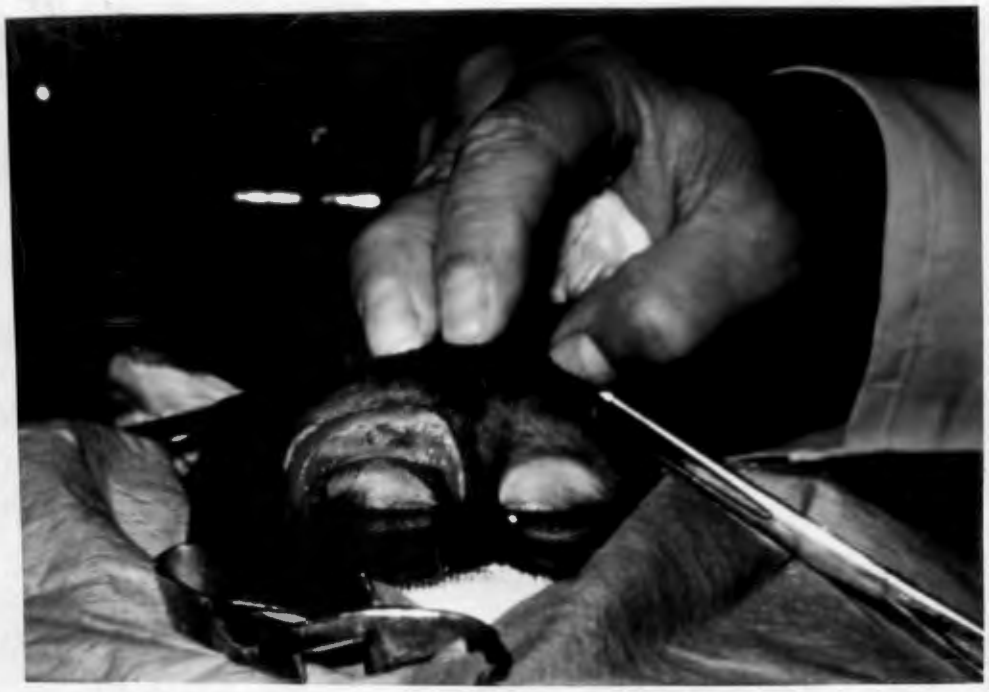


Figure I: Orbital area shaved for incision along supra-orbital margin

Figure II: Animal in stereotaxic frame

The pupil was then incised horizontally with a number 11 surgical blade to remove the aqueous humor and vitreous body. Dissection was now carried to the posterior aspect of the orbit by retracting the empty eye downwards, coagulating and cutting bridging orbital arteries and veins. The optic nerve, now exposed at the apex and the cone of orbital muscles, was coagulated with the bipolar diathermy and cut, taking great care in the vicinity of the ophthalmic artery, as bleeding at this stage would be difficult to control.

The eyeball, then freed at the apex, was removed in order to leave an empty orbit, with the eyelids intact: further soft tissue dissection was carried out at the apex to expose the optic strut and optic canal. Using the dental drill, a 5-7 mm hole was drilled at the apex, taking the optic strut, lateral half of the optic canal and a small area of adjacent sphenoid wing. Great care was taken not to transgress the dura and cause subarachnoid haemorrhage or vascular trauma to the underlying carotid artery and its branches. Haemorrhage from bone was controlled with bone wax.

The dura mater and arachnoid was carefully opened and reflected, exposing the frontal and temporal lobes, the internal carotid artery, the bifurcation with the perforators, the anterior cerebral artery curving medially across the optic nerve and the middle cerebral artery running laterally, in the shallow Sylvian fissure. Care was taken not to cause any haemorrhage at this stage. (Fig. IV)

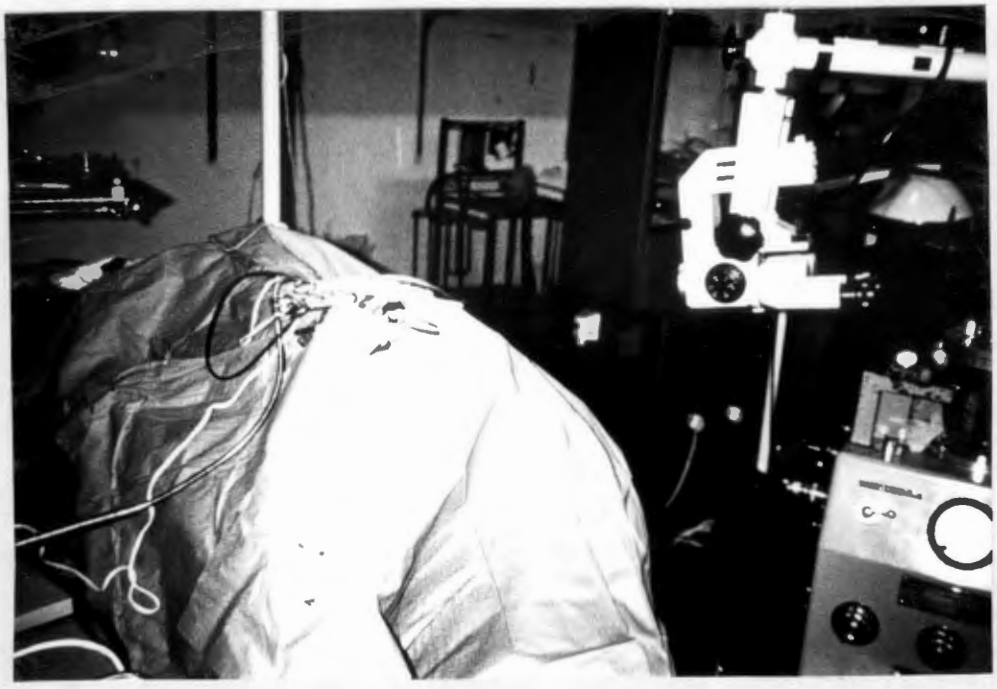


Figure III: Animal draped, with surgical microscope in view

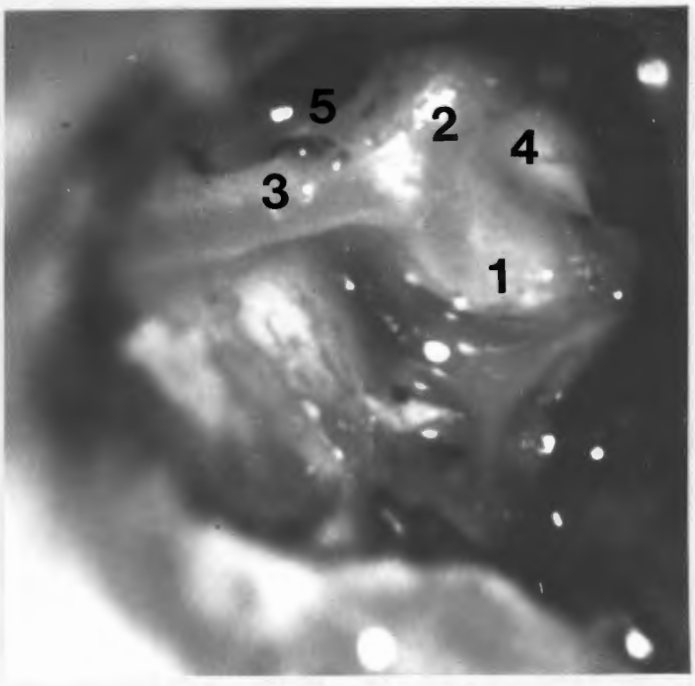


Figure IV:

View through microscope:

1. Internal carotid artery
2. Anterior cerebral artery
3. Middle cerebral artery
4. Optic nerve
5. Perforating artery

A Lewis aneurysm clip was then applied to the proximal middle cerebral artery just beyond the bifurcation and proximal to the small perforators coming off it. The orbit was then filled with saline warmed to body temperature and covered with a surgical swab.

(D) BARBITURATE DOSAGE/BLOOD LEVEL

The barbiturate group received a total dosage of 30 mg/kg of pentobarbital (May Baker) intravenously after 1 hour of middle cerebral artery occlusion. The timing was to simulate the expected delay in the clinical situation of a patient who had suffered a stroke. Half the dose of pentobarbital, 15 mg/kg, was given as quickly as possible, being guided by the blood pressure, so as not to let it drop below a mean of 60 mm of mercury, an arbitrary level at the lower limits of autoregulation. This usually took about 5 minutes. The remainder was then given slowly over the next 20 to 25 minutes, again guided by the blood pressure.

Thus the total dosage was given over 30 minutes. One should note that in the clinical situation one would be dealing with older patients who have a low tolerance to high dose barbiturates and a precipitous drop in blood pressure could aggravate the stroke or induce cardiac collapse.

Blood levels of pentobarbital were determined at various stages by Dr. Dave Morrel of the Department of Anaesthesia, using the gas liquid chromatography method: blood was taken half an hour after the full dose was given and again at the time of de-occlusion of the middle cerebral artery. Levels were expressed in micrograms/ml. (Ug/ml)

(E) DE-OCCLUSION

After 4 hours the Lewis clip was removed. The patency of the artery was tested with an intravenous injection of 1 cc Methylene Blue. Patency was confirmed through the operating microscope by rapid filling in the antegrade direction and not early retrograde filling, with a pale segment distal to the site of clip application.

The orbital defect was covered with gelfoam and the orbit filled with Methyl-Methacrylate injected as a liquid with a 20 cc syringe. The skin incision along the supraorbital margin and the palpebral fissure were sutured with 3/0 silk. The arterial and venous lines were removed, the vessels ligated and the skin sutured with 3/0 silk. All wounds were sprayed with a surgical plastic spray.

Animals were allowed to wake up and once breathing adequately, they were extubated and returned to their cages. Usually this was between 3-6 p.m., the animals having been in the surgical laboratory for 7 to 10 hours.

(F) NEUROLOGICAL EVALUATION

At this stage a careful neurological evaluation was usually not possible. The control group monkeys were still drowsy, whilst the barbiturate group monkeys were in a deep coma. Thus a careful neurological assessment was performed early the next morning and daily in the survivors till sacrificed. The following was noted: level of consciousness, presence of a hemianopia to food presentation or threat, abnormal leg posture, power assessment testing the animal's ability to grip objects or to support his weight and the direction of circling. Using these criteria, a simple practical

scale was used so that animals could be neurologically graded with confidence as follows:

GRADE I: No abnormality detected:
Normal

GRADE II: Minimal abnormality i.e. hemianopia, abnormal posture or grip, circling to one side:
Minor stroke

GRADE III: Significant weakness, but some movement:
Moderate stroke

GRADE IV: Hemiplegic, no movement, drowsy:
Major stroke

GRADE V: Death:
Death

(G) PATHOLOGICAL EVALUATION

Those monkeys that died overnight or during the subsequent days, had their brains perfused in situ with buffered formalin and then removed to be immersed in buffered formalin for another 6 weeks. The surviving monkeys were sacrificed at 2 weeks to allow infarcts to mature and thus become well demarcated and readily detectable. Monkeys were anaesthetized with 100 mg of Ketalar intramuscularly and brains perfused in situ with buffered formalin and then immersed for 6 weeks after removal.

The brains were cut, processed and stained with H + E by Mr. Casiano Gouveia of the Department of Pathology and Mrs. Heather McLeod of the Department of Surgery. The neuropathological assessment was done by Dr. Richard Hewlett of the Department of Neuropathology, Tygerberg Hospital, with the author in attendance but not knowing the experimental history of a particular brain examined.

Brains were cut coronally, the first anteriorly through the optic chiasm and then rostrally and caudally in 4 mm slices. The slices were examined for infarct size, location, presence of haemorrhage, microscopic evidence of neuronal death and acute ischaemic changes. Again a simple practical scale was used to grade the pathological findings as follows:

GRADE I:	No changes:	Normal
GRADE II:	Microscopic evidence only, ischaemic infarction:	Microscopic
GRADE III:	Macroscopic infarction: <1 cm in diameter	Macroscopic <1 cm
GRADE IV:	Macroscopic infarction: >1 cm in diameter	Macroscopic >1 cm
GRADE V:	Acute ischaemic change with oedema and haemorrhage:	Acute ischaemia

(H) STATISTICAL ANALYSIS

All the data was statistically analysed by Miss J. Hall of the Biostatistics Division of the South African Medical Research Council. Blood pressure, pulse, blood gases, haemoglobin, weight, neurological and pathological outcome were analysed and compared to determine whether high dose barbiturate management had any beneficial effect on the treated group of monkeys.

CHAPTER IV

RESULTS

As detailed in the previous chapter, the brains of 30 monkeys were made transiently ischaemic by occluding the middle cerebral artery for 4 hours. Fifteen monkeys constituted a control group and the remaining 15 the test group. Pentobarbital, 30 mg/kg, was given intravenously after a delay of an hour.

Various parameters were recorded and analysed as is shown on pages 42 to 73 and summarized in Tables I and II . The statistical analyses were done to ascertain the comparability of the 2 groups and the possible effect in the neurological and pathological outcome of high dose barbiturate treatment.

(A) CASE HISTORIES

To introduce uniformity, zero (0) hour was taken to be the moment of vessel occlusion, usually about 1½ hours from the time the monkey was intubated. The day of the experiment was called Day 1.

Blood pressure was recorded as the mean pressure in mmHg and pulse and respiration as the rate per minute. PO_2 and PCO_2 were expressed as mmHg and the pentobarbital levels in micrograms/ml (Ug/ml).

The prefix "B" was added to the barbiturate group and "C" to the control group.

TABLE I

CONTROL

MONKEY No.	B.P.mm Hg	Pulse / Minute	Respiration/ Minute	pH	pO_2 mmHg	pCO_2 mmHg	Hb./Gm%	Brain removed on day	NEUROLOGIC GRADE Day 2	NEUROLOGIC GRADE Sacri= fice	PATHOLOGIC GRADE	Weight kg
C.1	109 (12)	145 (7)	16	7,34 (0,031)	188 (30)	49 (2)		2	V		V	5
C.2	92,72 (9,04)	84 (5,6)	14	7,55 (0,05)	181 (10,7)	28,6 (2,8)		6	I	I	I	6
C.3	114 (8,9)	97,5 (5)	16	7,41 (0,14)	171,5 (21,9)	40,5 (5,6)		14	III	II	IV	6
C.4	96,6 (7,07)	80 (0)	14	7,53 (2)	172 (67)	36,5 (9)		18	III	II	IV	6
C.5	129 (3,2)	84 (8,9)	16	7,51 (0,37)	208 (31,7)	36 (9,9)		16	II	II	I	5
C.6	112 (8,3)	71 (9,5)	16	7,31 (0,21)	160 (20)	32,5 (3,5)		12	II	II	II	6
C.7	88,18 (6,03)	75 (5,34)	16	7,43 (0,1)	132 (21,9)	31 (1,41)		2	V		V	6
C.8	95 (5)	85,27 (2,4)	16	7,44 (0,04)	202 (21,2)	31,75 (5,6)		4	IV	V	IV	6
C.9	114,37 (7,2)	79,5 (8,3)	16	7,44 (0,06)	222 (31,11)	32,33 (6,35)		18	I	I	I	7
C.10	99,37 (10,8)	91 (2)	16	7,28 (0,02)	194,3 (25,9)	43,3 (2,08)		19	I	I	I	4
C.11	110 (9,12)	84,8 (3,4)	15	7,44 (0,01)	152,5 (3,5)	34,25 (3,8)	17	2	V		V	7
C.12	117,7 (7,57)	96,6 (3,6)	14	7,39 (0,07)	144 (74,2)	42 (10,5)	19	9	III	III	IV	6,5
C.13	114,5 (10,3)	89 (6,4)	14	7,35 (0,005)	101 (34,6)	45,20 (4,5)	18	14	III	III	IV	5,5
C.14	90 (6,2)	123 (9,1)	14	7,48 (0,01)	197,5 (3,5)	29 (1,4)	15	15	I	I	III	4
C.15	102 (4,2)	84 (0)	13	7,55 (0,07)	140 (14,1)	29 (1,41)	17	2	V		V	6
Mean Standard deviation	105,4 (11,83)	91,13 (19,19)	15 (1)	7,43 (0,08)	170,9 (32,86)	35,8 (6,5)	17,2 (1,48)					5,73 (0,8)

MONKEY "B" 1: Weight 7 kg

DAY 1: Anaesthesia: As described in the method.

Surgery: As described in the method. Minimal blood loss with no subarachnoid haemorrhage. Occlusion performed without any problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	80	80	80	70	70	80	80	90	100	90	90
Pulse	100	100	100	100	100	100	100	100	100	100	100
Resp.	14	14	14	14	14	14	12	12	12	12	12
ph	7,47		7,47		7,48		7,50			7,45	
pO_2	144		131		161		155			162	
pCO_2	33		35		30		27			29	
Dose Barb.				105	105						
Level					20,6					23,2	

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequate at 7 hours, extubated and returned to cage.

DAY 2: Left hemiparesis, circling, hemianopia: GRADE II

DAY 14: GRADE II
Sacrificed.

MONKEY "B" 2: Weight 5 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage. Occlusion performed without any problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	120	100	100	90	90	120	120	100	105	90	100
Pulse	90	100	100	110	110	100	100	100	100	100	100
Resp.	16	16	16	16	16	16	16	16	16	16	16
ph	7,3	7,32		7,32		7,38			7,38		
pO_2	107	114		100		100			150		
pCO_2	45	38		30		36			36		
Dose Barb.				75	75						
Level					7,2					12,1	

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours, extubated and returned to cage.

DAY 2: Alert, no deficit: GRADE I

DAY 16: GRADE I
Sacrificed.

MONKEY "B" 3: Weight 5,5 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage. Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	120	120	120	80	90	90	100	100	90	90	90
Pulse	60	60	60	60	60	60	60	60	60	60	60
Resp.	16	16	16	16	16	16	16	16	16	16	16
ph	7,53	7,6		7,6			7,5				
pO_2	212	202		122			133				
pCO_2	28	35		37			35				
Dose Barb.				85	85						
Level					20					22	

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 8 hours, extubated and returned to cage.

DAY 2: No neurological deficit: GRADE I

DAY 17: GRADE I
Sacrificed.

MONKEY "B" 4: Weight 6,5 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	100	110	120	90	85	100	110	115	100	100	100
Pulse	92	92	92	92	104	98	98	96	96	96	96
Resp.	15	15	15	15	15	15	15	15	15	15	15
ph	7,5	7,46			7,54			7,55		7,5	
pO_2	138	131			163			155		171	
pCO_2	35	38			30			31		29	
Dose Barb.				100	100						
Level					21,2					21,3	

De-occlusion: Segmental spasm of middle cerebral artery, cleared up over 10 minutes. Vessel patent. Routine closure of all wounds.

Breathing adequately at 7 hours, extubated and returned to cage.

DAY 2: No neurological deficit: GRADE I

DAY 14: GRADE I
Sacrificed.

MONKEY "B" 5: Weight 7 kg

DAY 1: Anaesthesia: Routine.

Surgery: 20 cc blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	120	100	120	90	100	110	115	100	100	100	120
Pulse	86	96	96	96	96	96	96	96	96	96	96
Resp.	15	15	15	15	15	15	15	15	15	15	15
ph	7,56		7,54					7,6			
pO_2	165		188					200			
pCO_2	18		20					22			
Dose Barb.				105	105						
Level					19					21	

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 6 hours, extubated and returned to cage.

DAY 2: Dead: GRADE V
Brain removed.

MONKEY "B" 6: Weight 7 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	110	120	120	90	80	110	115	120	120	120	120
Pulse	70	65	65	65	70	70	70	70	70	70	70
Resp.	15	15	15	15	15	15	15	15	15	15	15
ph	7,45		7,56				7,5				
pO_2	219		191				131				
pCO_2	49		23				26				
Dose Barb.				105	105						
Level				23,3						20	

De-occlusion: Vessel patent.
Routine closure of wounds.

Breathing adequately at 5 hours, extubated and returned to cage.

DAY 2: No neurological deficit: GRADE I

DAY 15: GRADE I

Sacrificed.

MONKEY "B" 7: Weight 6 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	130	120	110	85	70	95	90	90	90	100	100
Pulse	84	84	90	100	90	90	90	90	90	90	90
Resp.	12	12	16	16	16	16	16	16	16	16	16
ph	7,4	7,37			7,39			7,39		7,4	
pO_2	153	196			148			106		200	
pCO_2	39	46			46			44		46	
Dose Barb.				90	90						
Level					14					20	

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 7 hours, extubated and returned to cage.

DAY 2: In coma: GRADE IV

DAY 3: Dead: GRADE V
Brain removed.

MONKEY "B" 8: Weight 6 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	100	100	130	90	100	110	115	120	120	120	120
Pulse	70	70	70	80	100	100	100	100	100	100	100
Resp.	15	15	15	15	15	15	15	15	15	15	15
ph	7,51	7,51			7,52		7,5			7,5	
pO_2	220	165			180		200			140	
pCO_2	18	20			26		26			26	
Barb. Dose				90	90						
Barb. Level					19					25	

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 7 hours. Extubated and returned to cage.

DAY 2: Dead: GRADE V
Brain removed.

MONKEY "B" 9: Weight 4 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	120	120	110	80	70	110	120	110	110	110	110
Pulse	100	100	100	100	130	130	130	120	120	120	120
Resp.	14	14	16	16	16	16	16	16	16	16	16
ph	7,3	7,3		7,3			7,32			7,4	
pO_2	90	90		100			100			110	
pCO_2	50	45		44			36			41	
Dose Barb.				60	60						
Level					19					19	
Hb	14										

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing: Remained in deep coma, without any attempt at breathing. Had a cardiac arrest at 9 hours.

Dead: GRADE V
Brain removed.

MONKEY "B" 10: Weight 6,5 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	110	110	120	100	100	120	120	120	120	120	120
Pulse	76	76	76	88	84	86	84	86	86	86	86
Resp.	15	15	15	15	15	15	15	15	15	15	15
ph	7,56					7,55					
pO_2	93					119					
pCO_2	34					24					
Dose Barb.				100	100						
Level					17,3					16	
Hb	14										

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 6 hours, extubated and returned to cage.

DAY 2: Alert, left-hand hemiplegic posture: GRADE II

DAY 15: GRADE II
Sacrificed.

MONKEY "B" 11: Weight 7 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	100	110	110	100	100	115	120	120	120	120	120
Pulse	90	90	96	96	110	110	110	110	110	110	110
Resp.	14	14	14	14	14	14	14	14	14	14	14
ph	7,58					7,57					
pO_2	198					200					
pCO_2	32					26					
Dose Barb.				105	105						
Level					22,6					18,3	
Hb	16										

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours.

DAY 2: Still in coma.

DAY 3: Awake, hemiparesis, circling: GRADE III

DAY 20: GRADE II
Sacrificed.

MONKEY "B" 12: Weight 6,5 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	110	110	120	80	85	95	100	100	120	120	120
Pulse	90	90	110	110	110	110	110	110	110	110	110
Resp.	16	16	16	16	13	13	13	13	13	13	13
ph	7,5			7,5					7,42		
pO_2	216			212					188		
pCO_2	20			37					27		
Dose Barb.				100	100						
Level					21,9		29,9			21	

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing: Monkey remained in a deep coma.
Made some respiratory effort at 5 hours but then gradually deteriorated and died of a cardiac arrest at 10 hours.

Dead: GRADE V
Brain removed.

MONKEY "B" 13: Weight 4 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	110	100	120	80	90	90	95	95	100	100	100
Pulse	88	88	88	96	120	120	120	120	130	130	130
Resp.	15	15	15	15	15	15	15	15	15	15	15
ph	7,3		7,4					7,4			
pO_2	117		135					130			
pCO_2	45		42					42			
Dose Barb.				60	60						
Level							19,7			19	
Hb	14										

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Drowsy, left hemiplegia: GRADE IV

DAY 5: Dead: GRADE V
Brain removed.

MONKEY "B" 14: Weight 6 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	100	100	95	80	75	75	80	85	80	85	80
Pulse	90	96	96	96	108	108	108	108	108	108	108
Resp.	14	14	14	14	14	14	14	14	14	14	14
ph	7,6			7,5					7,44		
pO_2	180			160					150		
pCO_2	23			24					30		
Barb. Dose				90	90						
Barb. Level						20,8			18		
Hb	18										

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequate at 5 hours. Extubated and returned to cage.

DAY 2: Drowsy, hemiparetic: GRADE III

DAY 14: GRADE II
Sacrificed.

MONKEY "B" 15: Weight 6,75 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	90	100	90	90	80	95	100	100	110	110	110
Pulse	84	96	96	130	130	130	130	120	120	120	120
Resp.	14	14	14	12	12	12	12	12	12	12	12
ph		7,6					7,6				
pO_2		130					150				
pCO_2		30					28				
Dose Barb.				86	86						
Level						24,5				20,8	
Hb	19										

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 6 hours. Extubated and returned to cage.

DAY 2: Drowsy, hemiparesis, circling: GRADE III

DAY 13: GRADE II
Sacrificed.

MONKEY "C" 1: Weight 5 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	100	120	120	115	120	110	90	90	100	100	110
Pulse	130	140	150	150	150	150	150	150	150	150	150
Resp.	14	14	15	13	16	16	16	15	17	17	17
ph		7,32		7,33				7,38			
pO_2		224		168				174			
pCO_2		45		41				46			

De-occlusion: Vessel patent.
Routine closure of all wounds.
20 cc blood loss when catheter was removed.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Dead: GRADE V
Brain removed.

MONKEY "C" 2: Weight 6 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	90	80	100	100	90	100	90	90	90	90	90
Pulse	90	90	90	90	80	80	80	80	80	80	80
Resp.	16	16	16	14	14	14	14	14	14	14	14
ph	7,56	7,6		7,6			7,5			7,5	
pO_2	181	198		181			176			169	
pCO_2	27	24		27			31			33	

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Alert, no neurological deficit: GRADE I

DAY 6: GRADE I
Sacrificed.

MONKEY "C" 3: Weight 6 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	100	100	120	120	120	120	120	120	120	120	120
Pulse	100	100	90	100	100	100	100	100	90	100	100
Resp.	16	16	16	16	16	16	16	16	16	16	16
ph		7,40					7,42				
pO_2		156					187				
pCO_2		44					36				

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Alert, hemiparesis: GRADE III

DAY 14: GRADE II
Sacrificed.

MONKEY "C" 4: Weight 6 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	90	100	100	100	100	90	90	100	100	90	100
Pulse	80	80	80	80	80	80	80	80	80	80	80
Resp.	16	16	16	16	16	16	14	14	14	14	14
ph		7,55			7,52						
pO_2		220			124						
pCO_2		43			27						

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Alert, no neurological deficit: GRADE I

DAY 18: GRADE I
Sacrificed.

MONKEY "C" 5: Weight 5 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	130	130	130	130	130	125	130	130	130	125	125
Pulse	100	80	80	80	80	80	80	80	80	80	80
Resp.	16	16	16	16	16	16	16	16	16	16	16
ph	7,56			7,5			7,49				
pO_2	240			186			195				
pCO_2	37			35			36				

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Alert, poor hand grip, hemianopia: GRADE II

DAY 16: GRADE II
Sacrificed.

MONKEY "C" 6: Weight 6 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	120	120	110	110	100	130	100	120	120	120	120
Pulse	60	60	60	80	80	80	80	80	80	80	76
Resp.	16	16	16	16	16	16	16	16	16	16	16
ph	7,33						7,33			7,45	
pO_2	175						146			148	
pCO_2	42						30			34	

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Alert, left hand clumsy, hemianopia: GRADE II

DAY 12: GRADE II
Sacrificed.

MONKEY "C" 7: Weight 6 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	100	90	90	90	80	80	90	80	90	90	90
Pulse	70	70	70	70	80	80	80	80	80	80	80
Resp.	16	16	16	16	16	16	16	16	16	16	16
ph		7,56					7,3				
pO_2		148					117				
pCO_2		30					32				

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Dead: GRADE V
Brain removed.

MONKEY "C" 8: Weight 6 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	100	100	100	90	100	95	100	90	90	90	90
Pulse	84	84	90	84	84	84	84	84	84	86	84
Resp.	16	16	16	16	16	16	16	16	16	16	16
ph	7,48			7,38			7,47			7,45	
pO_2	233			199			192			185	
pCO_2	40			31			28			28	

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Drowsy, hemiplegic: GRADE IV

DAY 4: Dead: GRADE V
Brain removed.

MONKEY "C" 9: Weight 7 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	100	120	120	130	120	120	120	100	110	120	120
Pulse	88	88	88	84	70	70	76	72	80	84	84
Resp.	16	16	16	16	16	16	16	16	16	16	16
ph		7,44						7,38			
pO_2		200						244			
pCO_2		36						36			

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Alert, no neurological deficit: GRADE I

DAY 18: GRADE I
Sacrificed.

MONKEY "C" 10: Weight 4 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	110	90	115	100	90	90	90	90	90	110	110
Pulse	90	90	90	92	90	90	90	94	90	90	90
Resp.	12	12	12	16	16	16	16	16	16	16	16
ph	7,31		7,26		7,3			7,3			
pO_2	125		176		224			183			
pCO_2	52		45		44			41			

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Alert, no neurological deficit: GRADE I

DAY 19: GRADE I
Sacrificed.

MONKEY "C" 11: Weight 7 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	120	120	120	115	110	110	95	100	100	110	110
Pulse	80	80	84	84	88	88	88	88	86	90	86
Resp.	15	15	15	15	15	15	15	15	15	15	15
ph		7,45							7,43		
pO_2		155							150		
pCO_2		32							37		
Hb	17										

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Dead: GRADE V
Brain removed.

MONKEY "C" 12: Weight 6,5 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	120	130	120	110	130	120	120	120	120	115	110
Pulse	92	92	98	98	98	98	98	98	100	100	100
Resp.	14	14	14	14	14	14	14	14	14	14	14
ph		7,36		7,35				7,48			
pO_2		160		171				201			
pCO_2		50		46				30			
Hb	19										

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Drowsy, hemiparetic, circling: GRADE III

DAY 9: GRADE III
Sacrificed.

MONKEY "C" 13: Weight 5,5 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	130	130	110	110	110	120	120	120	110	100	110
Pulse	80	84	96	96	96	96	90	90	90	90	90
Resp.	14	14	14	14	14	14	14	14	14	14	14
ph	7,36	7,35					7,36				
pO_2	63	109					131				
pCO_2	50	44					41				
Hb	18										

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Awake, hemiparetic, circling: GRADE III

DAY 14: GRADE II
Sacrificed.

MONKEY "C" 14: Weight 4 kg

DAY 1: Anaesthesia: Routine

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	100	90	100	90	90	90	85	80	90	90	100
Pulse	110	110	120	130	130	130	130	130	130	130	130
Resp.	14	14	14	14	14	14	14	14	14	14	14
ph		7,49					7,47				
pO_2		195					200				
pCO_2		30					28				
Hb	15										

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Alert, no neurological deficit: GRADE I

DAY 15: GRADE I
Sacrificed.

MONKEY "C" 15: Weight 6 kg

DAY 1: Anaesthesia: Routine.

Surgery: Minimal blood loss.
No subarachnoid haemorrhage.
Occlusion performed without problems.

TIME AS HOURS	-1	0	½	1	1½	2	2½	3	3½	4	4½
BP	100	100	100	100	95	100	105	110	105	105	110
Pulse	84	84	84	84	84	84	84	84	84	84	84
Resp.	13	13	13	13	13	13	13	13	13	13	13
ph	7,6					7,5					
pO_2	130					150					
pCO	28					30					
Hb	17										

De-occlusion: Vessel patent.
Routine closure of all wounds.

Breathing adequately at 5 hours. Extubated and returned to cage.

DAY 2: Dead: GRADE V
Brain removed.

(B) COMPARABILITY OF THE GROUPS

WEIGHT

The monkeys weighed between 4 and 7 kg, with an average of 5,73 ($\pm$0,8) kg in the control and 5,86 ($\pm$0,99) kg in the barbiturate group. This difference was not statistically significant. The weight distribution is shown in Table III and again no difference was shown between the two groups.

BLOOD PRESSURE AND PULSE (BP AND PULSE)

Blood pressure and pulse varied considerably, depending on the depth of anaesthesia and the barbiturate dosage, as is shown in Tables I and II. In the control group the BP averaged 105,4 mmHg ($\pm$11,83) and the pulse rate was 91,13 ($\pm$19,19). The barbiturate group's BP was recorded as two sets, before and after pentobarbital was given. BP averaged 108,8 ($\pm$11,40) and 97,6 ($\pm$10,23) mmHg respectively, with a pulse rate of 92,8 ($\pm$14,67). This slightly lower BP after pentobarbital treatment was statistically different but not for the other values recorded.

pH, pO_2, pCO_2

Multiple blood gas determinations were made as is shown in Tables I and II. On the average, the barbiturate group showed a slight respiratory alkalosis with the pH 7,47 ($\pm$0,09), pO_2 159,26 mmHg ($\pm$32,20) and a pCO_2 of 32,53 ($\pm$8,08). The control group had a pH of 7,43 ($\pm$0,08), pO_2 170,9 ($\pm$32,86) and pCO_2 35,8 ($\pm$6,5) mmHg. These differences though were not statistically significant.

HAEMOGLOBIN (Hb)

This was determined only in the last 10 monkeys as is shown in Tables I and II. The control group averaged 17,2 ($\pm$1,48) and the barbiturate group 16,6 ($\pm$2,9) gm %, with no statistical difference.

STATISTICAL COMPARABILITY

No statistical differences were shown in these parameters, making this two well matched groups.

WEIGHT DISTRIBUTION

TABLE III

Weight - Kg	4-4,75	5-5,5	6-6,5	6,75-7
Control	2	3	8	2
Barbiturate	2	2	7	4
Total	4	5	15	6

(C) NEUROLOGICAL OUTCOME

Neurological assessments for analyses and comparing were those for Day 2 and at sacrifice.

The outcome on Day 2 for the 2 groups is shown in Table IV. It is clear from this table that 26,6% had no neurological deficit, 26,6% died in the acute phase and 46,6% developed some neurological deficit.

The outcome was virtually identical in the 2 groups with no statistical difference shown.

During the subsequent 2 weeks some of the animals improved whereas others died as is shown in Table V.

In the control group, 2 of the Grade III monkeys improved and 4 of the barbiturate monkeys, to Grade II. However, 1 Grade IV monkey in the control group and 2 barbiturate monkeys deteriorated and died. The remainder of the monkeys did not change their neurological status. The final outcome was also not statistically different between the 2 groups.

(D) PATHOLOGICAL OUTCOME

Details and photographs of the pathological classification adopted are shown on pages 79 to 81 and a graphic illustration of each monkey's pathological lesion on pages 82 to 98.

NEUROLOGICAL OUTCOME

(at DAY 2)

TABLE IV

GRADE	I	II	III	IV	V	TOTAL
Control Group	4	2	4	1	4	15
Barbiturate Group	4	1	4	2	4	15
TOTAL	8	3	8	3	8	30

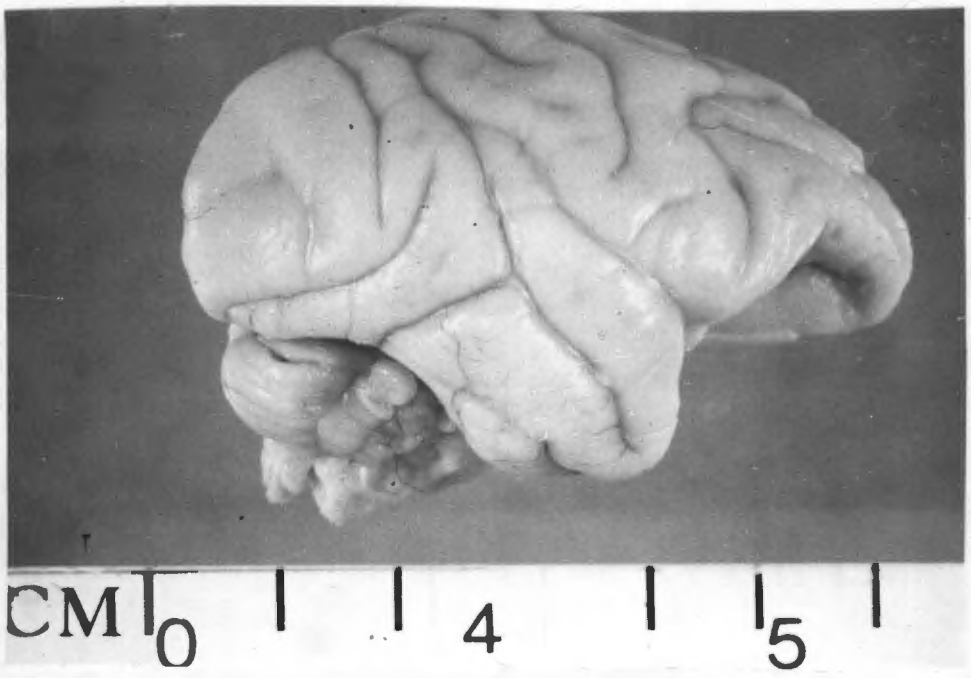
NEUROLOGICAL OUTCOME

(at Sacrifice)

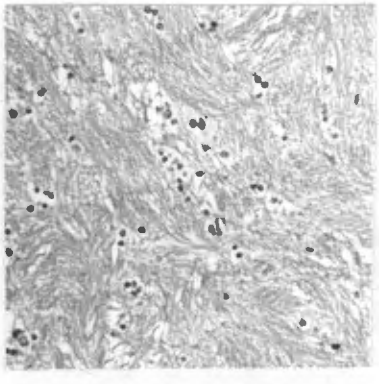
TABLE V

GRADE	I	II	III	IV	V	TOTAL
Control Group	4	4	2	0	5	15
Barbiturate Group	4	5	0	0	6	15
TOTAL	8	9	2	0	11	30

CLASSIFICATION OF PATHOLOGICAL LESIONS

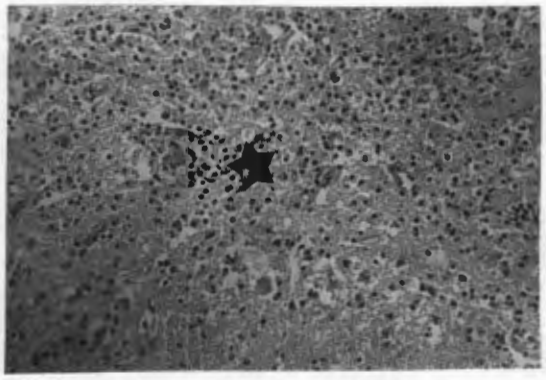


GRADE I: *Normal brain, lateral aspect.*

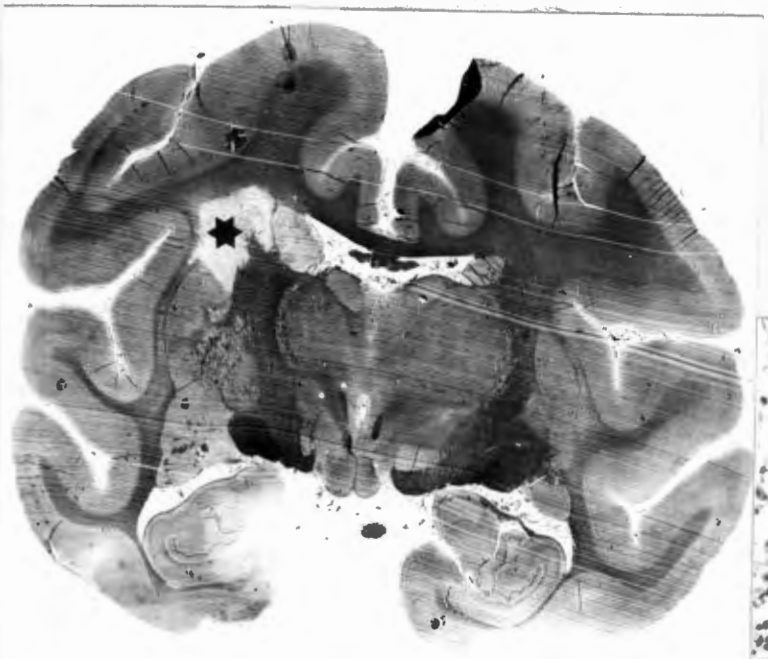


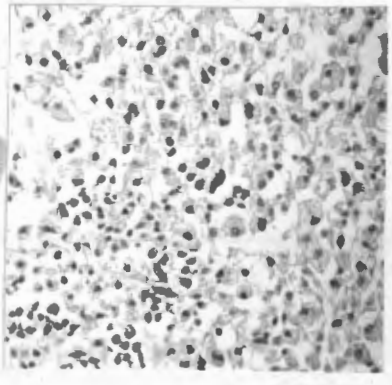
Normal Histology, H and E Stain.

GRADE II: Microscopic infarction.

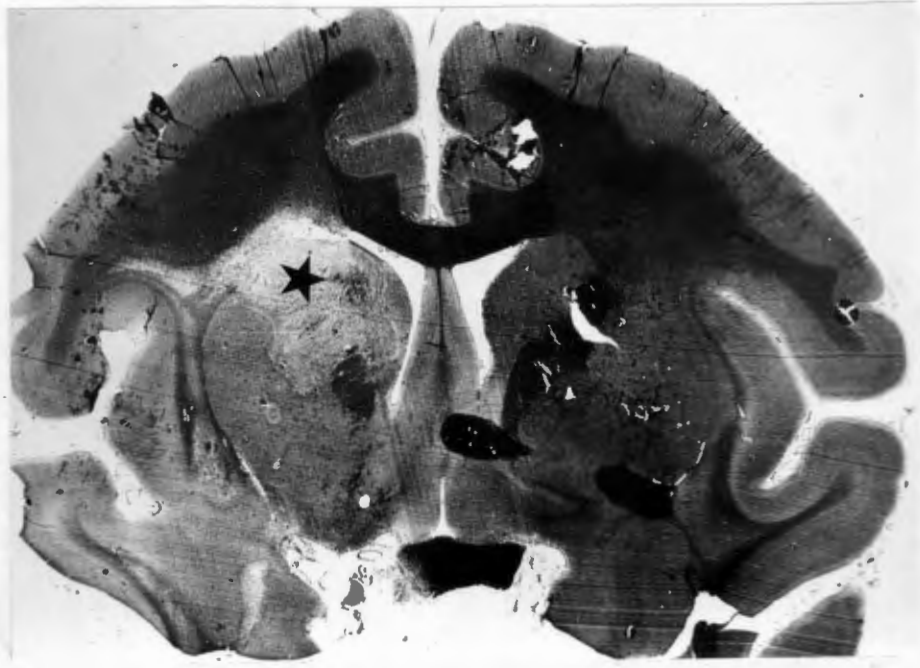


GRADE III: Macroscopic, well demarcated ischaemic infarct.
< 1 cm in diametre



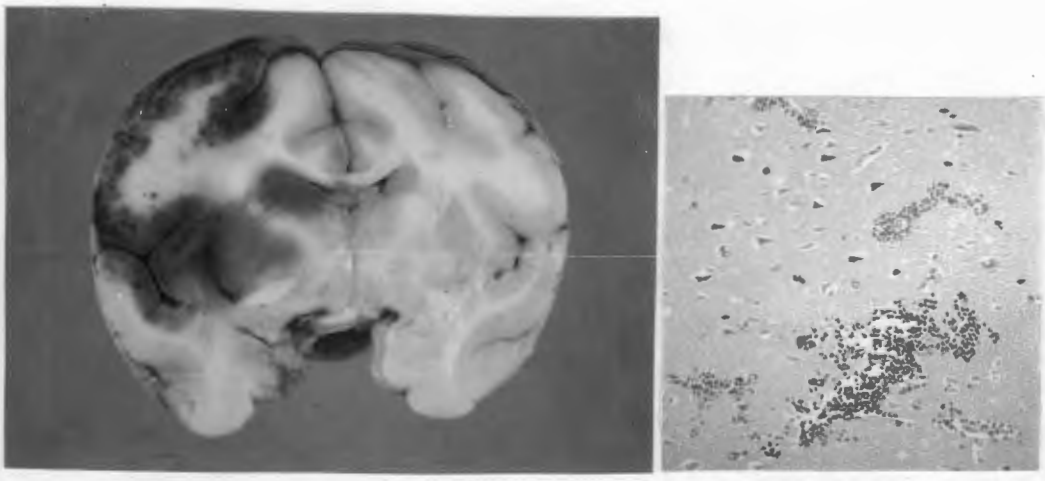


Infarct in right caudate nucleus. Organizing infarct.

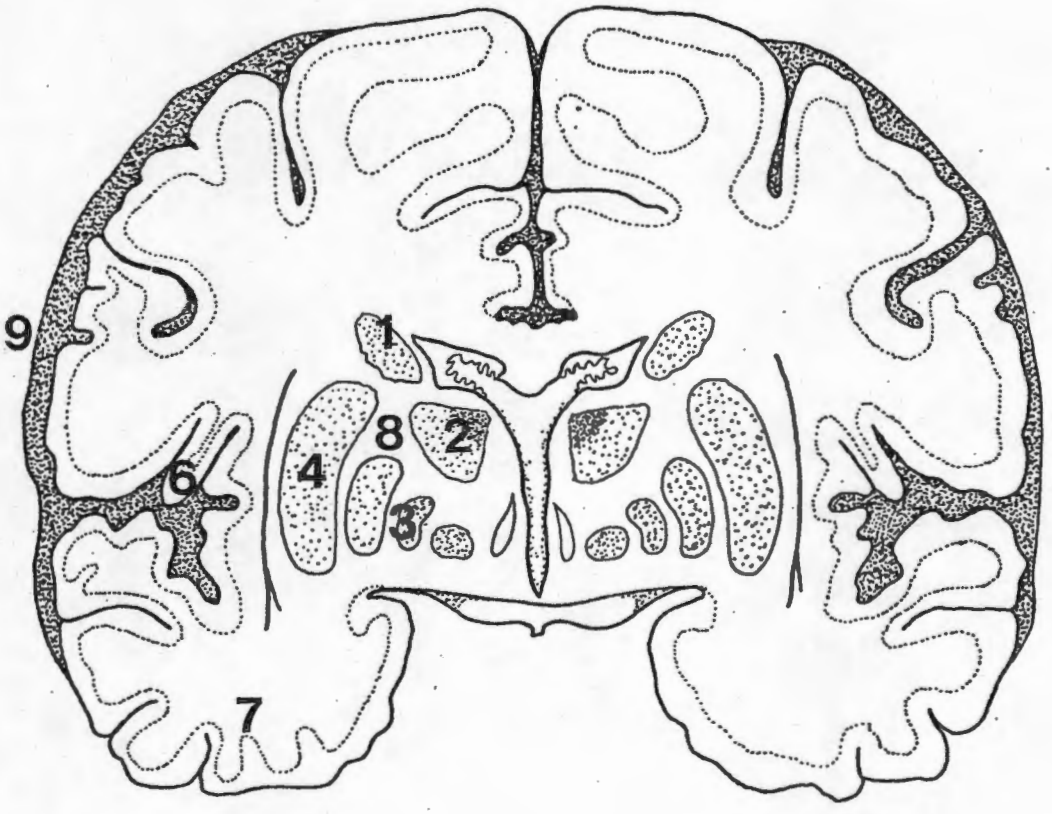


GRADE IV: Macroscopic, well demarcated ischaemic infarct, in lentiform and caudate nucleus, >1 cm in diameter.

GRADE V: Widespread, acute ischaemic cell changes, with oedema and petechial haemorrhage. Also areas of frank infarction present, distributed in the area of the middle cerebral artery, from the basal ganglia to the cortex.

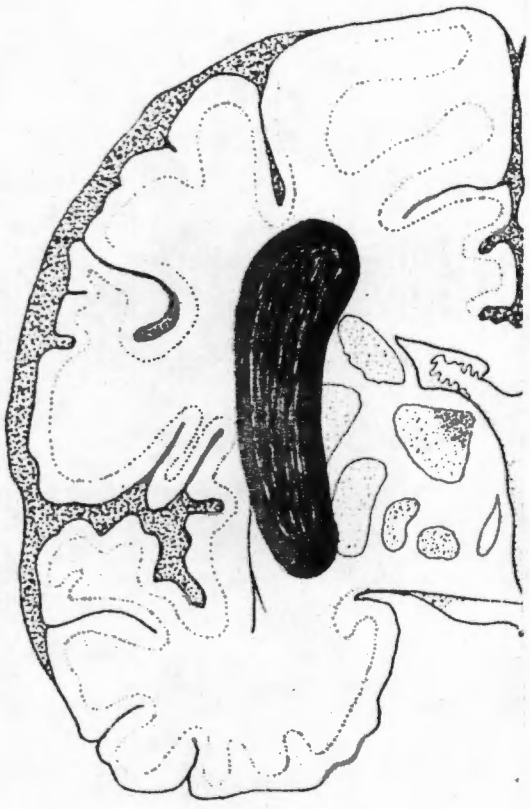


PATHOLOGICAL LESIONS: ILLUSTRATED



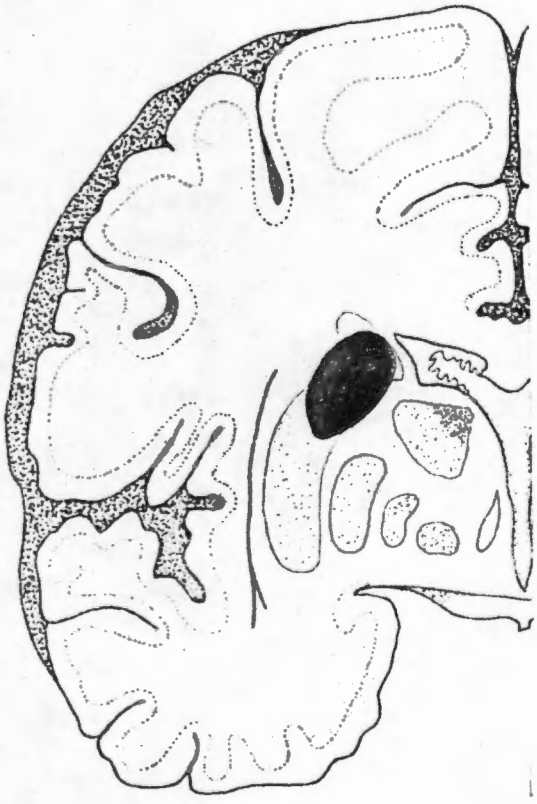
NORMAL ANATOMY:

1: Caudate nucleus
2: Thalamus
3: Globus pallidus] Lentiform nucleus
4: Putamen]
6: Insula
7: Temporal lobe
8: Internal capsule
9: Cortex



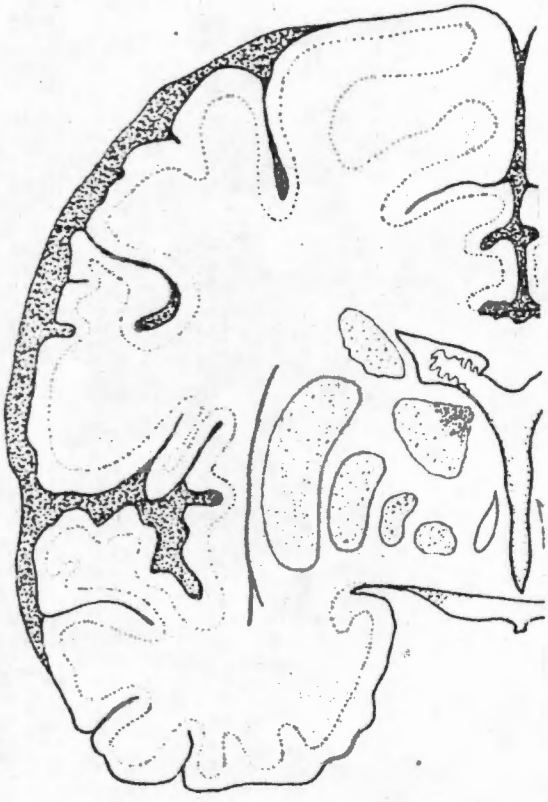
MONKEY "B" 1:

GRADE IV:
Putamen and adjacent white matter.



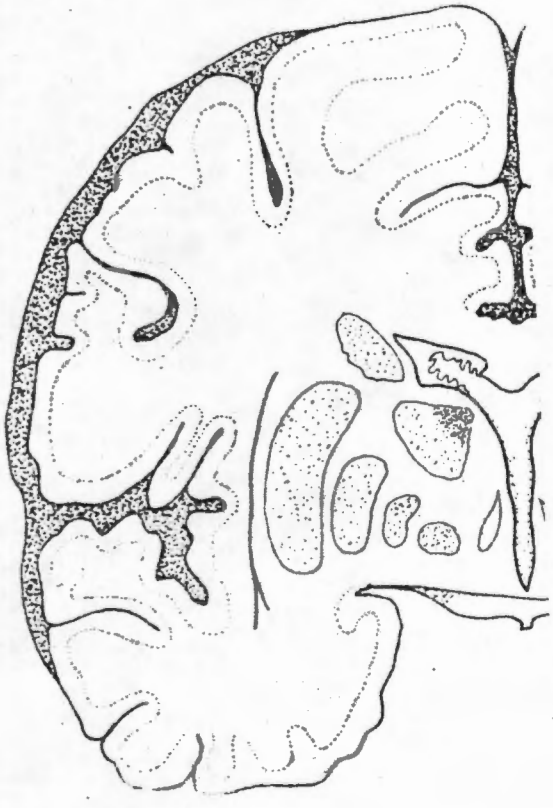
MONKEY "B" 2:

GRADE III:
Putamen and caudate nucleus.



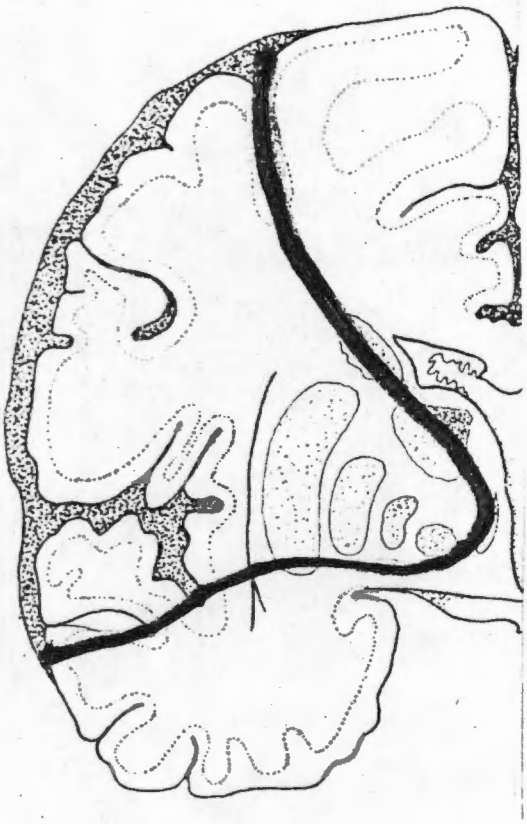
MONKEY "B" 3:

GRADE I:
Normal brain.



MONKEY "B" 4:

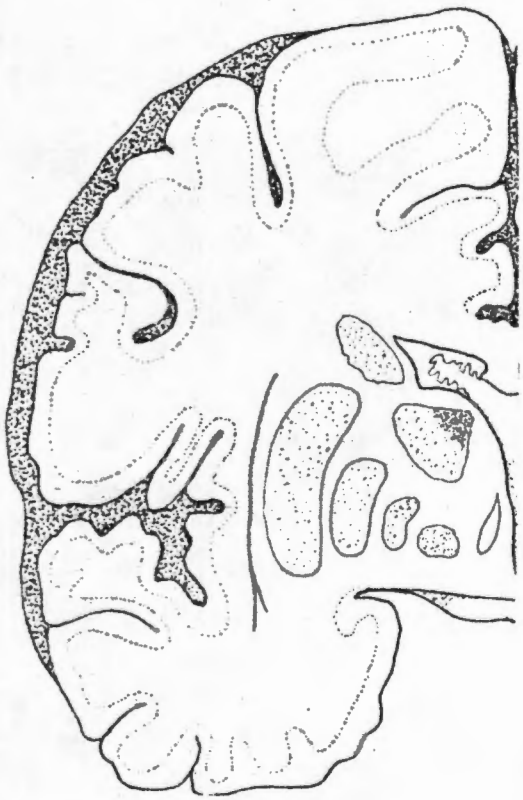
GRADE I:
Normal brain.



MONKEY "B" 5:

GRADE V:

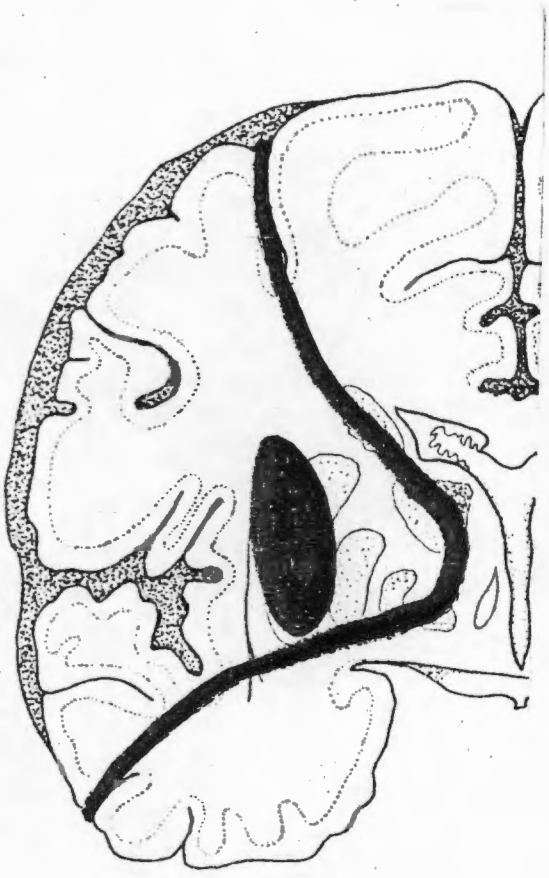
Lesion with acute ischaemic cell changes and petechial haemorrhage.



MONKEY "B" 6:

GRADE I:

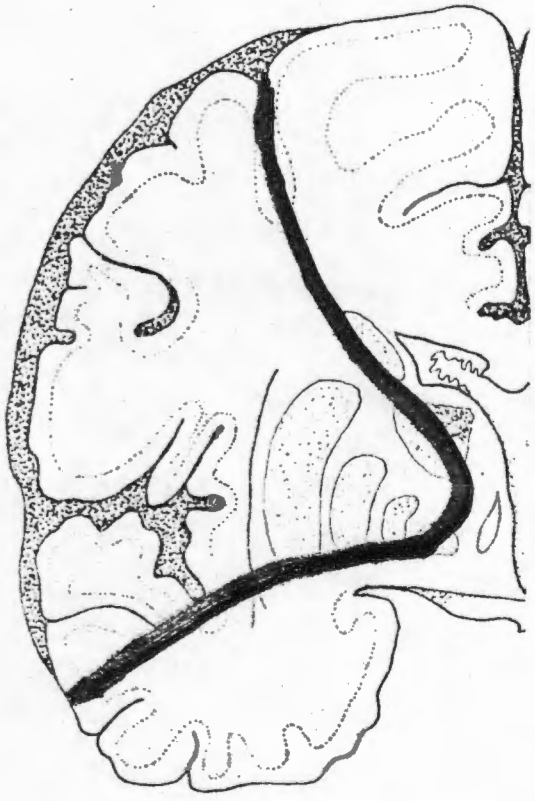
Normal brain.



MONKEY "B" 7:

GRADE V:

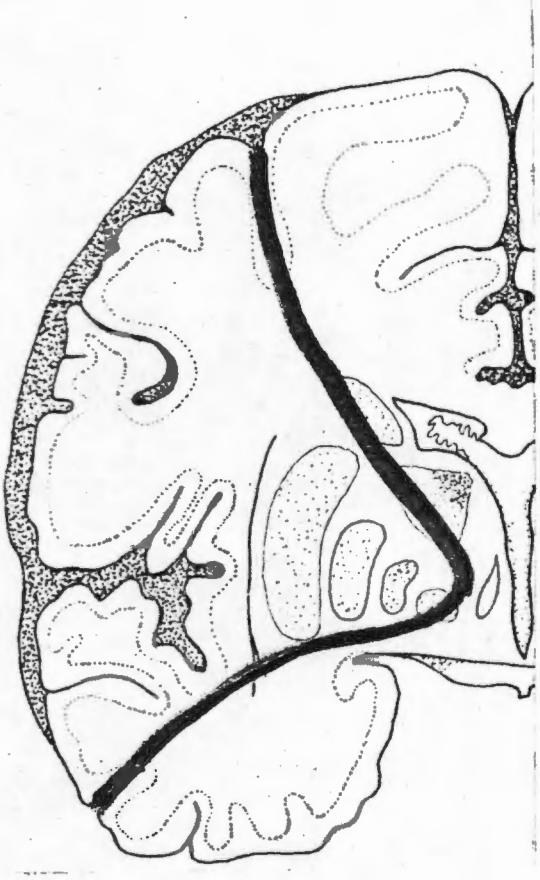
Lesion with acute ischaemic cell changes, petechial haemorrhages and a large 1,5 cm infarct in the putamen.



MONKEY "B" 8:

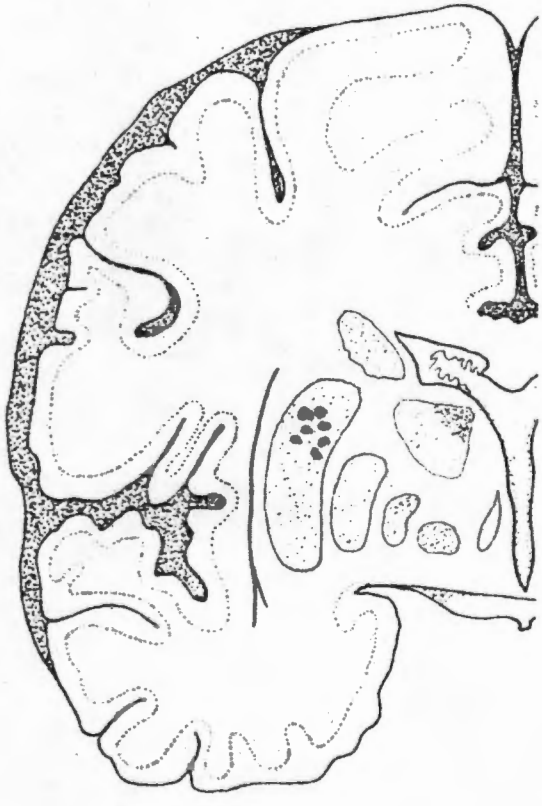
GRADE V:

Lesion with acute ischaemic cell changes and petechial haemorrhage.



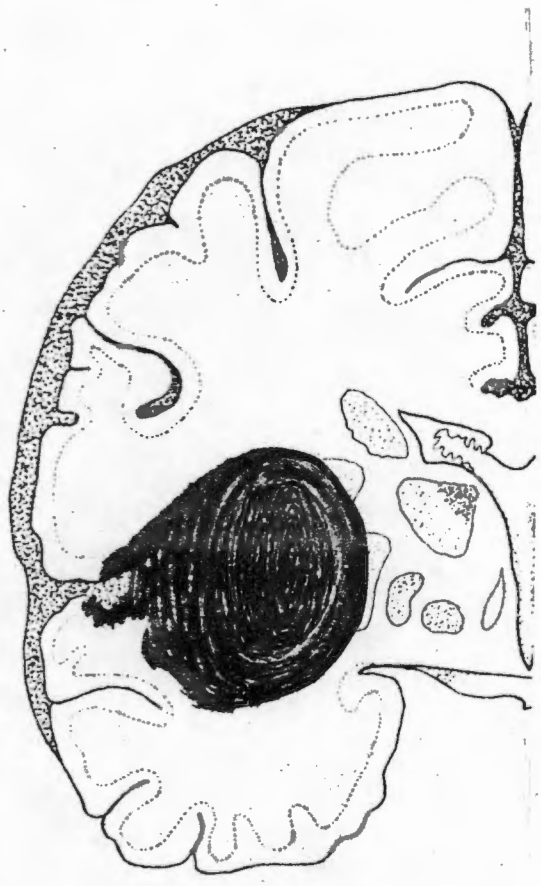
MONKEY "B" 9:

GRADE V:
Lesion with acute ischaemic cell changes and petechial haemorrhage.



MONKEY "B" 10:

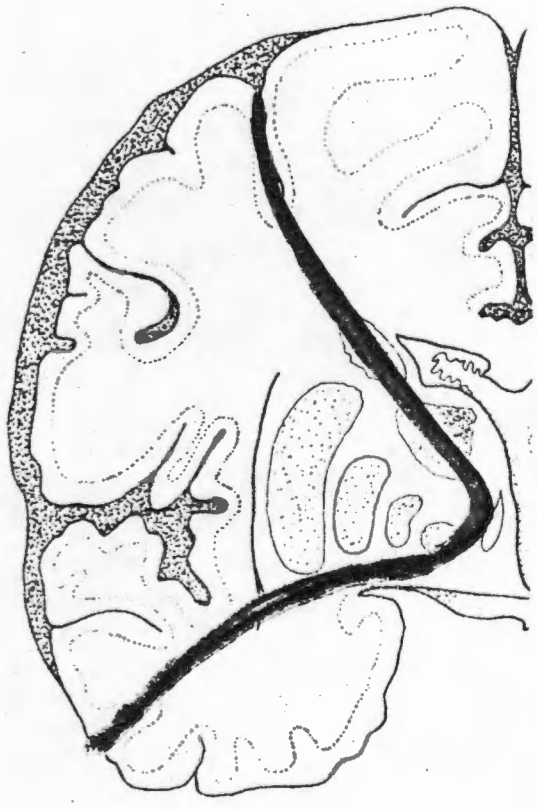
GRADE II:
Microscopic ischaemic infarction in the lentiform nucleus.



MONKEY "B" 11:

GRADE IV:

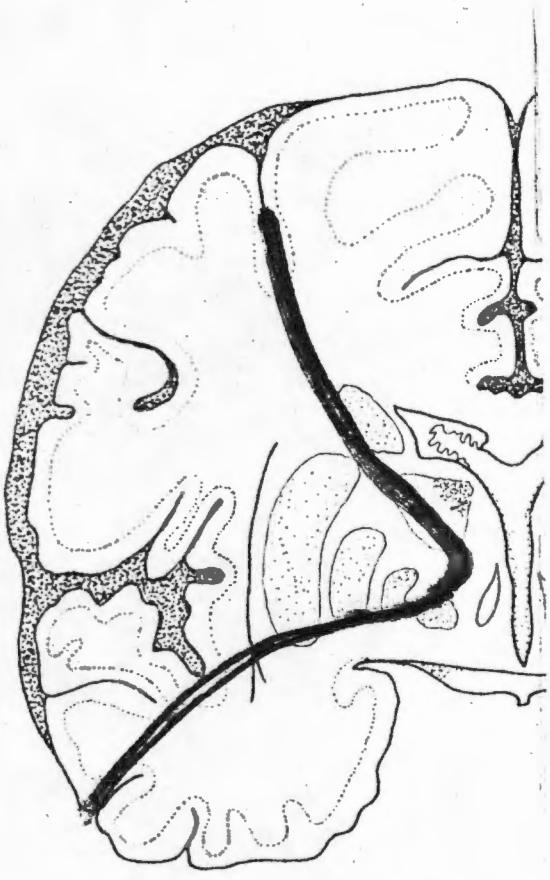
Infarct involving the insular cortex, lateral lentiform nucleus and white matter.



MONKEY "B" 12:

GRADE V:

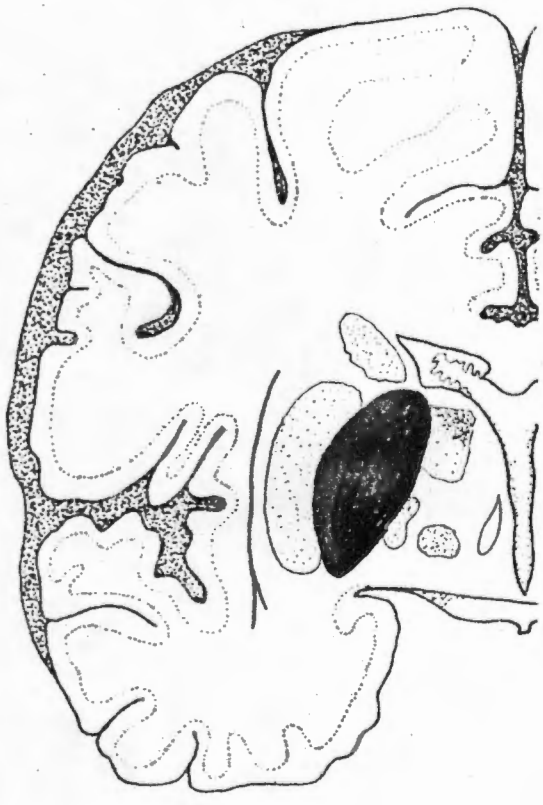
Acute ischaemic cell changes.



MONKEY "B" 13:

GRADE V:

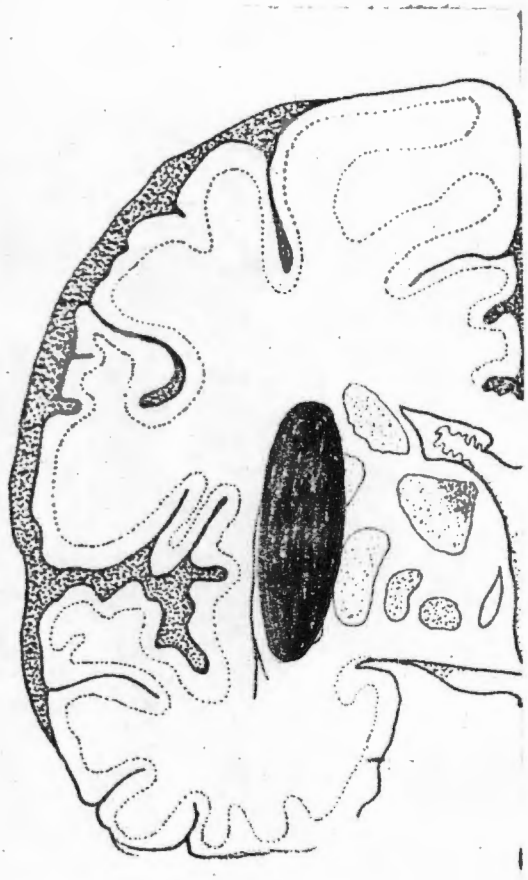
Acute ischaemic cell changes with petechial haemorrhage.



MONKEY "B" 14:

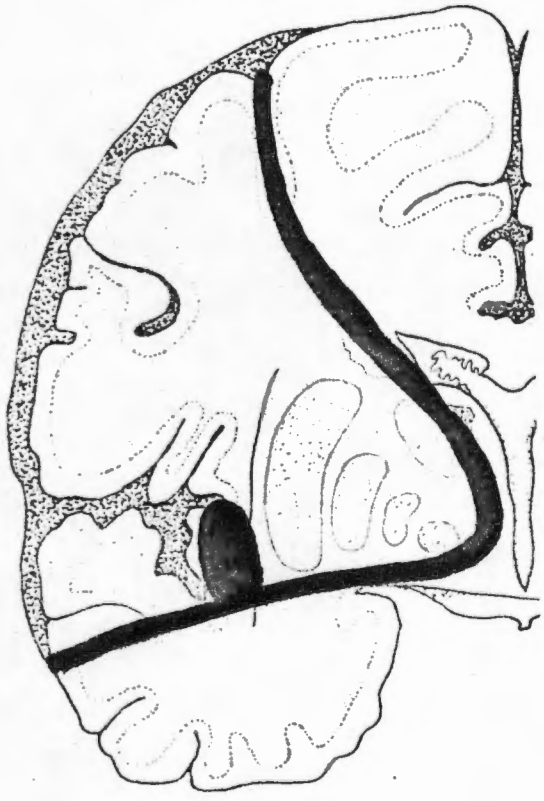
GRADE IV:

Involving lentiform nucleus and lateral thalamus.



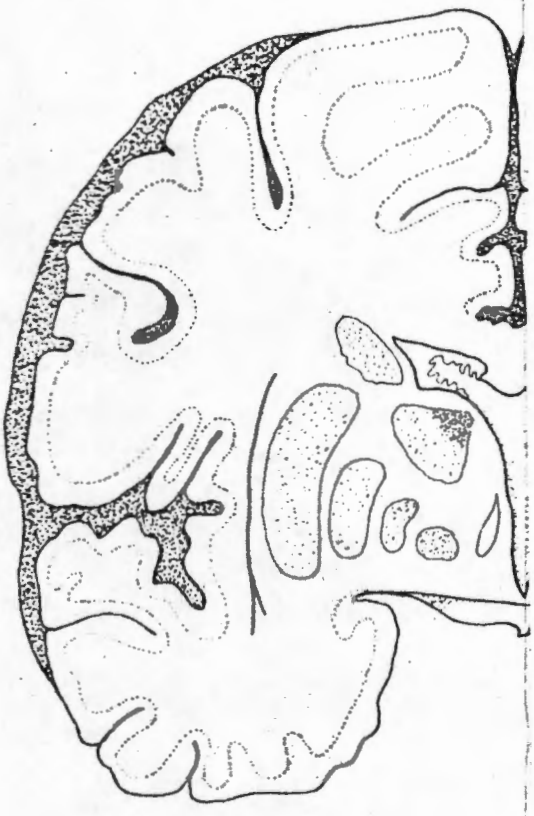
MONKEY "B" 15:

GRADE IV:
Lesion in the putamen.



MONKEY "C" 1:

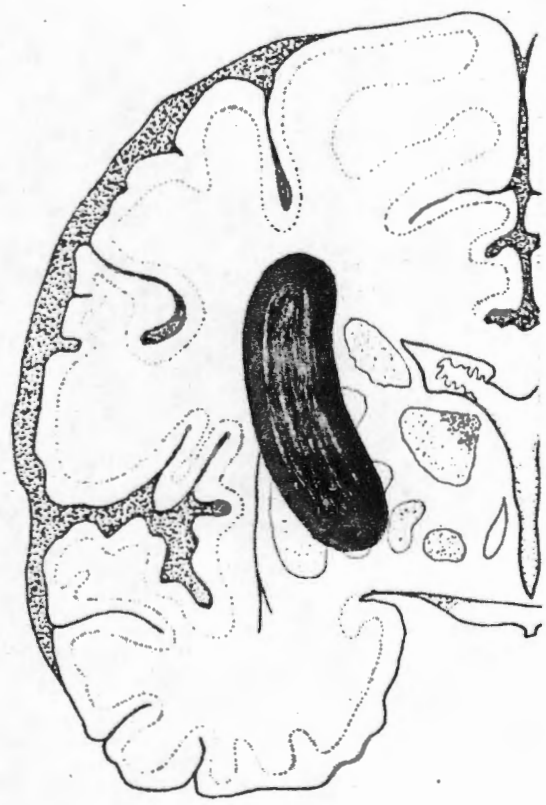
GRADE V:
Lesion with petechial haemorrhage and a focal infarct in the insula.



MONKEY "C" 2:

GRADE I:

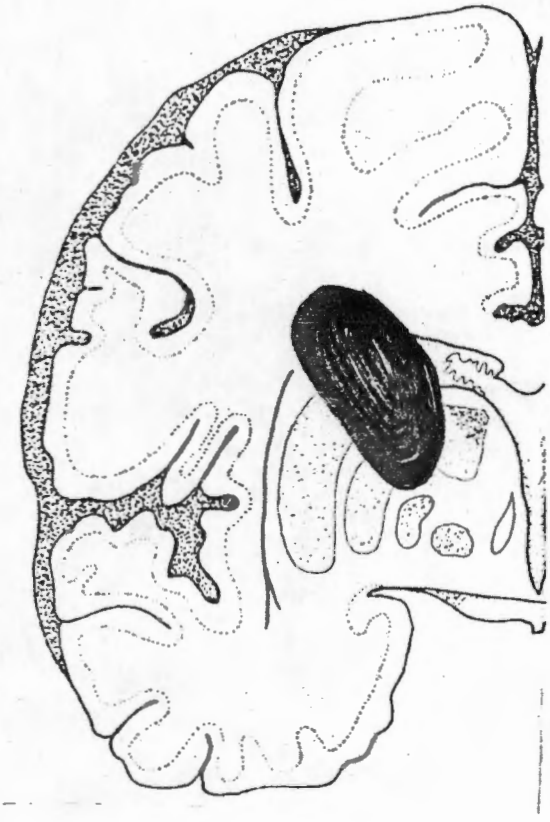
Normal brain.



MONKEY "C" 3:

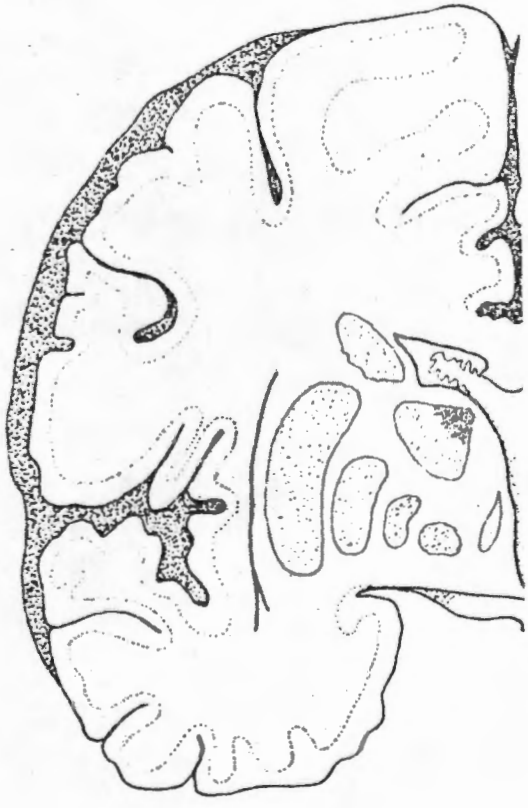
GRADE IV:

Putamen, globus pallidus and adjacent white matter.



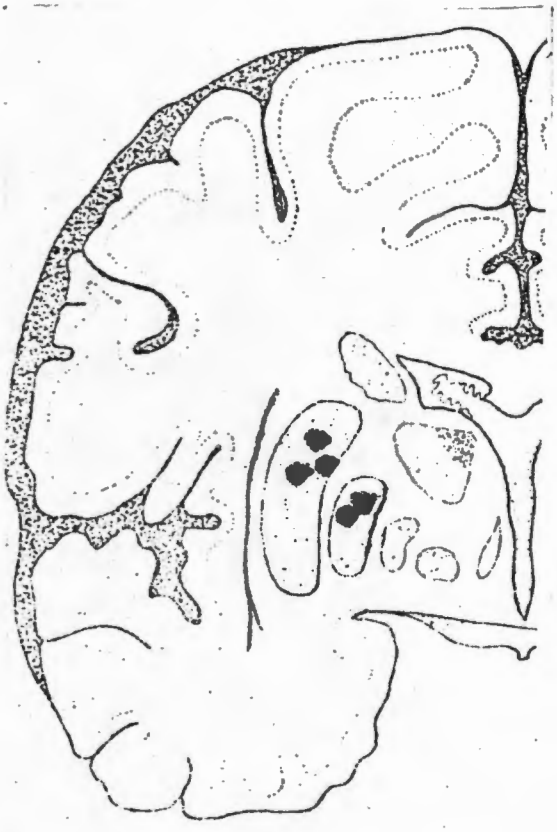
MONKEY "C" 4:

GRADE IV:
Head of the caudate nucleus and internal capsule abutting on to lentiform nucleus.



MONKEY "C" 5:

GRADE I:
Normal brain.



MONKEY "C" 6:

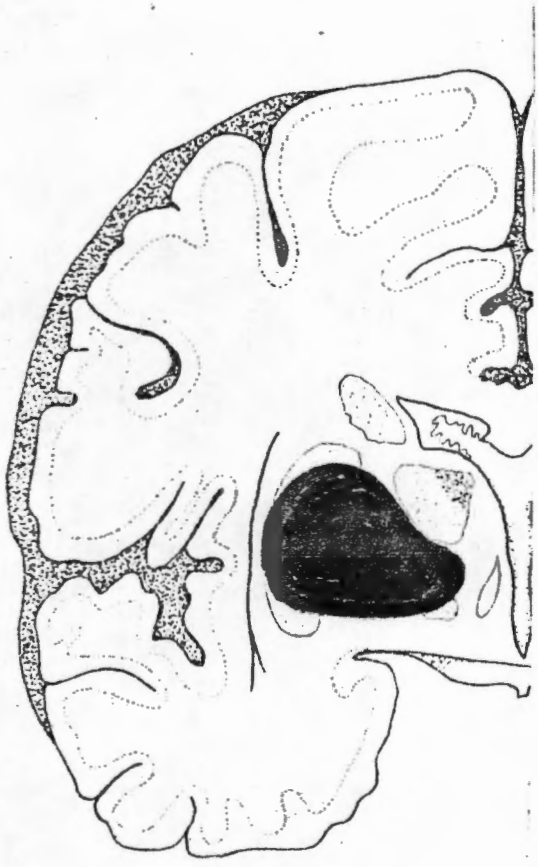
GRADE II:

Patchy microscopic ischaemic infarction in the lentiform nucleus.

MONKEY "C" 7:

GRADE V:

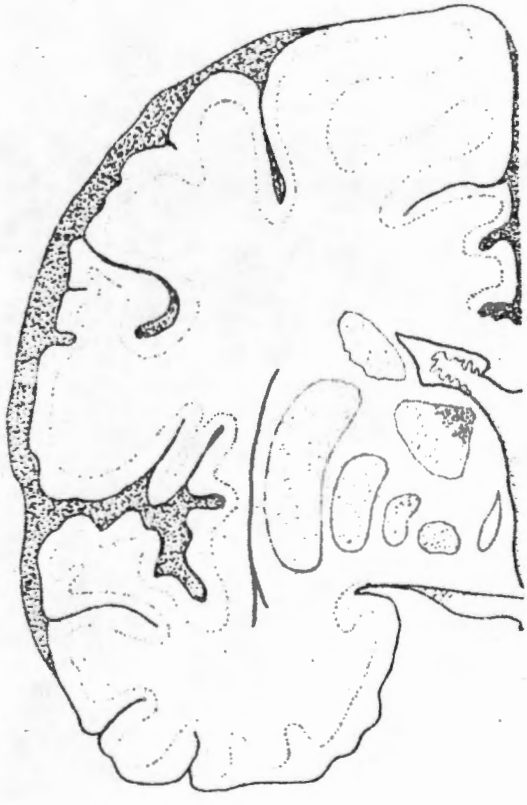
Lesion showing a large infarct extending from the basal ganglia to the cortex with petechial haemorrhage.



MONKEY "C" 8:

GRADE IV:

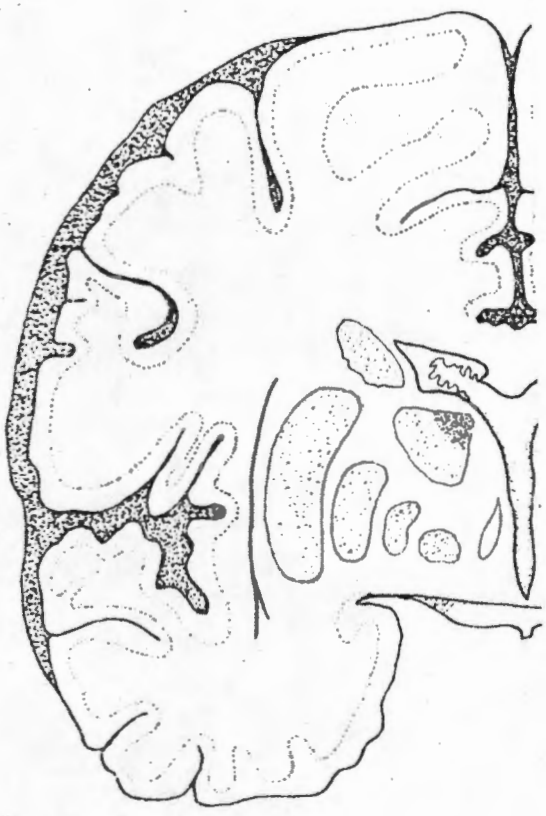
Lentiform nucleus and internal capsule.



MONKEY "C" 9:

GRADE I:

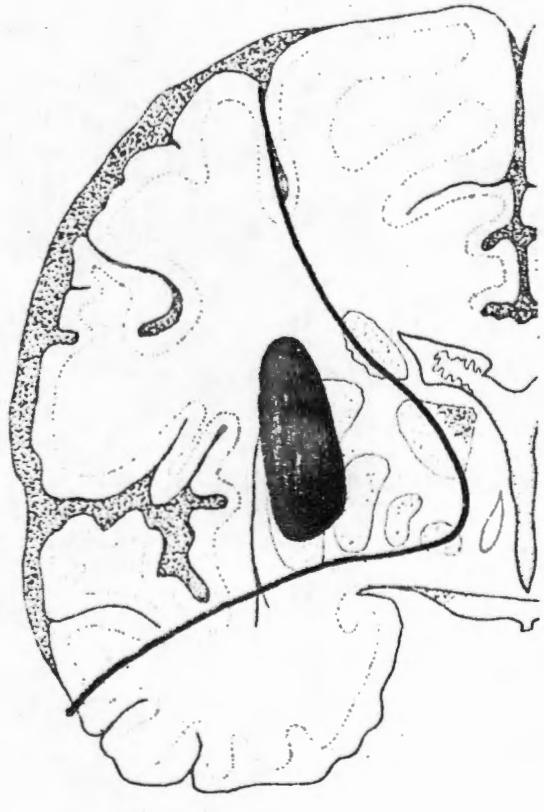
Normal brain.



MONKEY "C" 10:

GRADE I:

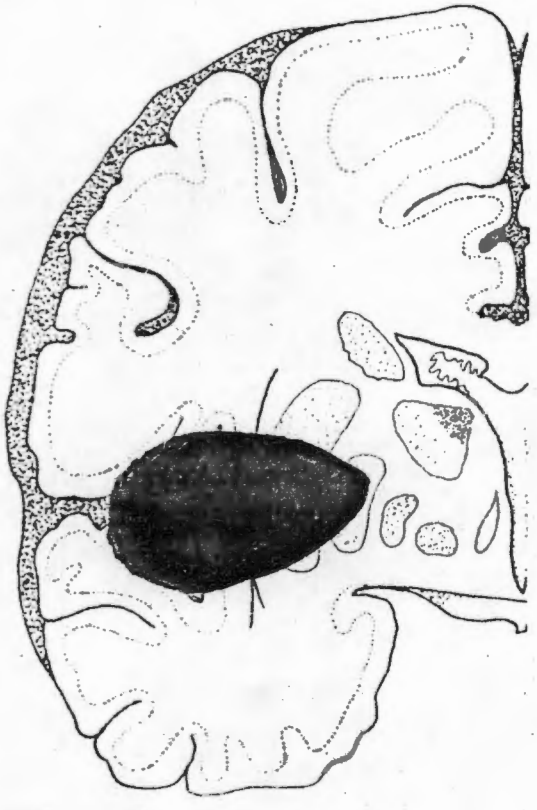
Normal brain.



MONKEY "C" 11:

GRADE V:

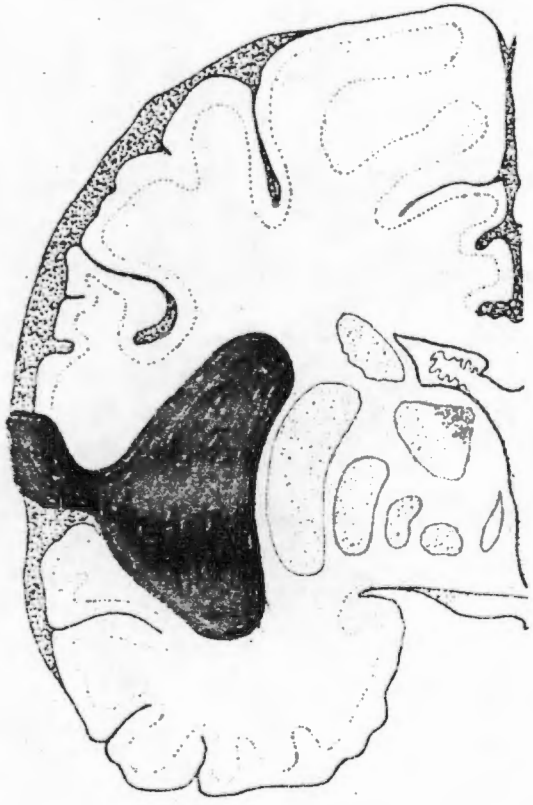
Acute ischaemic cell changes with large 2 cm pale infarct in the lentiform nucleus.



MONKEY "C" 12:

GRADE IV:

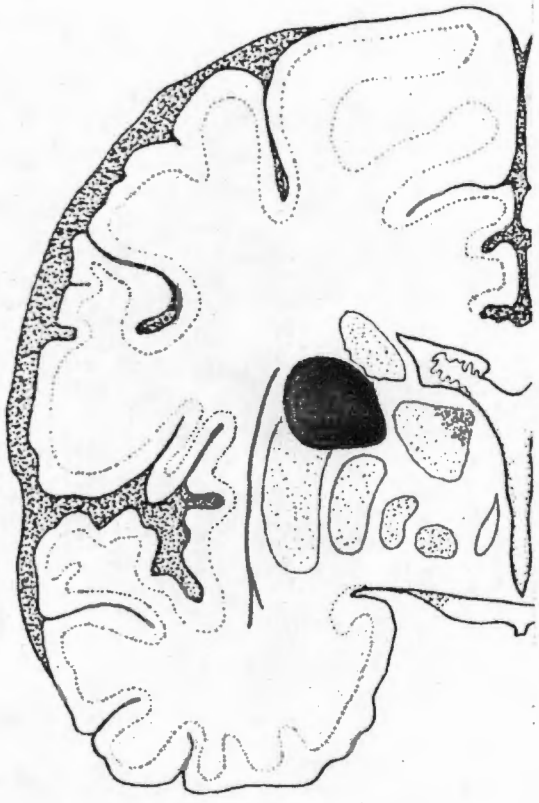
Infarct involving insular cortex, lentiform nucleus and white matter.



MONKEY "C" 13:

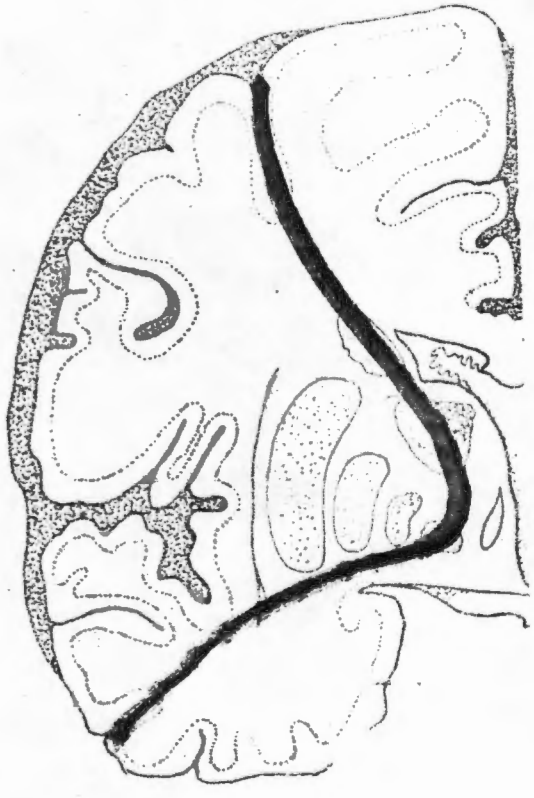
GRADE IV:

Infarct involving insular cortex and adjacent white matter.



MONKEY "C" 14:

GRADE III:
Infarct involving putamen and internal capsule.



MONKEY "C" 15:

GRADE V:
Acute ischaemic cell changes with petechial haemorrhage.

Table VI summarizes the distribution of lesions found in the pathological Grades II, III and IV. The 2 monkeys with Grade II lesions showed patchy changes in the lentiform nucleus, whereas the 11 monkeys with Grade III or IV lesions showed well developed ischaemic infarcts in the basal ganglia and insula. The Grade V lesions were widespread throughout the middle cerebral artery area involving basal ganglia, insula, white matter and cortex, with petechial haemorrhage in all but 2.

Table VII shows the pathological outcome with 33% in the control and 26% in the barbiturate group being normal or only showing microscopic changes, whereas the remainder showed infarction and acute ischaemic changes. These findings were not statistically different in the 2 groups.

(E) PATHOLOGICAL AND NEUROLOGICAL CORRELATIONS

The pathological and neurological outcome for the combined group was compared for both the Day 2 and the neurological assessment at sacrifice.

Table VIII shows the very good correlation found between the early neurological assessment on Day 2 and the eventual pathological lesion. Neurological Grades I and II monkeys showed Grades I and II pathological outcome, whereas the neurological Grades III, IV and V harboured Grades IV and V lesions. In 3 monkeys, however, there were discrepancies. Two neurologically intact monkeys (Grade I) harboured Grade III lesions in the putamen and in 1 neurological Grade II monkey, no lesion could be found. These discrepancies, however, were not statistically significant.

DISTRIBUTION OF GRADES II, III AND IV LESIONS

TABLE VI

Thalamus	1
Lentiform nucleus	7
Caudate	2
Putamen	4
Internal capsule	3
Insula	3

PATHOLOGICAL OUTCOME

TABLE VII

GRADE	I	II	III	IV	V	TOTAL
Control Group	4	1	1	5	4	15
Barbiturate Group	3	1	1	4	6	15
TOTAL	7	2	2	9	10	30

PATHOLOGICAL AND NEUROLOGICAL CORRELATION

(at DAY 2)

TABLE VIII

NEUROLOGICAL GRADE	PATHOLOGICAL GRADE				
	I	II	III	IV	V
I	6		2		
II	1		2		
III				8	
IV				1	2
V					8

Tables IX and X show the good pathological and neurological correlation for each group separately, whereas in Tables XI, XII and XIII, the neurological and pathological correlation on the day of sacrifice is shown. It is evident that 6 monkeys with Grade IV pathological lesions improved neurologically from Grade III to II. On the other hand, 1 monkey with a Grade IV lesion and 2 with Grade V lesions deteriorated from a neurological Grade IV and died.

(F) WEIGHT CORRELATION WITH NEUROLOGICAL OUTCOME

Table XIV shows the correlation of weight with neurological outcome in the 9 monkeys that were 5,5 kg or less and the 21 weighing more. It is evident that the lighter group did much better, 52% being Grades I or II, whereas in the heavier group only 28% were in these grades.

The 2 monkeys with the neurological Grade I and Grade III pathological lesions, were both in the lighter group. This difference was statistically not significant.

WEIGHT CORRELATION WITH PATHOLOGICAL OUTCOME

Table XV shows the correlation with the pathological outcome. In the light group 33% of the monkeys were in the Grade I or II groups whereas 28% of the heavier monkeys were in this group. This was not statistically significant.

(G) BARBITURATE BLOOD LEVEL (TABLE II)

This was determined half an hour after the drug was given and again at de-occlusion of the vessel. Levels varied between 16 ug/ml to 25 ug/ml, except in the monkey with an initial level of 29 ug/ml and in another monkey with levels of 8 ug/ml and 12 ug/ml. There was no correlation between blood levels and outcome.

PATHOLOGICAL AND NEUROLOGICAL CORRELATION

CONTROL GROUP - DAY 2

TABLE IX

NEUROLOGICAL GRADE	PATHOLOGICAL GRADE				
	I	II	III	IV	V
I	3		1		
II	1	1			
III				4	
IV				1	
V					4

PATHOLOGICAL AND NEUROLOGICAL CORRELATION

BARBITURATE GROUP - DAY 2

TABLE X

NEUROLOGICAL GRADE	PATHOLOGICAL GRADE				
	I	II	III	IV	V
I	3		1		
II		1			
III				4	
IV					2
V					4

PATHOLOGICAL AND NEUROLOGICAL CORRELATION

(at Sacrifice)

TABLE XI

NEUROLOGICAL GRADE	PATHOLOGICAL GRADE				
	I	II	III	IV	V
I	6		2		
II	1	2		6	
III				2	
IV					
V				1	10

PATHOLOGICAL AND NEUROLOGICAL CORRELATION

CONTROL GROUP - AT SACRIFICE

TABLE XII

NEUROLOGICAL GRADE	PATHOLOGICAL GRADE				
	I	II	III	IV	V
I	3		1		
II	1	1		2	
III				2	
IV					
V				1	4

PATHOLOGICAL AND NEUROLOGICAL CORRELATION

BARBITURATE GROUP - AT SACRIFICE

TABLE XIII

NEUROLOGICAL GRADE	PATHOLOGICAL GRADE				
	I	II	III	IV	V
I	3		1		
II		1		4	
III					
IV					
V					6

WEIGHT COMPARED TO NEUROLOGICAL OUTCOME

TABLE XIV

NEUROLOGICAL GRADE	I	II	III	IV	V	TOTAL
4-5,5 kg	4	1	1	1	2	9
6-7 kg	4	2	7	2	6	21

WEIGHT COMPARED TO PATHOLOGICAL OUTCOME

TABLE XV

NEUROLOGICAL GRADE	I	II	III	IV	V	TOTAL
4-5,5 kg	3	0	2	1	3	9
6-7 kg	4	2	0	8	7	21

CHAPTER V

(A) DISCUSSION

This study investigated a suggested protective effect of barbiturate treatment for transient focal cerebral ischaemia simulating the clinical event of a large cerebral vessel occlusion followed by revascularization.

The experimental and control groups were well matched in all respects. No protective effect for high dose pentobarbital coma could be demonstrated and the neurological and pathological outcomes were virtually identical in each group. Approximately a quarter of the animals were normal, a third developed neurological defects and a third died of their stroke. In each group a good correlation was found between the neurological and pathological outcome, which suggested that our simple, practical classification has merit. There were, however, 3 exceptions: 1 Grade II monkey showed no pathological abnormality and 2 Grade I monkeys showed Grade III pathological lesions in the putamen. This did not involve the internal capsule or cortex, perhaps explaining the absence of obvious neurological signs.

Revascularization is reported to be beneficial in clinical and experimental strokes, Sundt et al (1974), Ojeman et al (1979), Kieck and Crowell (1979), Dujovny et al (1976), Morawetz et al (1978) and Jones et al (1981), where well selected cases with moderate neurological deficits may show dramatic improvement. The danger, however, of converting an ischaemic stroke into a

haemorrhagic one, as is well described in the clinical and experimental literature, Wylie et al (1964), Crowell et al (1970), Morawetz et al (1978) and Hayashi et al (1978), was demonstrated in our animals. Those monkeys who suffered a major neurological deficit, developed haemorrhages of varying degrees in addition to acute ischaemic cell changes and most of them went on to die without any improvement.

The pathological lesions were present in the region supplied by the middle cerebral artery. The deep grey matter structures were involved in monkeys with less severe neurological deficits, whereas the insula and cortex were also infarcted in monkeys with more severe neurological deficits. This is in keeping with the other workers reporting on middle cerebral artery occlusion in the primate.

It remains to examine why this experiment did not show a protective effect for barbiturates. The model and experiment will be examined in the light of what we know from the literature and any major discrepancies, if present, will be pointed out so as to explain this negative result as apparent or real.

DELAYED TREATMENT

Whereas in our model therapy was delayed for 1 hour, other workers delayed it for 15 minutes to 4 hours, Smith et al (1974), Moseley et al (1975), Michenfelder et al (1976), Corkill et al (1976), Levy and Brierley (1979), Yonas et al (1980a,1981) and Selman et al (1981b), with some apparent therapeutic effect, although Corkill stated that no effect was shown if therapy was delayed for an hour or longer.

DOSAGE REGIMES

A considerable variety of dosage regimes have been reported to afford protection, from 60 mg/kg to as low as 15-20 mg/kg. Hankinson et al (1974) and Corkill et al (1978). The 30 mg/kg used in our study induced deep coma lasting 12 hours or more, without causing major cardiovascular difficulties.

BLOOD LEVELS

Although the usefulness of barbiturate blood level determination has been questioned by Miller (1979) and Bruce et al (1978), we, as others, Hoff et al (1975), Yonas et al (1979, 1981) and Weidler et al (1979), measured it as an indication of therapeutic efficacy. Whereas the levels in this study ranged between 16-29 ug/ml without any correlation with the outcome, Yonas et al (1979), showed protection in 2 groups of dogs with levels between 9-16 ug/ml and 19-49 ug/ml. In contrast, Weidler et al (1979), showed that all cats with levels over 30 ug/ml, died.

DURATION OF THE OCCLUSION

The earlier reports on barbiturate protection were for permanent focal ischaemia. Yonas et al (1981) and Selman et al (1981b), reported on apparent protection during 6 hours of transient occlusion, whereas in the present study, a 4 hour period of occlusion was chosen.

DISCUSSION OF THE LITERATURE ON TRANSIENT ISCHAEMIA

The overall review of the literature made it clear that positive and negative results were shown for permanent focal ischaemia and global ischaemia with tremendous variability in models used and results reported. The reports by Yonas et al (1981) and Selman et al (1981b), showing apparent protection for 6 hours of transient occlusion, revealed some major discrepancies and raised a number of questions.

Yonas et al (1981), showed no protection for pentobarbital treated animals, but only for thiopental. However, the statement that the "grace" period to revascularization has been extended from 5 to 6 hours is somewhat questionable, because this refers to a previous study by Dujovny et al (1976), in which occlusion of only 3, 4, 5 and 7 hours is discussed in the text, though a 6 hour occlusion, showing infarction, is noted in a Table. Also, no control group without any barbiturate anaesthesia is available for comparison. It is also noteworthy that these workers showed similar extension of the "grace" period for dimethyl sulfoxide (DMSO) and prednisolone. Dujovny et al (1979).

Similarly, Selman et al (1981b), reported protection in 6 hours of transient occlusion in a group of baboons treated and ventilated for 96 hours. However, the control group breathed spontaneously, had a lower PO_2 and developed severely raised intracranial pressure, cerebral infarction and death. One can thus only speculate on how much the sedation and ventilation played a rôle in the outcome.

Thus the model and variables in this experiment were not at variance with work which reported apparent protection under a variety of conditions; it is our results that are at variance with reported work.

(B) CONCLUSION

This study specifically investigated the theoretically attractive situation of transient focal cerebral ischaemia simulating a cerebral vessel occlusion, treated with high dose pentobarbital and subsequent revascularization. No protection during the period of occlusion was shown for pentobarbital treated animals as compared to the untreated control animals.

Revascularization after 4 hours resulted in a third of the animals remaining normal or suffering minor deficits, a third developing significant deficits and the remaining third dying of their stroke. No statement can be made whether revascularization as such benefited these animals because they were sedated during the ischaemic period and no control group with permanent occlusion of the vessel was investigated.

The experimental model used to simulate the clinical event worked satisfactorily and no major discrepancies compared to other reported works were apparent.

Finally, the tremendous variation in reported results, ranging from apparent protection to no protection or to it even being detrimental, argues against a general protective effect in cerebral ischaemia. Certainly, the very conclusive outcome in this study specifically showed no protection for delayed high dose barbiturate treatment in transient focal cerebral ischaemia.

APPENDIX

STATISTICAL DETAILS

ANALYSIS OF BARBITURATE MANAGEMENT IN TRANSIENT FOCAL CEREBRAL ISCHAEMIA

(A) VARIABLES

In this study, 30 monkeys were randomly allocated to 2 groups; an experimental group and a control group. Initially the blood pressure in mm/Hg was measured in both groups. The barbiturate was administered to the experimental group and the blood pressure measured again in the experimental group.

Other variables measured are:

1. Pulse/minute
2. Respiration/minute
3. pH
4. PO_2 mm/Hg
5. PCO_2 mm/Hg
6. Weight
7. Haemoglobin

The number of observations in the control and experimental groups are so small, that the assumptions on which the parametric techniques of analysis are based, could not be checked. Also not being aware of previous work which would point to a preferred distribution type, it was decided to use non-parametric methods which make no assumptions about the underlying distributional structure of the

VARIABLE	STATISTIC USED	CALCULATED VALUE	TABULATED VALUE		CONCLUSION
			X=0,05	X=0,10	
Blood pressure (mm/Hg) before administration between groups	Mann-Whitney U	U = 89	64	72	Cannot reject the null hypothesis.
Blood pressure (mm/Hg) after administration between groups	Mann-Whitney U	U = 68,5	64	72	Cannot reject the null hypothesis at the 0,05 level but can reject it at X=0,10 level.
Blood pressure in experimental group before and after administration	Wilcoxon Matches Pairs Signed Rank Test	T = 8	21		Reject the null hypothesis that the BP/mmHg does not differ before and after barbiturate is administered in the experimental group.
Pulse	Mann-Whitney U	U = 80	64	72	Cannot reject the null hypothesis.
Respiration	Mann-Whitney U	U = 91	64	72	Cannot reject the null hypothesis.
pH	Mann-Whitney U	U = 81	64	72	Cannot reject the null hypothesis.
PO_2	Mann-Whitney U	U = 88	64	72	Cannot reject the null hypothesis.
PCO_2	Mann-Whitney U	U = 82	64	72	Cannot reject the null hypothesis.
Day of removal of brain	Mann-Whitney U	U = 107	64	72	Cannot reject the null hypothesis.
Weight	Mann-Whitney U	U = 84	64	72	Cannot reject the null hypothesis.
Haemoglobin	Mann-Whitney U	U = 82	64	72	Cannot reject the null hypothesis.

population from which the sample is drawn, to analyse the data set.

In comparing the measurements made on a variable in the control group with the corresponding variable in the experimental group, the Mann-Whitney U test was used. It tests whether 2 samples represent populations which differ in central tendency (location). The general, null hypothesis:

H_0: The variable under consideration from the monkeys in the control group and the experimental group is the same as tested against the alternative hypothesis.

H_1: The variable under consideration from the monkeys in the control group and the experimental group, differs.

The hypotheses are two-tailed. A shift in the central tendency was being sought, without preference being given to any direction.

In the case of the comparison of the blood pressure before and after the administration of the barbiturate, the Wilcoxon Matched Pairs Signed Rank Test was used, as the 2 sets of values are made on the same sample. The null hypothesis tested is:

H_0: The blood pressure does not differ before and after the barbiturate is administered in the experimental group.

Against the alternative hypothesis:

H_1: The blood pressure does differ after the administration of the barbiturate in the experimental group.

This, again, is a two-tailed hypothesis test.

The results of these tests are summarised in Table 1.

From the conclusion column it can be deduced that at the 5% significance level there is no significant difference between the experimental and control groups for the variables measured. The blood pressure variable between the groups after the administration of the barbiturates does show a difference at the 1% significance level. However, the blood pressure measurements within the experimental group, after the administration of the barbiturate, differs significantly at the 5% level from the values taken before the administration of the barbiturate.

(B) NEUROLOGICAL AND PATHOLOGICAL OUTCOME

To determine whether, in comparing the experimental and control groups, the barbiturate made a difference between the Pathological and Neurological outcomes - a Chi-square test was done for various groupings.

The null hypothesis tested in each case was that:

H_0: The grade is independent of barbiturates in the animals.

The alternative hypothesis against which the null hypothesis is tested is:

H_1: The grade is dependent upon the presence of barbiturates in the animal.

Pathological Results:

$X^2 = 0,66$

The tabulated values are $X_4^{2(0,05)} = 9,49$ and $X_4^{2(0,10)} = 7,78$

Conclusion:

The pathological grade is independent of the level of barbiturates in the animal at both 5% and 1% significance levels.

Neurological Results:

For Day 2:

$X^2 = 0,67$

For results at sacrifice:

$X^2 = 2,52$

The tabulated value at p = 0,05 significance level is 9,49 and at p = 0,10 significance level is 7,78

Conclusion:

Since $X^2 < X_4^{2(0,10)} < X_4^{2(0,05)}$ we cannot reject the null hypothesis for both cases. The neurological grade is independent of the barbiturates administered to the monkeys can be concluded.

(C) NEUROLOGICAL AND PATHOLOGICAL CORRELATIONS

In considering the relationships between the Pathological and Neurological grades from both the experimental and control groups combined, a Chi-square test was calculated. In both the pathological and neurological variables, grades had to be combined to get cells with enough observations, as the test is sensitive to the distribution of the frequencies.

The hypothesis:

H_0: The pathological and neurological grades are independent of one another was tested against

H_1: The pathological and neurological grades are dependent on one another.

$$X^2 = 30,03$$

$$X_1^{2(0,05)} = 3,84 \quad \text{and} \quad X_1^{2(0,01)} = 6,63$$

Since the calculated X^2 value is larger than the tabulated value, the null hypothesis cannot be accepted and a very strong dependence is shown. A numerical value to this dependence can be assigned by calculating the Spearman Rank Correlation Coefficient. A correction factor to adjust for the large number of ties in the data had to be used in the calculation. The effect of the ties is to inflate the value of the correlation between Pathological and Neurological grades.

The results are:

For both groups combined, with the neurological grades measured on Day 2:

$$r_s = 0,95$$

For the experimental groups, with the neurological grades at Day 2:

$$r_s = 0,96$$

Neurological grade at sacrifice

$$r_s = 0,91$$

For the control group:

Neurological grades at Day 2: $r_s = 0,96$

Neurological grades at sacrifice: $r_s = 0,76$

There is a very strong positive dependence between the Neurological and Pathological grades for all groupings, except the control group with the neurological grade measured at the sacrifice.

The significance of the Spearman's Rank Correlation was calculated

For pathological and neurological observations for experimental and control groups combined, the t-value of significance for the Spearman's Rank Correlation Coefficient is:

$$t = 15,90$$

Tabulated value at 5% significance level is:

$$t_{28}^{0,05} = 1,701, \quad t_{28}^{0,001} = 3,64$$

Since $t < t_{28}^{0,05}$ the correlation coefficient is significant.

The correlation coefficient is significant for $p << 0,0001$

For experimental group:

Neurological grades at Day 2:

$t = 12,24 \quad t_{13}^{0,05} = 2,160 \quad t_{13}^{0,001} = 4,221$

Neurological grades at sacrifice:

$t = 3,52 \quad t_{9}^{0,05} = 2,262$

$t_{9}^{0,001} = 4,781$

Both correlation coefficients are significant for p 0,001

For control group:

Neurological grades at Day 2:

$t = 12,24 \quad t_{9}^{0,05} = 2,160 \quad t_{13}^{0,001} = 4,221$

$t_{9}^{0,001} = 4,781$

Both correlation coefficients are significant for p 0,05. The correlation coefficient for the neurological grades at Day 2 is highly significant for $p << 0,001$. However, the significance for the correlation coefficient for the neurological grades at sacrifice lies between $0,05 < p < 0,001$.

(D) WEIGHT DISTRIBUTION

There is independence between the weight of the control and barbiturate group of monkeys.

Chi-square value 0,16 at p = 0,05; $X^2 = 3,84$

(E) WEIGHT VS NEUROLOGICAL OUTCOME

Calculated X^2 value

$$X^2 = 0,28 + 0,51 + 0,38 + 0,22$$
$$= 1,99$$

Tabulated X^2 value (1° of freedom) at 5% significance level

$$= 3,84$$

$X^2 < X^2$, $\therefore$ cannot reject the null hypothesis.

(F) WEIGHT VS PATHOLOGICAL OUTCOME

Calculated X^2 value

$$X^2 = 0,03 + 0,01 + 0,01 + 0,01$$
$$= 0,66$$

$$X^{2(0,05)} = 3,84$$

$X^2 << X^{2(0,05)}$ $\therefore$ cannot reject null hypothesis of independence between pathological grades and weight.

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