Gordon McDowall
MB ChB FFARCS MD

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A scientist starts with disorder and through his work attempts to comprehend the problem and produce solutions to the chaos.

To review the work of one man in academic medicine is difficult; it is akin to unravelling cottons in a needlework basket. Some cotton ends obviously belong together but others are deceptive in their origins. Academic medicine is usually the domain of teamwork and, unless one is in the team, it is difficult to identify the originator(s) of ideas. It also has to be accepted that a person who successfully organises a complex project is as worthy as his innovative co-worker.

This review of the published work of Gordon McDowall will by necessity not differentiate between the work that was, by and large, his and that in which he played a minor role. All the other workers are named in the references, some just once, some many times and without them the important work that was carried out-could not have been completed.

Gordon McDowall and his colleagues, after a shaky start, made a determined effort to investigate pathophysiological mechanisms in neurosurgical patients and hence rationalised their anaesthetic management. Teamwork is essential for his type of protracted study and the following names should be recognised as eminent team members: AM Harper, I Jacobson, I McA Ledingham, J Barker, and WB Jennett 1963 - 1969. VW Pickerodt, NJ Coroneos, NP Keaney, W

[i] Photograph courtesy of Professor PM Hopkins, Academic Unit of Anaesthesia, Leeds General Infirmary

Fitch, JM Turner, JR Lane and MM Ali 1968 - 1978. E Moss, Y Okuda, NM Dearden, D Powell, and T Ishikawa, 1973 – 1986. RM Gibson worked with McDowall for a period of 15 years, publications dating from 1971 – 1986.
Dates given in this text, as in all other sections, refer to dates of publication. McDowall's papers that are discussed are references 1- 63, references 64-107 are papers not discussed in the text.

To create order out of the many papers published the work has been divided into the following categories:

I The effect of drugs on cerebral blood flow and intracranial pressure

Ia The effect of drugs or procedures on cerebral blood flow.
This is rather non specific in that changes in cerebral blood flow may be brought about in several ways but it enabled the early quantification of effect.

lb The effect of drugs or procedures on intracranial pressure.
Similarly this is also a simple approach to the work but the combination of **Ia** and **lb** culminated in McDowall's MD Thesis in 1967.

Ic Postdoctoral work on the effect of anaesthetic agents on cerebral blood flow and intracranial pressure.

II The effect of drugs or procedures on cerebral metabolism

III The effect of induced hypotension on cerebral blood flow

IV Head injury, its pathophysiology and management.

V Measurement of intracranial pressure

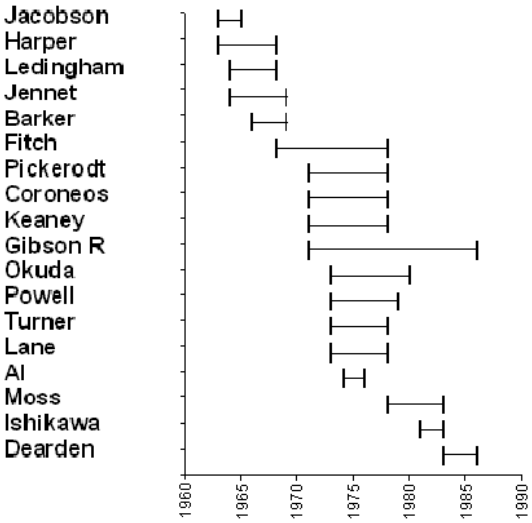
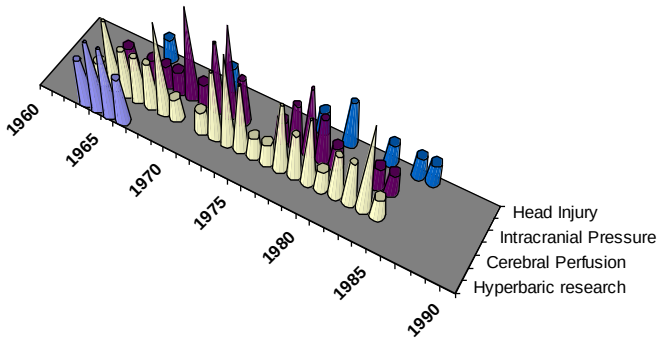


Fig. 1. Timelines for McDowall's co-workers who had more than three publications with him.



Incidence of publications from 1960 -1990

Ia The effect of drugs or procedures on cerebral blood flow

McDowall was an anaesthetist working in the University Department of Surgery at the Western Infirmary Glasgow where he was the ICI research Fellow. The earliest research paper that includes Gordon McDowall as an author was in 1963 in the British Journal of Anaesthesia [1]. Halothane 0.5% was shown to reduce cerebral blood flow by 46% and oxygen uptake by 49%. Halothane was labelled as a cerebral vasoconstrictor, to quote "In view of this evidence…we feel that it is possible that al1 potent general anaesthetic agents, intravenous and inhalational will prove to be constrictors of the cerebral vasculature…" This paper stands out as being one that caused some concern as it became established that halothane was a potent cerebral vasodilator. Reasons advanced for the results were the use of nitrous oxide in the control studies but not when halothane was used, the possibility of regional differences in blood flow at low concentrations of halothane and the low concentrations of halothane used, 0.5% or less. However, no significant change in cerebral blood flow was noted when halothane concentration was increased by 0.5% increments up to 3%.

In this same year, 1963, McDowall had three further papers published in prestigious journals - the Lancet [2, 3] and Nature [4]. The first Lancet paper described an internal carotid endarterectomy under two atmospheres of pressure. The increased partial pressure of oxygen was insufficient to enable the procedure to proceed without using an intraluminal bypass. His third publication followed immediately being the next paper in the same Lancet, an auspicious start. This paper demonstrated that cerebral blood flow decreased significantly at one and two atmospheres of oxygen and thus nullified the improvement in blood oxygen carriage at these pressures. This study confirmed previous work by Harper, Kety,

Schmidt, and Lambertson.[ii] The decreased blood flow did not return to normal on return to air at one atmosphere.

The principal co-author in this work, and in future work, was AM Harper, Wellcome Senior Research Fellow in Clinical Science. He had multiple publications on measurement of cerebral blood flow. Krypton 85 was injected into a carotid artery and the flow in the cerebral cortex deduced from its clearance — this was the method of Lassen and Ingvar, 1961. [iii]

The article in Nature demonstrated the lack of influence of large changes in venous pressure on cerebral blood flow.

A paper in 1964 [5] presented the results of a further study into cerebral blood f1ow and oxygen uptake at one and two atmospheres pressure. The results seem to repeat the results presented earlier [2]. However, one area in the discussion that merits noting is that it was suggested that hypoxic brain may not respond to oxygen at high pressure by vasoconstriction. This wi11 be studied further in section II.

Another study published in 1964 [6] compared the effects of halothane and trichloroethylene on cerebral blood flow and confirmed the absence of effect of the latter, oxygen uptake fell by 20%. The results were presented at the International Symposium on Regional Cerebral Blood Flow in March 1965.

The fluctuations of cerebral blood flow with and without nitrous oxide were also demonstrated and it was postulated that there were two opposing forces

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[ii] Harper AM, Glass HI, Glover MM. Measurement of blood flow in the cerebral cortex of dogs by the clearance of krypton - 85. Scott Med J 23(1):98 1961;6:12.
Kety SB, Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. Journal of Clinical Investigation 1948;27:484-492.
Lambertsen CJ, Kough RH, Cooper DV, Emmel GL, Loeschicke HH, Schmidt CF. Oxygen toxicity. Effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. J Appl Physiol 39(5):714-7 1953;5:471-486.

[iii] Lassen NA, Ingvar DH. The blood flow of the cerebral cortex determined by radioactive krypton. Experientia (Basel) 1961;17:42 - 43.

determining cerebral blood flow, the vasoconstrictor effect of cerebral metabolic depression and a direct vasodilator effect [7].

With the knowledge that chloroform was a potent cerebral vessel dilator and increased cerebral blood flow the first study in which McDowall had participated was repeated [8]; two patients scheduled to undergo carotid endarterectomy were anaesthetised using 0.5%-1.0% chloroform in 100% oxygen in a hyperbaric chamber. Only one patient had an endarterectomy, the jugular venous pO_2 was 72 mm Hg at 1 atmosphere pressure, 125 mm Hg at 2 atmospheres and following the endarterectomy it rose to 240 mm Hg. These were higher values than had previously been recorded and it avoided the use of an intraluminal shunt. One patient became mildly jaundiced after the chloroform anaesthetic.

At the Second European Congress of Anaesthesiology in Copenhagen (1966) data was presented on cerebral blood flow and halothane that was more in line with other workers [9] Wollman et al. and McHenry et al.[iv] With 0.5% halothane the cerebral blood flow in dogs rose by 16% over the first twenty minutes and then fell towards control values, with 2% halothane the increase in flow was 24% and it was sustained. Four percent halothane caused a lowering of blood pressure and cerebral blood flow fell. There was a progressive decrease in oxygen uptake with increasing halothane concentration which was thought to be due to depression of oxidative mechanisms.

Returning to the effects of oxygen on the cerebral vasculature a presentation in International Anesthesiology Clinics [10] demonstrated the effects of oxygen on cerebral vessel tone from hypoxic to hyperoxic levels. Cerebral blood flow was shown to increase at about 50 mm Hg PaO_2 (30-40 mm Hg PvO_2) and had doubled at 40 mm Hg PaO_2. At hyperoxic levels cerebral blood flow had been shown

[iv] Wollman H, Alexander SC, Cohen PJ, Chase PE, Melman E, Behar G. Cerebral circulation of man during halothane anesthesia: effects of hypocarbia and of d-tubocurarine. Anesthesiology 59(6):526-31 1964;25:180 - 184.
McHenry LC, Slocum C, Bivens HE, Mayes HA, Hayes GJ. Hyperventilation in awake and anesthetized man. Effects
on cerebral blood flow and metabolism. Archives of Neurology 1965: 270-277.

to steadily decrease, being 75% of control at three atmospheres.[v] This contradicts work presented by McDowall to the 3rd International Congress on Hyperbaric Oxygenation [11] where it was shown that cerebral blood flow did not change at three atmospheres of pressure if the carbon dioxide level was maintained (hyperbaric oxygen leads to hyperventilation and a lowered $PaCO_2$ in the spontaneously breathing patient). This presentation showed the great reserve of cerebrovascular dilatation enabling 60% of the circulatory oxygen to be available at 30% saturation.

It was also noted that during hypovolaemia (50mmHg systolic blood pressure) where the cerebral blood flow was down by 40%, hyperoxia did not reduce flow further and oxygen uptake, which was depressed, returned to normal. This work was also thought to demonstrate that metabolic rate was not determined by $PaCO_2$.

Continuing the work with halothane in 1967[12], it was demonstrated that cerebral blood flow still increased with increasing concentration even if the blood pressure was low, but above 90 mm Hg systolic. During hypotension it was not possible to demonstrate vasodilatation as the hypotension itself caused vasodilatation. Cerebral blood flow was therefore increased at a time when oxygen need was decreased, and therefore halothane was said to increase cerebral tissue $P0_2$ and decrease tissue PCO_2.

lb The effects of drugs or procedures on intracranial pressures

In 1965 McDowall presented a paper at the Annual Meeting of the Association of Anaesthetists of Great Britain and Ireland in Edinburgh, “Cerebrospinal fluid pressure measurements during anaesthesia”. This was

[v] Lambertsen CJ, Kough RH, Cooper DV, Emmel GL, Loeschicke HH, Schmidt CF. Oxygen toxicity. Effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. J Appl Physiol 39(5):714-7 1953;5:471-486.

subsequently published in Anaesthesia in 1966 [13].[vi]

The work presented by McDowall at the Anaesthetic Association meeting involved CSFp measurement during anaesthesia for surgery on patients with prolapsed discs, it was assumed that they had normal CSF pathways. Following induction of anaesthesia lumbar puncture was performed with the patient in the lateral position - in the first 12 patients the CSFp was measured using a fine bore saline filled manometer and in the remaining 12 patients the pressure was transduced and recorded. It is pertinent to be reminded that in the early 1960s electronic measurement was not as ubiquitous as it is today.

Control measurements were made with N_2O / O_2 / IPPV and then the volatile agent was added and the changes followed for ten minutes. Halothane 0.5% caused the CSFp to rise by a mean of 68.2 mm H_2O from a mean control value of

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[vi] Previous work by Stephen et al, Small et al. and Bozza et al. considered the changes in intracranial pressure following the use of volatile agents to be insignificant - possibly because the changes occurring were obscured by other factors in their investigative methodology. Marx et al., and Galindo and Baldwin , (1962 and 1963 respectively) had demonstrated increases in cerebrospinal fluid pressure (CSFp) with halothane. Marx et al. thought there was a relationship between a rise in venous pressure and CSFp and Galindo and Baldwin had difficulty differentiating between the effects of hypotension and the effects of halothane. However Hunter, in his book on Neurosurgical Anaesthesia, showed quite clearly his demonstration that in the clinical situation with controlled ventilation intracranial pressure could rise with halothane. According to his writing he was obviously confused by the conflicting research - a reference was made to McDowall's paper showing the increased cerebrovascular resistance with halothane.

Stephen CR, Woodhall B, Golden JB, Martin R, Nowill WK. The influence of anesthetic drugs and techniques on intracranial tension. Anesthesiology 59(6):526-31 1954;15:365-377.

Small HS, Weitzner SW, Nahas GG. Cerebrospinal fluid pressure during hypercapnia and hypoxia in dogs. Am J Physiol 234(1):H74-9 1960;198:704-708.

Bozza ML, Maspes PE, Rossanda M. The control of brain volume and tension during intracranial operations. Br J Anaesth 58(5):494-7 1961;33:132-146.

Marx GF, Andrews IC, Orkin LR. Cerebrospinal fluid pressure during halothane anesthesia. Canadian Anaesthetist Society Journal 1962;9:239-245.

Galindo A, Baldwin M. Intracranial pressure and internal carotid blood flow during halothane anesthesia in the dog. Anesthesiology 59(6):526-31 1963;24:318-326.

117.1 mm H_2O. The increase in pressure occurred in less than three minutes and peaked between 3 and 16 minutes. Venous pressure rose by a mean of 6 mm H_2O. The discussion indicates that the authors did not consider the rise in CSFp related consistently to the initial CSFp or $PaCO_2$. Ryder et al.,[vii] 1952, had shown that increases in CBF had less effect on CSFp when that pressure was initially 1ow which was the case after hyperventilation, and this therefore explained the reduced effect of halothane on CSFp following hyperventilation.

In the same paper the results from some animal work was included in which recordings of cerebrovenous pressures were made - they demonstrated that the venous pressure was always less than the CSFp; they considered this at strong evidence against the hypothesis that it was the increase in cerebrovenous pressure that raised the CSFp. This work appears to be the definitive paper confirming once and for all that halothane (and trichloroethylene) did cause an increase in CSFp, and presumably intracranial pressure. It was considered that the increased cerebral blood flow was the most likely cause of the increased intracranial bulk.

A previously noted paper [9] referred to the small changes "of doubtful clinical importance" in CSFp in patients with normal CSF pathways, the $PaCO_2$ was kept constant and thus the rise in CSFp was thought to be due to cerebrovasodilatation.

It was reported in the Journal of Neurosurgery [14] that two patients with papilloedema were anaesthetised using thiopentone, suxamethonium, N_2O, oxygen and d-tubocurare; burr holes were made and a brain cannula inserted, intraventricular CSFp measurements were made using a transducer and halothane administered. The first patient (0.5% halothane) had a rise of ICP from 180/160 mm H_2O to a peak of 520/460 mm H_2O, the second (1%) had a rise of *ICP* from 155/130 to 800/620 mm H_2O. This second patient was also hyperventilated ($PaCO_2$

Hunter AR. Neurosurgical Anaesthesia: Blackwell, Oxford University Press, 1964.

[vii] Ryder HW, Espey F, Kimbell FD, et al. Influence of changes in cerebral blood flow on the cerebrospinal fluid pressure. Archives of Neurology and Psychiatry 1952;68:165-169.

19 mm Hg) and then halothane added - on this occasion the ICP rose to 350/300 mm H_2O. These two patients demonstrated the marked difference between those patients with normal physiology and those with intracranial pathology, it also demonstrated, in an anecdotal way, the value of hyperventilation.

In 1967 the University of Edinburgh accepted Gordon McDowall's MD Thesis, "The influence of volatile anaesthetic drugs on the blood flow and oxygen uptake of the cerebral cortex and on cerebrospinal fluid pressure".

Ic. Post doctoral work on the effect of anaesthetic agents on cerebral blood flow and intracranial pressure.

In 1969 [15] the ICP of thirty-four patients with intracranial space occupying lesions was studied. Halothane, trichloroethylene and methoxyflurane were used together with nitrous oxide, oxygen, opiate and relaxant. The patients were ventilated to normocapnia and were then given the volatile agent ten minutes after base line measurements had been made. Once again there was no clear correlation between the initial ICP and the pressure response to the volatile agent. Cerebral perfusion pressure fell in every patient; 1% halothane - 40 mm Hg, 0.9% trichloroethylene - 23 mm Hg. 1.5% methoxyflurane - 56 mm Hg. The mechanism mooted was that of cerebrovascular dilatation with an increase in sagittal sinus pressure, the rise in intracranial pressure being secondary to CBF and hence cerebral blood volume.

A further paper in 1969 [16] described the effect of methoxyflurane 1.5% on CSFp in patients with normal and abnormal CSF pathways. A rise in pressure occurred in both groups but in the latter the rise was of a much greater magnitude. However, methoxyflurane 0.5% in the presence of a normal CSF pathway was shown to lower the CSFp in half the patients studied. This was in keeping with work carried out on dogs in 1965, [7]. Autoregulation of CSFp was described;

CBF ↑ ICP ↑ CPP ↓ CBF ↓ ICP ↓ CPP ↑ CBF ↑ ICP ↑

The comment was made that a decreased $PaCO_2$ may protect against the adverse effects of volatile agents but not in every patient.

McDowall studied neuroleptanalgesic mixtures in 1969 also [17], noting that droperidol and phenoperidine had a biphasic effect on CSFp whereas droperidol end fentanyl caused a fall in CSFp in both normal and abnormal CSF pathways and the decrease was significant. It was suggested that fentanyl had a different effect on cerebral metabolism.

In 1971 work with dogs [18] indicated that halothane increased the supratentorial pressure more than the infratentorial pressure and thus increased the likelihood of brain impaction with pupillary changes.

In 1972 Althesin was studied [19] in relation to CBF and ICP in baboons. Artificial intracranial space occupying lesions were created by thin walled latex balloons. Althesin 50 $\mu l\ kg^{-1}$ was shown to decrease CBF and ICP very quickly (90s - 120s) by 20% and 25% respectively. Cerebrovascular resistance rose to a maximum (133%) after one minute. Work continued in 1973 [20] and 1978 [21]. In the first paper 50 $\mu l\ kg^{-1}$ of Althesin was shown to reduce CSFp by more than 60% with recovery in 10 minutes - mean arterial pressure only falling 10 – 20% and heart rate was unchanged; blood pressure could not account for the CBF changes because the patients were in the autoregulatory range. There was good correlation between the initial CSFp and the fall in CSFp. The second paper was a randomised comparison of Althesin and thiopentone with regard to ICP during induction of anaesthesia and tracheal intubation. Mean ICP decreased following induction and increased slightly after intubation. Five minutes after induction the patients who received Althesin had a statistically lower ICP than those that had received thiopentone. The mean change in ICP with intubation was an increase of 2.8 mm Hg from control, or 4.6 mm Hg from immediate pre-laryngoscopy values.

A paper was published in 1978 in an attempt to sort out contradictory reports

[17][viii] on the value of fentanyl in neurosurgical anaesthesia [22]. In ten patients with $PaCO_2$ of < 4 kPa, and in the absence of hypotension, it was concluded that fentanyl 0.2 mg was a good neurosurgical agent. Mean arterial pressure fell to less than 60 mm Hg in two patients, CPP was less than 60 mm Hg in four patients and less than 4O mm Hg in one patient. Intracranial pressures increased or decreased slightly.

In 1979 Etomidate 0.2 mg kg^{-1} [23] was shown to be satisfactory in neurosurgical patients with space occupying lesion. The decrease in ICP was maximal at two minutes. In 1983 enflurane 2% was shown, overall, to produce very little effect on ICP [24], however there was marked variability. Four out of ten patients had to have the agent discontinued because the CPP was less than 5O mm Hg. It was considered to have less of an effect on ICP and CBF than halothane but arterial pressure had to be closely monitored.

An editorial in the European Journal of Clinical Investigation in 1982 [25] McDowall defined more accurately the meaning of the word 'autoregulation' and argued against its use when discussing the action of drugs. For example - halothane caused a fall in blood pressure but CBF was maintained, this superficially could be seen as autoregulation but in fact drugs that directly dilate the cerebral vessels paralyse their responsiveness and the increase in blood flow was a passive response to changing cardiovascular parameters. Barbiturates and hypocapnia which cause vasoconstriction maintain autoregulation.

Direct vasodilators →	CBF ↑ → ICP ↑ → CPP ↓
Opiates / hypnotics →	Metabolism ↓ → CBF ↓→ ICP ↓ → CPP ↔

[viii] Lassen NA, Ingvar DH. The blood flow of the cerebral cortex determined by radioactive krypton. Experientia (Basel) 1961;17:42 - 43.
Wollman H, Alexander SC, Cohen PJ, Chase PE, Melman E, Behar G. Cerebral circulation of man during halothane anesthesia: effects of hypocarbia and of d-tubocurarine. Anesthesiology 59(6):526-31 1964;25:180 - 184.

II The effect of drugs or procedures on cerebral metabolism and hence on cerebral blood flow and intracranial pressure.

It is reasonable to speculate that the rate of metabolism of an organ will determine, through some unspecified mechanism, the blood flow through the organ above a certain basal level. Metabolism is associated with oxygen uptake, carbon dioxide production and cellular function. McDowall and his co-workers studied cerebral metabolism using oxygen uptake as their indicator of metabolic change. To recapitulate; hyperbaric oxygen at 1 and 2 atmospheres pressure resulted in a decrease in oxygen uptake of 16% and 38% respectively [2, 5]. However in 1965, in the Proceedings of the 2nd International Congress on Hyperbaric Oxygenation [26], it was reported that the oxygen uptake which was reduced by hypovolaemic hypotension, was returned to normal at two atmospheres pressure of oxygen. Halothane 0.5% was shown to reduce oxygen uptake by 49% [4]; trichloroethylene reduced it by 20% and halothane by 16% [6]; methoxyflurane by 13% and chloroform by an insignificant 10% [7].

In 1966 [9] the oxygen uptake with halothane 0.5% was reported to fall 14% and 33% with 2% halothane. This paper, with regard to cerebral blood flow, was the one more in keeping with the work of others.

A more detailed investigation into the cerebral metabolism/cerebral blood flow mechanism was reported in 1967 [27]. It was professed that cerebral vasomotor tone may be determined by brain extracellular (ecf) pH, this idea being supported by the so called 'luxury perfusion', the pH of ischaemic brain being low and the blood flow increased. Cerebral blood flow was measured in dogs and the ecf pH was measured using a flat surfaced glass electrode as described by Severinghaus[ix] . Control values were recorded at normocapnia, following hyperventilation (CBF ↓, pH↑) and following the infusion of lactic acid; the pH returned to normal but the cerebral blood flow stayed low. In a second experiment

[ix] Severinghaus JW. Regulation of pH on the cerebral cortex. J Physiol (Lond) 232(1):30P-31P 1965;181:35P.

after the recording of the control values at normocapnia carbon dioxide was administered (CBF ↑, pH ↓), this 'hypercapnia' was then reversed (CBF and pH returned to normal) and then lactic acid was infused (pH ↓, CBF stayed the same). From these two experiments it was concluded that acute changes in ecf pH do not influence cerebral blood flow and that the potent effect of CO_2 was not due to a pH change. It was suggested that the intracellular pH of the arteriolar wall determined cerebral blood flow.

Similar work was reported at the III International Symposium on Cerebral Blood Flow and Cerebro-Spinal Fluid (Lund - Copenhagen) in May 1968 [28, 29]. This work was performed on baboons and confirmed the failure of pH to control cerebral blood flow providing the carbon dioxide level was maintained constant. At the same meeting a paper was presented on luxury perfusion [30]. Luxury perfusion was a term coined by Lassen in 1966,[x] it had other names including 'relative cerebral venous hyperoxia'. Aortic cross-clamping was used to create cerebral ischaemia and cerebral blood flow and CSFp were measured. After hyperventilation it was found that there was dissociation between cerebral blood flow and CSF pH. It would appear from much of this work that it was difficult to disentangle the time courses of pH changes in the various body compartments and the changes in cerebral blood flow.

Some time elapsed before there was another onslaught on the effects of cerebral metabolism on cerebral blood flow and intracranial pressure. The six papers to be discussed spanned the years 1972 - 1979 and revolved around the marked effect of Althesin on cerebral function.

The onset of metabolic depression was detected by monitoring the electroencephalogram (EEG), sometimes the result was electrical silence. In the first of these studies [31] Althesin 50 μl kg^{-1} was given to baboons, the cerebral changes occurred rapidly being maximal at 90s. Cerebral blood flow fell 40%, oxygen uptake approximately 46% and CSFp approximately 29%. Carbon dioxide and arterial

pressure were maintained within normal limits for autoregulation. In some of the animals electrical silence occurred, the onset being almost instantaneous and the cerebral blood flow reduction occurred so quickly that the "metabolism - flow" control mechanism was deemed to have a very short time constant.

Two presentations in 1973 [32, 33], one to the Physiological Society and one to the Anaesthetic Research Society, pushed this work along further but both contained the same information. Althesin was 'laced' with Technetium 99 and its arrival in the brain could be detected. Drug bolus arrival, changes in EEG, CBF and CVR were all recorded and thus the sequence of events determined. It was calculated that the maximum fall in carbon dioxide tension in the time between arrival of the Althesin and the change in vascular tone (11.8s - 7.6s) was less than 0.5 mm Hg. Carbon dioxide was therefore considered unlikely to be the metabolism - flow link.

At an Anaesthetic Research Society meeting in 1975 [34] the following argument was put forward -if changes in cerebral blood flow lagged behind a reduction in metabolism then the oxygen content of venous blood should rise, or, if metabolism and flow decreased together cerebral venous oxygen content should remain the same. It was discovered that cerebral venous oxygen content fell. Did this support the hypothesis that Smith et al.[xi] put forward that anaesthetic drugs reset the steady state level of the CBF / metabolism link?

Pursuing the link between metabolism and flow in 1978 [35] further studies into the circulatory response to cerebral metabolic depression were carried out; in these studies cervical sympathectomy and alpha adrenergic block were used to exclude the involvement of the sympathetic nervous system. The direct injection of Althesin into the carotid arteries demonstrated that the reduction in metabolism was a secondary effect, presumably from the brain stem.

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[x] Lassen NA. The luxury perfusion syndrome and the possible relation to acute metabolic acidosis localised within the brain. Lancet 1:369 1966:1113-1115.
[xi] Smith AL. Dependence of cerebral venous oxygen tension on anaesthetic depth. Anesthesiology 59(6):526-31 1973;39:291-298.

The final paper in this series [36] demonstrated that brain extracellular fluid hydrogen ion changes occurred at least 6s after changes in cerebrovascular resistance and this was at least l0s after depression of the EEG. This confirmed the previous work described above. It would appear that cerebrovascular changes were not initiated by extracellular pH but it was thought that it may be maintained by it. It was suggested that some fast responding mechanism existed, either neurogenic or perhaps a change in [K^+]. Astrup had proposed that the increase in extracellular K^+ during seizures may be the link with the associated increase in cerebral blood flow.[xii]

III The effect of induced hypotension on cerebral blood flow, cerebral metabolism and intracranial pressure.

This work spanned the years 1972 -1983 and involved the study of the effects of hypotension caused by (a) deep halothane anaesthesia (b) sodium nitroprusside (NTP), (c) trimetaphan (TMP) and (d) hypovolaemia

a) Halothane:

The effects of hypotension due to halothane will be presented first [37-40]. Reducing the mean arterial blood pressure in baboons to 33 mm Hg for two hours resulted in reactive hyperaemia even though evidence was presented to show that hypoxia did not occur. The cerebral metabolic rate ($CMRO_2$) fell by 30%. It was obvious that autoregulation had been lost [37]. It was suggested that loss of autoregulation may have been due to very subtle ischaemic changes. Electrical silence and burst suppression had been noted in all animals that lost autoregulation; these changes were not seen if the blood pressure was above 40 mm Hg or the CBF greater than 35 ml/min. Because of the loss of autoregulation it

[xii] Astrup J, Heuser, Lassen NA, Nilsson K, B.K. S. Evidence against H+ and K+ as main factors for the control of cerebral blood flow; a micro-electrode study. Cerebral Vascular Smooth Muscle and its Control. Ciba Foundation Symposium. Amsterdam: Elsevier, 1978:313.

was suggested that postoperative hypertension should be avoided after deep halothane anaesthesia.

At an ARS meeting in 1974 [39] it was shown that with a normal mean arterial pressure and cerebral perfusion pressure there was a linear response between CBF and $PaCO_2$ (25 - 70 mm Hg). It was a 4% change per mm Hg CO_2. During hypotension with a cerebral perfusion pressure of 32 mm Hg there was no such relationship. This work was set out in more detail in 1976 [40] where autoregulation was tested with noradrenaline and an 'autoregulation index' described. It appeared that responsiveness to carbon dioxide disappeared below a (?) mean arterial pressure of 60 mm Hg and autoregulation below 40 mm Hg. It followed from this that cerebral blood flow would not be impaired further by hyperventilation if the blood pressure was low. It was suggested here that if halothane induced hypotension had been used then postoperative IPPV should be used to prevent a rising blood pressure due to a rising $PaCO_2$ in the presence of lack of autoregulation, a reiteration of the advice in 1974.

(b) Sodium nitroprusside:

The use of NTP for the production of hypotension was reported in 1973 [41] at an ARS meeting. A hypotension of <40 mm Hg MAP of two hours duration resulted in a small fall in CBF; $CMRO_2$ was unchanged and autoregulation was abolished - this recovered gradually over several hours. Four of the animals died as a result of the irreversible cardiovascular collapse - this was reported and investigated [42, 43] and would now be accepted as due to NTP toxicity. The maintenance of cerebral blood flow with hypotension was a major difference when compared to the effects of halothane.

(c) Trimetaphan:

TMP was also being used for inducing hypotension and in 1977 and a comparison was carried out between it and NTP [44]. There was found to be no

change in intracranial pressure with TMP but a statistically significant rise with NTP on induction of hypotension. When the blood pressure had fallen below 70% of control the intracranial pressure returned to control levels and then fell as blood pressure fell. The use of hypocapnia minimised the rise in intracranial pressure with NTP. It was suggested that the change in intracranial pressure was due to cerebral vasodilatation and that it should only be used if a significant degree of hypotension was to be produced and then only after the dura was opened.

(d) Hypovolaemia:

In the same year recordings of oxygen tension on the brain surface were made during hypotension [45]. Haemorrhagic hypotension resulted in an incidence of $P0_2$ of <10 mm Hg of 23%, 7.2% and 12.4% with TMP and 0.9% with NTP. NTP was showing itself to be a mixed blessing - early rises in intracranial pressure but maintained cerebral oxygenation during profound hypotension.

Studies in 1979, 1981 and 1983 [46-48] elaborated on this work. In brief, changes in cerebral blood flow, hypoxia, and EEG changes were worse with TMP than with NTP. In the 1983 study in K^+ flux was measured. An increase in extracellular [K^+] was considered to be the result of cell membrane damage due to anaerobic metabolism with lactate production - K^+ flows out and Ca^{++} flows in. The normal [K^+] is about 3 mM l^{-1}. With membrane damage there appeared to be three phases of [K^+] rise - a slow progressive rise to 13-15 mM l^{-1}, a rapid rise from 16-40 mM l^{-1} and then a slow rise to peak at 60-75 mM 1^{-1}. Calcium ion influx occurred at about the time when [K^+] was 15 mM l^{-1}. NTP, once again, was shown to preserve membrane integrity longer at lower levels of cerebral perfusion.

The last study in this section created more confusion than confirmation of previous work [49]. The effect of the hypotensive agents on the blood brain barrier was tested using Evans blue. Hypotension was induced and then the Evans blue was injected. With an intact blood brain barrier the dye should not penetrate the cerebral tissue. It was discovered that there was far greater penetration with NTP than with TMP. Could this be due to ischaemic damage? The dye appeared in the

boundary areas of blood supply even though previous work had shown that cerebral blood flow was better with NTP. Had vasodilatation with NTP opened up capillary tight junctions and, together with the raised blood pressure at the termination of the infusion (and lack of autoregulation), caused the dye to pass the breached barrier? Another suggestion was that the cerebral perfusion pressure probably increased most at the boundary areas on cessation of the hypotensive infusion and another was that NTP accelerated pinocytotic activity. Certainly the pool had been muddied.

IV Head injury — pathophysiology and management

McDowall's work in this field can be subdivided into three sections, the effect of raised intracranial pressure on the systemic vascular system, factors that effect intracranial pressure and the intensive care of head injuries.

Work on the systemic vascular responses to raised intracranial pressure was first presented at an ARS meeting in 1970 [50]. With inflation of an intracranial balloon in dogs blood pressure rose and heart rate fell. Cardiac output was unchanged but the arrhythmia index rose and remained high. A set of papers published by the Journal of Neurology Neurosurgery and Psychiatry [51-53] looked at the cardiovascular responses in detail. The animal model used, dogs and baboons, was similar to that described above and the work was divided into three phases.

Phase 1 was a study of the early changes due to the increasing size of an intracranial space occupying lesion -as intracranial pressure increased mean arterial pressure fell, heart rate fell and cerebral perfusion pressure fell. The transtentorial pressure gradient increased and so did the arrhythmia index. The arrhythmia index seemed to be the most reliable predictive factor for the onset of the systemic vascular response.

Phase 2 was the study of the changes that occurred following continued inflation of

the intracranial balloon to the point where there was total decompensation and death of the animal. Intracranial pressure increased more quickly and both mean arterial pressure and heart rate increased dramatically. The increase in blood pressure did not improve cerebral blood flow or cerebral perfusion pressure. The transtentorial gradient increased further but the arrhythmia index fell. The systemic hypertensive response was shown to be the result of an increase in systemic vascular resistance (± 42%), heart rate changes lagged behind blood pressure changes. The factors causing the onset of the systemic hypertensive response were debated, at the transition point between phases I and 2 the supratentorial perfusion pressure was about 28 mm Hg and thus poor perfusion was considered a possibility, distortion (axial rotation) of the brain stem was also considered. The systemic hypertensive response started as the mean supratentorial pressure approached the diastolic arterial pressure thus allowing only intermittent blood flow. The terminal event was associated with vasodilatation, tachycardia, falling blood pressure and supratentorial perfusion (loss of autoregulation) and an increasing cardiac output.

Phase 3 was a detailed 1ook at the effect of incremental inflation of the intracranial balloon.

It was shown that a transient vasopressor response could be evoked even at low intracranial pressures. Once again the view that acute brain stem distortion caused the increase in systemic vascular resistance was propounded; local brain compression was also mooted as a cause.

Three publications warned of the dangers of using volatile agents [54], Entonox (N_2O / O_2 50%) [55] and opiates [56] in the head injured patient. The first and last were letters but the Entonox study was carried out with intracranial pressure monitoring and included the effects of physiotherapy. Gibson et al. [57] in '75 had shown the adverse effects of physiotherapy on intracranial pressure and McDowall's study was terminated prematurely because of the gross changes recorded.

The final three papers in this section deal in some detail with the intensive management of head injuries. In 1983 the outcome of management of 76 patients was reported [58]. Two thirds of the patients had a Glasgow Coma Score (GCS) of less than or equal to five. The management regimen was controlled hyperventilation, steroids, dehydrating agents, hypnotics and intracranial pressure measurement. The aim was to keep the intracranial pressure less than 25 -30 mmHg and to avoid rises in intracranial pressure during noxious stimulation. At six months 46% had died, 4% were vegetative survivors and 43% were recovered or moderately disabled. The bad omens were a low GCS, pupil abnormalities, respiratory dysrhythmia and an intracranial pressure greater than 30 mmHg. The presence of 'A' waves was associated with 61% mortality and if artificial ventilation was required for longer than seven days then 60% were in the group of severely disabled survivors. It was noted that there was some rise in intracranial pressure on recovery and this was thought to be due to abnormal vasomotor activity.

The 1985 study [59] compared the effects of Althesin and etomidate infusions on intracranial pressure in the head injured patient. This was a double blind randomised study. Intracranial pressure fell faster with Althesin than with etomidate; both caused arterial pressure to fall (about l0%) but cerebral perfusion pressure was well maintained. Althesin caused some liver enzyme derangement and etomidate caused adrenocortical suppression.

The final paper [60] was published posthumously and was a double blind, placebo controlled study (54 patients) of the use of steroids in the management of head injuries. The outcome at six months was reported. Both groups were shown to have the same severity of injury on admission and there was no difference between the two groups at the time of final assessment. There was an increased mortality in the patient group receiving steroid and it was suggested that they did not have a role in the management of head injuries.

V Measurement of intracranial pressure

A paper presented to the ARS in 1971 described a device for measuring extradural pressure [61]. It comprised a metal disk with perforations that led to a catheter. Pressures measured with this device correlated very well with CSFp. In 1973 the complete work using the extradural 'capsule' was published [62], for comparison a balloon measuring system was also used and related to intraventricular CSFp. The metal capsule was 9mm diameter and 2mm thick. The balloon measurements were unreliable but the metal capsule was very good; the correlation with intraventricular pressure improved with time as the bone flap sealed.

Modifications led to the development of the Leeds device, a pressure monitoring system that screwed into the skull. This had been used for ten years prior to the next publication in 1984 [63]. It was first used extradurally and then for the six years prior to publication the dura had been incised and thus subarachnoid pressure had been measured. Mendelow et al.[xiii] had reported that the device under-read pressures particularly if the intracranial pressure was high and thus an assessment was made of the device by the Leeds team and an infusion test devised to confirm the integrity of the system. Readings were found to be accurate 33 out of 69 measurements, of the remaining 36 measurements correction of the fault was possible and accurate measurements then made. If the intracranial pressure was less than 20 mmHg then the device was found to under read.

References [64-109] are for publications with McDowall as an author that are not discussed above; they are either papers on topics not in the mainstream of McDowall's research, reviews or teaching articles. A few of these papers have not been seen by the author.

[xiii] Mendelow AD, Rowan JO, Murray L, Kerr AE. A clinical comparison of subdural screw pressure measurements with ventricular pressure. J Neurosurg 64(1):81-8 1983;58:45-50.

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