Introduction

Surgical necessity has yielded anesthesia development and advances in anesthesia have provided the further development of surgery. This is also true for neurosurgery and neuroanesthesia. In this paper the history of neuroanesthesia will be reviewed in relation to the development of neurosurgery and the future of neuroanesthesia will be prospected.

Dawn of neurosurgery

Discovery of ancient trephined skulls found in Lozere in France aroused a great interest. These skulls were found to belong the neolithic period (= BC 8000). It is uncertain whether brain surgery had been performed at that time. The trepanation might have been made as a part of a religious or social ritual.

It is uncertain when the neurosurgery started but the earliest written record is Edwin Smith papyrus, which was written perhaps by Imhotep in Egypt (= BC 3000−2500) (Fig. 1). The papyrus contains 48 case reports with descriptions of injuries to the head, neck, vertebral column and other parts of the body.

Fig. 1 The Edwin Smith Papyrus.

Key words: Neuroanesthesia, brain circulation and metabolism, anesthesia for functional neurosurgery, brain protection, cross-tolerance
body. Discussion on surgical treatments of all parts of the body is seen. In this record, the term of “brain, as original term iesh” is seen.

Trephined skulls have also been found in Cuzco in Peru and these are found to belong to the period of the Inca (13th century). The skull bone defect appears very similar to that found in France in the neolithic period. The similarity of bone defects in these skulls can be recognized despite the big time difference. The trephined skulls were also discovered in Paracas, Peru (≈ BC 500), and the surgical holes are covered with roles of cotton dressing (Fig. 2A). It therefore appears that brain operation had been performed in South America at this period (≈ BC 500). The trepanation had been performed using obsidian blades (Fig. 2B).

**Anesthesia in ancient period**

In the prehistorical period, anesthesia was assumed done by chewing or locally applying the mixture of coca and yucca. Daturas had also been used, and the anesthetic action is thought being produced by the effects of its contents, scopolamine, hyoscymine and atropine.

In Greek and Roman period, anesthesia was performed with daturas, hyoscymine, and opium. Alcohol may have been used for its hypnotic action. Compression of the carotid artery (“the artery of sleep”) was used to suppress consciousness. However, none of these techniques was adequate to produce satisfactory anesthesia and thus the speed of neurosurgery was assumed quite important.

**Advances in anesthesia**

**Middle Ages and pre-modern period**

In the Middle Ages and pre-modern period, anesthesia had been performed by using opium, hyoscymine, and sometimes wine. Cannabis indicus and henbane were used from time to time. Sponge containing opium, murberry, water hemlock, and ivy were also applied to the patients nose during the surgery.

**Modern period**

In the modern period, marked development of neurosurgery was brought during the latter half of the 19th century, major contributions to which include the accumulation of the knowledge of functional neuroanatomy, establishment of the concept of asepsis, and discovery and development of general anesthesia. Diethyl ether (ether) and chloroform were successfully used and neurosurgeon could operate the patients more carefully and accurately because the speed of surgery became less important.

William MacEwen is the first neurosurgeon who had excised the brain tumor (meningioma) under endotracheal intubation. He suggested the necessity of tracheal intubation in neurosurgical anesthesia. Victor Hoseley had experiences himself to receive many anesthesia with different anesthetics. He investigated also the effects of ether, chloroform and morphine on the intracranial contents. He concluded that chloroform is the best choice of anesthetic agent. Its hypotensive effect is of benefit to decrease bleeding.

Concerning the use of ether or chloroform, there had been a great controversy across the Atlantic Ocean. British group preferred chloroform because it decreases blood pressure and secondarily decreases bleeding. Also the incidence of excitement, mucous secretion and headache are less with chloroform. In contrast, ether was preferred in the United States because it was believed to be safer than chloroform, respiration was maintained and elevation of blood pressure did not both-
er. Chloroform causes necrosis of the liver not infrequently but ether does not.

Harvey Cushing, the founder of modern neurosurgery, was the first to have made an anesthesia record (so called “ether record”). He recorded pulse rate, respiration, and temperature, and later he started to record blood pressure also. He used ether but his preference was regional anesthesia using cocaine because the anesthesia accident with ether was high at that time and probably because of his personal sad experience when he was a medical student and giving ether anesthesia to a patient. He stressed the importance of maintenance of blood pressure, pulse rate and artificial ventilation during neurosurgery. Doctor Davis GS, anesthesia specialist, has supported Dr. Cushing.

After the World War II, great advances in neuroanesthesia were brought by the development of new anesthetic agents and advanced knowledge of neurophysiology and pharmacology. Three major anesthesia groups had contributed to the development of specialization: Glasgow group, Pennsylvania group and Mayo Clinic group. The term “neuroanesthesia” has been coined by Doctor Michenfelder of Mayo Clinic.

Effects of anesthetics on brain function, cerebral circulation and metabolism

Commonly used intravenous anesthetics (barbiturates, propofol and benzodiazepines) produce anesthetic action by acting mainly on GABA$_A$ receptor. These drugs produce almost exclusively amnesia/unconsciousness with minimum analgesic effect. The immobilizing effect of these drugs against noxious stimuli is far less than that of inhalation agents at clinical doses.

In general, these intravenous anesthetics suppress neural function and decrease cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMRO$_2$) in parallel fashion. The effect of propofol on evoked sensory or motor responses is less compared to volatile inhalation anesthetics. Opioids evoke strong analgesic action by activating various types of opioid receptors either supraspinally or spinally. Opioids also have sedative and hypnotic actions, and produce a minimal or modest decrease in CBF and CMRO$_2$.

Among the intravenous anesthetics, ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, is unique because it produces a cataleptic state in addition to analgesia and unconsciousness, this state probably being produced by stimulation of the limbic system and cortical/thalamic suppressing effect. Ketamine is known to increase both CBF and CMRO$_2$.

At clinical anesthesia doses, volatile anesthetics decrease CMRO$_2$ and increase CBF, the increase in CBF with isoflurane and sevoflurane being mild compared to halothane. Enflurane (stereoisomer of isoflurane) is known epileptogenic. Epileptic activity is exaggerated by hypocapnia and CMRO$_2$ increases. We measured CMRO$_2$ in dogs at moderate and deep enflurane anesthesia. During moderate level of anesthesia, there were no significant changes in CMRO$_2$ when PaCO$_2$ levels were changed in a range of 20–80 mmHg. In contrast, at deep anesthesia, increase in CMRO$_2$ was induced with hypocapnia (PaCO$_2$ at 20 mmHg) in association with increased spike activities in EEG. These data suggest that hyperventilation during deep enflurane anesthesia may cause hypoxic brain damage.

We investigated the effects of stereoisomers, enflurane and isoflurane, on local cerebral glucose metabolism in rats (Fig. 3). Anesthetic level was set at comparable level between two drugs. The metabolic pattern was quite different. Glucose metabolism was markedly higher in the hippocampal CA3, ventro-basal (VB) complex of the thalamus and corpus callosum in the animals anesthetized with 4% enflurane. It seems that metabolic activation of intercortical and corticothalamic pathways occur during enflurane anesthesia. With excision of ipsilateral cerebral cortex, the increased glucose utilization in the thalamic VB complex was obliterated and that of corpus callosum was attenuated.

It is suggested that epileptogenic property of enflurane is related to activation of these pathways.

Nitrous oxide (N$_2$O) is a gaseous anesthetic that has been used more than 150 years. N$_2$O has minimal effects on GABA$_A$ receptor but exhibits marked blockade of NMDA receptors. This drug has long been thought to be
inert but it turned out physiologically not inert. Global CBF increased markedly with 60% N2O and CMRO2 was also increased modestly (Fig. 4A).

The changes in local cerebral glucose utilization in the various brain structures were measured in rats using 14C-deoxyglucose. Glucose utilization was variable depending on the structures. When nitrous oxide (67%) was added to pentobarbital background anesthesia at a dose (30mg/kg, iv.) that maintain EEG activity, glucose utilization increased in most brain structures.

Controversies in neuroanesthesia

For the last 20～30 years, there have been several controversies in neuroanesthesia, including neuroprotection by barbiturate, steroid therapy in neurotrauma, and adverse effect
of fluid infusion containing glucose, etc.\textsuperscript{16 - 19} Barbiturate has now been proven effective in focal cerebral ischemia but not in complete global cerebral ischemia. There has been no evidence that corticosteroid is effective in stroke or severe traumatic brain injury.

Perioperative glycemic control is one of the important topics in neuroanesthesia and neurocritical care. Hyperglycemia in ischemic condition has been proven detrimental and strict control of plasma glucose level has been shown to provide better outcome in the critically ill patients, including neurological disorders.\textsuperscript{20,21} Both ICU survival rate and hospital survival rate were significantly higher in the group of patients whose plasma glucose level was intensively controlled with insulin at 110 mg/dl. Figure 5 (A, B) shows the plasma glucose levels in the patients those who received either glucose-containing fluid or glucose-free fluid during neurosurgical anesthesia. The plasma glucose level was well maintained at normal range in the patients who received glucose free fluid, whereas, plasma glucose levels were high or fluctuated markedly in the patients who received glucose containing solution. Therefore, routine use of glucose-containing fluid should be avoided in neurosurgery.

Figure 5 (C, D) shows plasma glucose levels during anesthesia in the patients who underwent aneurysmal clipping, either electively (un-ruptured) or in emergence (ruptured). The patients were anesthetized with sevoflurane for elective case, and fentanyl/propofol for emergency case. The plasma glucose level was well maintained at normal range in the patient who received elective surgery, whereas, plasma glucose levels were high or fluctuated markedly in many patients who received emergency surgery even though the patients received glucose-free IV fluid and some received insulin.\textsuperscript{*} It is difficult to demonstrate definite evidence of better outcome with controlling plasma glucose level in this clinical setting. However, from the accumulated evidence of detrimental effects of hyperglycemia in the experimental setting, it would be recommended to maintain blood glucose levels below 150 mg/DL in neurosurgical patients.

Some investigators recommend intensive insulin therapy (IIT).\textsuperscript{21} Insulin may have neuroprotective effect via several suggested mechanisms. It may be the result of indirect effect, such as decreasing blood glucose level (preventing hyperglycemia), or of direct effect such as anti-inflammatory effect, vasodilatation, or AKT activation that can inhibit apoptotic neuronal death. Although the precise mechanism for neuroprotection remains to be determined, it seems advisable to control hyperglycemia with insulin in patients with neurological injury. However, the benefit of intensive insulin therapy, if any, may be negated by the incidental hypoglycemia.

\textsuperscript{*} Matsumoto M et al. (unpublished data)
mic episodes. Therefore, careful management should be exercised and the optimal levels of blood glucose should be clarified.

Concerning hypothermia, one of the remaining important issues may be defining the indication and application of mild hypothermia in neurosurgery and neurointensive care. In recent human trials, induced hypothermia (32-34 °C) in adults resuscitated from ventricular fibrillation cardiac arrest has been demonstrated to be beneficial. However, more recent multicenter trial of intraoperative hypothermia for aneurysm surgery trial (IHAST) failed to show any beneficial effect of mild hypothermia (33 °C) but showed that the hypothermic group had a higher incidence of perioperative bacteremia than those in normothermic group. It may be necessary to further define the indication of mild hypothermia in neurosurgery and neurointensive care.

**Anesthesia management for functional neurosurgery**

During the last half century, tremendous amount of knowledge of neurophysiology and neuropharmacology has been accumulated and modern diagnostic and monitoring tools have been developed. These all provided marked improvement of patient care in neurosurgery. The challenge in new era will be how we can further improve the quality of life of the patients.

In this context, one important area in neuroanesthesia is anesthetic management for functional neurosurgery, such as awake craniotomy and stereotaxic surgery such as electrode implantation for Parkinson’s disease or intractable thalamic pain or central pain syndrome, and intravascular intervention. Highly advanced airway management and careful titration for sedation and analgesia are essential to provide satisfactory condition to both patients and surgeons. Following is the summary of our experience in perioperative management for functional neurosurgery and intravascular interventional procedure.

**Deep brain stimulation (DBS)**

Deep brain stimulation (DBS) is an effective treatment for Parkinson’s disease. Microelectrodes are implanted into certain nuclei in the thalamus (Vim, Voa, Vop). During this procedure, the patient should be comfortably sedated and analgesia controlled, airway and spontaneous respiration secured. Further, it should still be possible to assess responses in tremor or spasticity/rigidity to stimulation. The course of the procedure is summarized in Fig. 6. On the day of operation, anti-Parkinson drugs are stopped. After patient’s entering into the operating room, 1) cranial frame is applied under sedation with propofol and fentanyl supplemented with local anesthetic infiltration, then 2) CT scan is obtained and the image fused with preoperative MRI. Thereafter, 3) burr holes are made and electrodes are implanted into thalamic nuclei. During electrode implantation, propofol concentration is decreased. To confirm appropriate electrode position, microelectrical activity is recorded and also assured by clinical sign such as inhibition of tremor, spasticity and rigidity or involuntary movement obtained by test stimulation. During this period, patient should be adequately sedated but still has secured airway and adequate spontaneous respiration. For generator implantation, general anesthesia with tracheal intubation is performed. At the end of the procedure, CT scan is re-checked to confirm electrode position and rule out intracranial complications.

Table 1 shows the patients’ profile in 29 patients (Yahr’s classification: III–V) under-
went implantation of electrode for deep brain stimulation.

The propofol concentration required for target sedation was 0.5 to 2.5 g/ml and total dose of fentanyl was 3 to 6 g/kg. The concentration required for target sedation varies depending on the patients' age. The appropriate concentration of propofol was 1 to 2 g/ml for the patients with age less than 65 years, and 0.5 to 1 g/ml in the patient with age above 70 years.

Alpha-2-adrenergic agonist dexmedetomidine may be the other choice of drug for sedation because it gives adequate sedation without respiratory depression. Dexmedetomidine has theoretical advantages over propofol such as lack of respiratory depression, hemodynamic stability, and possible ability to suppress dyskinesia induced by GABA-ergic drugs. However, optimal dose and the incidence of complications should be investigated further.

During operation, airway was compromised in 5 patients and nasal airway was required. Four patients developed intraoperative hypertension treated with calcium antagonist, nicardipine. Poor responder to nicardipine developed postoperative intracranial hemorrhage, which is the most serious complication, and seen in two patients, one had remained right side hemiparesis and the other developed no abnormal neurological symptoms. The incidence of intracranial hemorrhage during this procedure has been reported to be 1.2 to 5.5% in the literature, and that of our series was 6.9% (2/29). In general, the risk appears increased in the patients those have hypertension and multiple electrodes implanted. Therefore, careful control of hypertension and positioning of electrodes are necessary.

Nausea and vomiting are not infrequently seen, 4 patients in our series, and antiemetic drugs were needed. Air embolism, though rare, can occur during this procedure. One patient exhibited air embolism in our series during the procedure. Cough, tachypnea and decrease in SpO₂ in association with decreased end-tidal PCO₂ are important signs. Trendelenburg position was taken and respiratory and circulatory condition recovered in our patient. Operation on the other side was postponed for few weeks. Although its occurrence is rare, one may be aware of air embolism and careful monitoring is necessary during this procedure.

Awake craniotomy

Anesthetic management for awake craniotomy is also challenging. Task force of Japanese Society for Neuroanesthesia and Critical Care investigated the current status of anesthetic management for awake craniotomy in Japan to establish a standard procedure for safe anesthesia (Please refer to reference for detail).

Carotid artery stenting (CAS)

Carotid artery stenting (CAS) is nowadays a widely used procedure, which can be performed under either local or general anesthesia. Many patients have various preoperative complications such as hypertension, coronary artery disease, and diabetes mellitus. Meticulous care for controlling blood pressure, plasma glucose level, as well as brain monitoring is needed. Transcranial Doppler (TCD), near-infrared reflectance spectrophotometry (NIRs), and bispectral index (BIS) are useful monitors.

It has been known that hyperperfusion syndrome is responsible for neurological deterioration following carotid endarterectomy or stenting. Because autoregulation of cerebral blood flow is lost due to chronic internal carotid artery stenosis, increasing of blood

### Table 1 The patients’ profile of Parkinson disease

<table>
<thead>
<tr>
<th>Age</th>
<th>M / F</th>
<th>Year Classification</th>
<th>Pre-op. complications</th>
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</thead>
<tbody>
<tr>
<td>63 ± 9 yo (37~74 yo)</td>
<td>9 / 20</td>
<td>III ~ V</td>
<td>Hypertension 7</td>
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<td></td>
<td></td>
<td></td>
<td>Asthma 2</td>
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<td>Polymiositis 1</td>
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<td>Chronic thyroiditis 1</td>
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- Propofol TCI 0.5~2.5 μg / ml
- Fentanyl total dose 3 ~ 6 μg / kg
flow after CAS causes various symptoms, such as delirium, seizures and cerebral hemorrhage. In the patients having high blood flow ratio to contralateral side after the procedure may develop headache, delirium and excitation more often than the patients with no hyperperfusion. Ca²⁺ blocker nicardipine and propofol were more frequently needed to control blood pressure and provide adequate sedation. Phenytoin may be needed for preventing seizures. Blood flow ratio greater than 1.5 to contralateral side requires intensive therapy, including antihypertensive drugs, propofol, phenytoin, and edaravone until hyperperfusion resolves.

**Advances in basic research: Ischemic cross-tolerance induction**

Central nervous system acquires tolerance against ischemic insult by a prior exposure to a brief period of ischemia/hypoxia. The mechanism for this is still not fully understood. Various environmental changes other than ischemia/hypoxia as well as various substances have now been known to induce tolerance. These include drugs such as anesthetics, non-lethal hyperthermia, hypothermia, oxidative stress. The tolerance induced by these stimuli has been designated ‘cross-tolerance’.

Among the various preconditioning stimuli that might induce cross-tolerance, hyperbaric oxygen (HBO) is attractive because it has already been used safely for various disorders. Accumulated data show that exposure to HBO prior to ischemia induces tolerance against ischemic damage in the CNS. Production of heat shock protein (HSP) 72 and

![Fig. 7 Neuroprotective effect of preconditioning with HBO and protein synthesis](image)

Fig. 7 Neuroprotective effect of preconditioning with HBO and protein synthesis. 27) I: Percentage of normal neurons in the hippocampal CA1 referenced to those of the age matched normal rats (mean +/- SE). Neuronal damage was significantly less in HBO-6, HBO-12, and HBO-24h groups compared with untreated and HBO-72 h groups, respectively (*p< 0.01 vs. untreated group, **p< 0.01 vs. HBO-72h). II: The protein levels of p75NTR, C/EBP δ and CD74.

Top panels: the figure shows representative immunoblots obtained. (A) p75NTR, (B) C/EBPδ and (C) CD74. Lower panels: bar graphs determined from the immunoblots by densitometric analysis, and represent by the target density as referenced to density to beta actin. (D) p75NTR, (E) C/EBPδ and (F) CD74 (mean +/- SE).

The protein levels of p75NTR, C/EBPδ and CD74 were significantly increased, the time course expression being corresponded to HBO-induced neuroprotection.
antiapoptotic protein or activation of radical scavenging system has been postulated as the mechanism.

We have recently demonstrated in rats that preconditioning with HBO (100% O₂ 3.5-atmosphere absolute (ATA), 1h/day for 5 days) provided neuroprotection (hippocampal CA1 neurons) against transient (8 min) forebrain ischemia possibly through protein synthesis relevant to neurotrophin receptor (p75<sup>NTR</sup>), and inflammatory-immune system (C/EBP δ and CD74) (Fig.7). HBO significantly reduced loss of hippocampal CA1 neurons that normally follows transient ischemia when the last HBO session was 6 h, 12 h, or 24 h before ischemia, whereas if there was a 72-h delay before the ischemic insult, HBO was not protective. The protein levels of p75<sup>NTR</sup>, C/EBPδ and CD74 were significantly increased, the time course expression being corresponded to HBO-induced neuroprotection. In the dose comparison study (1, 2, and 3.5 ATA), most prominent protective effect on hippocampal CA1 neurons was observed with 3.5 ATA-HBO (survived neurons: 69% [62-73%] vs. untreated: 3.9% [2-8%], 1 ATA: 8.8% [0-26%], 2 ATA-HBO: 46% [22-62%]) (median [range]) (7 days after ischemia).

Most recent report by Ostrowski et al. suggested that HBO-induced neuroprotection is relevant to brain derived neurotrophic factor (BDNF) and its downstream event involving suppression of p38 mitogen activated kinase (p38) activation. To further determine the mechanism of induction of tolerance, we investigated pharmacological modification by 10 mg/kg anisomycin (protein synthesis inhibitor and a potent activator for p38) and 200 μg/kg SB203580 (p38 inhibitor), which were given (ip.) 60 and 30 min before every

### Fig. 8 Neuroprotective effect of preconditioning with HBO and modification by anisomycin and/or SB203580.

Box plots show percentage of normal neurons in hippocampal CA1 in each group as referenced to those of the age-matched normal rats (the median, minimum, and maximum values and 25th-75th percentiles for each group).

A: HBO pressure dependent neuroprotection.
In 2 and 3.5 ATA-HBO group, neuronal damage was significantly less compared with that in 1 ATA group. 3.5 ATA-HBO most prominently protected neurons (*p< 0.05 vs. oxygen-treated group, #p < 0.05 vs. untreated, respectively).

B: Modification of HBO neuroprotection by anisomycin and/or SB203580.
Anisomycin (AM, 10 mg/kg) given prior to every 3.5 ATA-HBO (AM+HBO) treatment abolished a neuroprotective effect of HBO. When SB203580 (200 μg/kg) was given between administration of anisomycin and HBO treatment (AM+SB+HBO), ratio of surviving neurons was resumed, though it was significantly less than 3.5 ATA-HBO group (*p< 0.05 vs. HBO-treated group, #p < 0.05 vs. untreated, respectively).
Anisomycin (p38 activator) abolished HBO-induced neuroprotective effect (survived neuron: 1.2% [0-7%]) without inhibiting p75NTR protein expression. SB203580, p38 inhibitor, when given between administration of anisomycin and HBO-treatment, resumed neuroprotective effect (survived neuron: 52% [37-62%]). The level of phosphorylated p38 (p-p38) at 10 min reperfusion was significantly decreased in 3.5 ATA-HBO group (32% [12-53%] of sham). Single pretreatment with 100 and 200 μg/kg of SB203580 exerted similar neuroprotective effect (39% [25-51%] and 59% [50-72%]) to 2 and 3.5 ATA-HBO preconditioning, respectively.

At present, the exact event executed via p38 signal pathway in an acquisition of ischemic tolerance remains controversial but we speculate that p75NTR protein expression as a result of BDNF-secretion and subsequent suppression of p38 activation (p-p38) may be the cascade exerting neuroprotection by HBO preconditioning. It is concluded that suppression of p38 phosphorylation plays a key role in HBO-induced neuroprotection and that pretreatment with p38 inhibitor (SB203580) can provide similar neuroprotection.

**Summary**

In summary, during the last half century, tremendous amount of knowledge of neurophysiology and neuropharmacology has been accumulated. In addition, modern diagnostic and monitoring tools including CT, MRI and multimodality of neuromonitoring have been developed. These all provided marked improvement of patient care in neurosurgery. The challenge in new era will be how we can further improve the quality of life of the patients. For this purpose, functional neurosurgery and less invasive interventional procedure would be deserved. Anesthetic management for these procedures would be of challenging. Further, it is hoped that the measures to induce ischemic cross-tolerance either by HBO or by certain physico-pharmacological measures can be applied in clinical practice in the future.

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**References**


