

TREATMENT
OF CEREBRAL
INFARCTION

EXPERIMENTAL
AND CLINICAL STUDY

JIRO SUZUKI



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PREFACE

It is a great honor and pleasure for me to have Springer-Verlag publish this volume entitled "Treatment of Cerebral Infarction". I am much indebted to my colleagues for my success in publishing this book.

I have engaged in clinical work in the field of neurosurgery for these few decades and I have performed more than 5,000 major operations of intracranial surgery. Throughout this time, it has been my privilege to conduct a 2-hour-morning research seminar in our department every Wednesday and to supervise a great deal of research. At these seminars my fellow research workers and I have exchanged many ideas about the study of neurosurgery and we have designed many animal experiments. The results of the research performed in the previous week have always been reported at such seminars and research workers have benefited from the advice and criticisms given there.

In 1969 I found that the permissible occlusion time for cerebral blood flow could be prolonged by mannitol. In that year Dr. Takashi Yoshimoto started a difficult series of animal experiments to prove my hypothesis. Since then, many researchers have joined our department and many research programs and experiments on

cerebral infarction have been carried out. Dr. Yoshimoto hoped that the results of research done in our department over the last sixteen years concerning cerebral infarction could be published. Moved by his enthusiasm, my colleagues took their share in writing each article. I suggested to them that this volume should cover primarily the results of our own research, but that at the same time it should also include the results of related work done by neurosurgical experts throughout the world. Therefore, I hope that this book will interest many investigators who have devoted themselves to research in the field of neuroscience.

My colleagues acknowledge that our research has been stimulated and promoted by our weekly "think tank" sessions and that any achievement we may have attained is due largely to those fruitful discussions. This is the reason why this book is of my authorship. I am very happy and honored that my own contribution to our study of neurosurgery is thus recognized, but I am very conscious that this book was completed thanks to the cooperation of the clinical neurosurgeons who have studied and engaged in clinical neurosurgery with me in Sendai. I must therefore mention those who took part in writing this book: Dr. Takashi Yoshimoto (Chap-

ter 1), Dr. Takao Watanabe and Dr. Michiyasu Suzuki (Chapter 2), Dr. Hirobumi Seki (Chapter 3), Dr. Takamasa Kayama (Chapter 4), Dr. Shigeki Imaizumi (Chapter 5), Dr. Kazuo Mizoi (Chapter 6), Dr. Akira Ogawa and Dr. Tetsuo Kogure (Chapter 7), Dr. Satoru Fujiwara (Chapter 8), Dr. Takehide Onuma and Dr. Yoshihide Nagamine (Chapter 9A), Dr. Motonobu Kameyama (Chapter 9B), Dr. Yoshiharu Sakurai (Chapter 9C), Dr. Hiroshi Niizuma (Chapter 10), Dr. Ryuichi Katakura and Dr. Ryuichi Konda (Chapter 11), Dr. Akira Taka-

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Jiro Suzuki

Nagamachi, Sendai
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CONTENTS

INTRODUCTION	1
Part I Experimental Study	
1. EXPERIMENTAL MODELS	9
1.1 Introduction.	9
1.2 Cerebral Infarction Models	10
1.2.1 Experimental Models Using the Monkey	10
1.2.2 Experimental Models Using the Dog	11
1.2.3 Experimental Models Using the Cat	11
1.2.4 Experimental Models Using the Rat	12
1.2.5 Experimental Models Using the Gerbil	13
1.3 The Cerebral Infarction Model Developed in Sendai	13
1.3.1 Production of Various Cerebral Infarction Models in the Dog by Means of Occlusion of Intracranial Trunk Arteries	13
1.3.1.1 Thalamic Infarction Model	13
1.3.1.2 Cerebral Mantle Infarction Model	15
1.3.1.3 Complete Cerebral Hemisphere Infarction Model	16
1.3.1.4 Incomplete Cerebral Hemisphere Infarction Model	16
1.3.1.5 Complete Ischemic Brain Regulated with the Perfusion Method	17
1.3.2 A 3-Vessel Occlusion Model for Bilateral Hemispheric Infarction Using the Rat	19
1.3.2.1 Production of the Ischemia-Model	19
1.3.2.2 EEG Studies	20
1.3.2.3 Studies of the Cerebral Blood Flow Using Autoradiography	20
2. HISTOLOGICAL STUDY	23
2.1 Introduction.	23
2.2 Sequential Changes in Cerebral Ischemia	25
2.2.1 Sequential Changes in Focal Ischemia	25

2.2.1.1	Acute Stage Changes in an Ischemic Focus . . .	25
2.2.1.2	Changes in the Ischemic Focus Following Acute Stage Recirculation	31
2.2.1.3	Changes in Ischemic Foci During the Subacute and Chronic Stages	40
2.2.2	Sequential Changes in Global Ischemia	45
2.2.2.1	Observations Using the Light Microscope . . .	46
2.2.2.2	Observations Using the Electron Microscope .	46
2.2.2.3	Observation Using the Freeze Fracture Method	50
3.	CEREBRAL BLOOD FLOW	54
3.1	Introduction.	54
3.2	Correlation Between Regional EEG and rCBF	56
3.3	Regional Cerebral Hemodynamics Following Recirculation . .	58
3.3.1	Hemodynamics at the Center of an Ischemic Focus . .	58
3.3.2	Hemodynamics of the Border and Periphery of an Ischemic Focus	66
3.4	Sequential Changes in Vascular Reactivities	72
3.4.1	Autoregulation	72
3.4.1.1	Sequential Change in Autoregulation Occurring at the Center of an Ischemic Focus	73
3.4.1.2	Sequential Changes in Autoregulation at the Border and in the Periphery of an Ischemic Focus	76
3.4.2	CO ₂ Response	78
3.5	Hemorrhagic Infarction	84
3.5.1	Conditions Conducive to Hemorrhagic Infarction . .	84
3.5.2	Hemodynamics Following Recirculation.	85
4.	ISCHEMIC BRAIN EDEMA	89
4.1	Introduction.	89
4.1.1	The Definition of Ischemic Brain Edema	89
4.1.2	Pathophysiology of Ischemic Brain Edema	89
4.1.2.1	Causal Factors	89
4.1.2.2	The Onset and Natural Course of Ischemic Brain Edema	94
4.1.2.3	Ischemic Brain Edema Following Recirculation	96
4.1.2.4	The Disappearance of Edema.	97
4.1.3	The Treatment of Ischemic Brain Edema	99
4.1.3.1	General Therapeutic Steps.	99
4.1.3.2	Drug Therapy	99
5.	CEREBRAL METABOLISM AND FREE RADICAL PATHOLOGY	102
5.1	Introduction.	102
5.2	Phospholipids as Biomembrane Constituents.	104
5.3	Ca ²⁺ Homeostasis.	107

5.4	Lipid Metabolism in Cerebral Ischemia	108
5.5	The Free Radical Reaction in Cerebral Ischemia	112
5.5.1	Fundamental Knowledge Concerning Free Radicals.	113
5.5.2	Lipid Peroxidation	114
5.5.3	Detection of Free Radicals	116
5.5.3.1	Chemiluminescence	116
5.5.3.2	Electron Spin Resonance (ESR)	119
5.5.4	Initiators of Autoxidative Lipid Peroxidation	123
5.5.4.1	Superoxide Anion (O_2^-)	123
5.5.4.2	Hydroxy Radical ($OH\cdot$)	124
5.5.4.3	Oxygen-Metal Complexes	124
5.5.4.4	Singlet Oxygen (1O_2)	125
5.5.5	Energy Metabolism and Free Radical Generation	126
5.5.6	The Problem of "Intra-Ischemic Peroxidation" and "Post-Ischemic Peroxidation"	134
5.6	Pharmacological Mechanisms of Mannitol, Vitamin E, Glucocorticoids and Phenytoin	138
5.6.1	Mannitol	138
5.6.2	Vitamin E (α -tocopherol)	141
5.6.3	Glucocorticoids	143
5.6.4	Combined Therapy with Mannitol, Vitamin E and Glucocorticoid	146
5.6.5	Phenytoin (Aleviatin)	153
6.	THE DEVELOPMENT OF NEW BRAIN PROTECTIVE AGENTS	158
6.1	Introduction.	158
6.2	Brain Protective Agents—Short Review	160
6.2.1	Barbiturates	160
6.2.2	Naloxone	164
6.2.3	Prostaglandins and Indomethacin	167
6.3	Development of a New Brain Protective Substance—Our Study	169
6.3.1	Mannitol	169
6.3.1.1	The Effect of Mannitol on Cerebral Ischemia— Histological Study	169
6.3.1.2	Recirculation in the Acute Period of Cerebral Infarction: Brain Swelling and Its Suppression Using Mannitol	170
6.3.1.3	The Effect of Mannitol on Cerebral Ischemia— CBF Study	175
6.3.2	Perfluorochemicals (PFC)	177
6.3.2.1	Introduction	177
6.3.2.2	PFC and Brain Tissue Partial Oxygen Pressure (PtO_2)	178

6.3.3	Combined Administration of Mannitol and PFC	182
6.3.3.1	Recovery of Brain Electrical Activity in the Severely Ischemic Brain	182
6.3.3.2	Suppression of Hemorrhagic Infarction	184
6.3.4	The Protective Effects of Various Free Radical Scavengers	185
6.3.5	Combined Administration of Mannitol, Vitamin E, Dexamethasone and PFC	189
6.3.5.1	Experimental Results: Untreated Control Group (22 Dogs)	190
6.3.5.2	Drug-Treated Animals (61 Dogs)	192
6.3.6	Phenytoin (Aleviatin)	195
6.3.7	Calcium Antagonist (Flunarizine)	199

Part II Clinical Study

7.	EPIDEMIOLOGY AND SYMPTOMATOLOGY	205
7.1	Introduction	205
7.2	The Natural Course of the Acute Stage of Cerebral Infarction: a Study of 1,000 Cases	208
7.2.1	Analysis of 1,000 Cases: Prognosis	211
7.2.1.1	Description of the 1,000 Cases	211
7.2.1.2	Lesion Site and Outcome	211
7.2.1.3	Age and Prognosis	213
7.2.1.4	Study of Fatalities	213
7.2.2	Occlusion of the Internal Carotid Artery	216
7.2.2.1	ICA Occlusion and Prognosis	216
7.2.2.2	Acute Stage Disturbances of Consciousness and Prognosis	218
7.2.2.3	Acute Stage Motor Deficits and Prognosis	218
7.2.2.4	CT Findings in ICA Occlusion	219
7.2.2.5	Fatalities Among the ICA Cases	220
7.2.3	Occlusion of the Middle Cerebral Artery	221
7.2.3.1	MCA Occlusion and Prognosis	221
7.2.3.2	Acute Stage Disturbances of Consciousness and Prognosis	222
7.2.3.3	Acute Stage Motor Deficits and Prognosis	224
7.2.4	Ischemic Cerebrovascular Disease Without Positive Angiographical Findings	226
7.2.4.1	Relationship to Prognosis	226
7.2.4.2	Acute Stage Neurological Deficits and Prognosis	228
7.2.4.3	CT Findings	228

8. DIAGNOSTIC TECHNIQUES	231
8.1 Introduction.	231
8.2 Techniques for Obtaining Information Concerning the Cerebral Vessels	232
8.2.1 Cerebral Angiography Using the Direct Puncture and Seldinger's Methods	232
8.2.2 Digital Subtraction Angiography (DSA).	233
8.3 Techniques for Obtaining Morphological Information	236
8.3.1 X-ray Computerized Tomography (CT).	237
8.3.1.1 Low Density Areas	237
8.3.1.2 Mass Signs Due to Cerebral Edema	238
8.3.1.3 Cerebral Atrophy	239
8.3.1.4 Contrast Enhancement Effects	239
8.3.1.5 High Density Areas	241
8.3.2 Nuclear Magnetic Resonance Computed Tomography (NMR-CT)	242
8.4 Techniques for Obtaining Information Concerning Cerebral Blood Flow and Metabolism	246
8.4.1 Two-dimensional Measurement Techniques	247
8.4.2 Three-dimensional Measurement Techniques.	247
8.4.2.1 Dynamic CT	248
8.4.2.2 The Stable Xenon-enhanced CT Technique.	248
8.4.2.3 Single Photon Emission CT Scanning (SPECT)	249
8.4.2.4 PET Scanning.	249
8.4.3 The Pathophysiology of Cerebral Infarction as Seen from Measurements of Cerebral Blood Flow and Metabolism	250
9A. MEDICAL TREATMENT OF CEREBRAL INFARCTION	252
9A.1 Introduction.	252
9A.2 Control of Blood Pressure	252
9A.2.1 Control of Blood Pressure in the Acute Stage	252
9A.2.2 Control of Blood Pressure in the Chronic Stage	253
9A.3 Treatment to Suppress Cerebral Edema	254
9A.3.1 Hypertonic Solutions	254
9A.3.2 Corticosteroids	255
9A.4 Antithrombotic Therapy	255
9A.4.1 Antiplatelet Agents	255
9A.4.2 Anticoagulants	256
9A.4.3 Thrombolytic Agents	256
9A.5 Facilitators of Cerebral Blood Flow	257
9A.5.1 Cerebral Vasodilators	257
9A.5.2 Low Molecular Weight Dextran (Dextran 40).	258
9A.5.3 Exsanguination	259
9A.6 Activators of Cerebral Metabolism	259

9A.7 Cerebral Protective Agents	259
9A.7.1 Barbiturate Therapy	259
9A.7.2 The Sendai Cocktail	261
9A.7.3 Other Drugs with Protective Effects on the Brain	261
9B. SURGICAL TREATMENT FOR CEREBRAL INFARCTION	262
9B.1 Introduction.	262
9B.2 Surgical Treatment for Occlusive Diseases of the Extracranial Carotid Arteries	262
9B.2.1 Internal Carotid Endarterectomy (ICEA)	262
9B.2.2 External Carotid Endarterectomy (ECEA)	265
9B.2.3 Stumpectomy.	265
9B.2.4 Tortuosity, Coiling and Kinking	265
9B.3 Surgical Therapy for Occlusive Lesions of the Extracranial Vertebral Artery	266
9B.4 Intracranial Vascular Reconstruction	267
9B.4.1 Vascular Reconstruction of the Anterior Circulation	267
9B.4.2 Vascular Reconstruction of the Posterior Circulation	268
9B.4.3 Vein Grafts	268
9C. REVASCULARIZATION IN ACUTE STAGE	270
9C.1 Introduction.	270
9C.2 Surgical Therapy in the Acute Stage of Major Stroke Cases	271
9C.3 Acute Stage Vascular Reconstruction Using the "Sendai Cocktail"—Our Series of Patients	272
9C.3.1 Treatment and Indication	272
9C.3.2 Materials	273
9C.3.3 Results	273
9C.3.3.1 Overall Results	273
9C.3.3.2 Results of Cases of Thrombosis and Embolism	273
9C.3.4 Conclusion.	276
9C.4 Acute Vascular Reconstruction for Progressing Stroke	277
9C.5 The Present Series of Progressing Stroke Cases.	278

Part III

Appendixes

10. TEMPORARY OCCLUSION OF TRUNK ARTERIES OF THE BRAIN DURING SURGERY	283
10.1 Introduction.	283
10.2 Decrease in Cerebral Blood Flow Due to Temporary Clipping and Countermeasures—the Development of Methods to Prolong the Safe Time Limit for Vascular Occlusion	284
10.3 Damage to the Vascular Wall Due to the Temporary Clip	289

11. THE PATHOLOGY OF CEREBRAL VASOSPASMS AND ITS TREATMENT	291
11.1 Introduction	291
11.2 The Pathology of Cerebral Vasospasm	291
11.3 Mechanisms of Onset and Causal Factors of Vasospasm	296
11.4 Treatment of Cerebral Vasospasm	301
11.4.1 Drug Therapy	301
11.4.2 Surgical Treatment	305
11.4.3 Our Procedure for Prevention and Treatment	306
12. SURGICAL THERAPY FOR MOYAMOYA DISEASE	307
12.1 Introduction	307
12.2 The Characteristic Pathophysiology of Moyamoya Disease	308
12.3 Surgical Therapy for Ischemic Moyamoya Disease	310
12.3.1 Durapexia	310
12.3.2 Cervical Perivascular Sympathectomy and Superior Cervical Ganglionectomy	310
12.3.3 Superficial Temporal Artery-Cortical Branch of the Middle Cerebral Artery Anastomosis (STA-MCA Anastomosis) and Encephalo-myo-synangiosis (EMS)	310
12.3.4 Transplantation of Omentum	311
12.3.5 Encephalo-Duro-Arterio-Synangiosis (EDAS)	311
12.3.6 Other Techniques for Improving Cerebral Blood Flow	312
12.4 Our Own Therapeutic Technique: Cervical Perivascular Sympathectomy (PVS) and Superior Cervical Ganglionectomy (SCG)	312
12.4.1 The Surgical Method	313
12.4.2 Follow-up Clinical Symptoms	314
12.4.3 Angiographical Follow-up	316
12.4.4 Electroencephalographical Follow-up	319
12.4.5 The Effects of PVS and SCG, as Monitored During Surgery	320
12.5 Anesthesia, Pre- and Postoperative Management in Moyamoya Disease	321
12.5.1 Study of the "Re-build Up" Phenomenon Using EEG, Angiography and PET	321
12.5.2 Anesthesia, Pre- and Postoperative Management	324
References	326
Chapter 1	326
Chapter 2	328
Chapter 3	331
Chapter 4	333
Chapter 5	336
Chapter 6	347

Chapter 7	352
Chapter 8	353
Chapter 9A	355
Chapter 9B	357
Chapter 9C	360
Chapter 10	362
Chapter 11	363
Chapter 12	367
Subject Index	371
12.1 Introduction	371
12.2 The Characteristic Pathophysiology of Moyamoya Disease	371
12.3 Surgical Therapy for Ischemic Moyamoya Disease	371
12.3.1 Durpakia	371
12.3.2 Cervical Perivascular Sympathectomy and Superior Cervical Ganglionectomy	371
12.3.3 Superficial Temporal Artery-Cortical Branch of the Middle Cerebral Artery Anastomosis (STA-MCA Anasto-	371
mosis) and Encephalo-my-sphangioma (EMS)	371
12.3.4 Transplantation of Omentum	371
12.3.5 Encephalo-Duro-Arterio-Synangiosis (EDAS)	371
12.3.6 Other Techniques for Improving Cerebral Blood Flow	371
12.4 Our Own Therapeutic Technique: Cervical Perivascular Symp-	371
thectomy (PVS) and Superior Cervical Ganglionectomy (SCG)	371
12.4.1 The Surgical Method	371
12.4.2 Follow-up Clinical Symptoms	371
12.4.3 Angiographical Follow-up	371
12.4.4 Electroencephalographical Follow-up	371
12.4.5 The Effects of PVS and SCG as Monitored During Surgery	371
12.5 Anesthesia, Pre- and Postoperative Management in Moyamoya	371
Disease	371
12.5.1 Study of the "Re-splid Up" Phenomenon	371
Using EEG, Angiography and PET	371
12.5.2 Anesthesia, Pre- and Postoperative Management	371
References	371
Chapter 1	371
Chapter 2	371
Chapter 3	371
Chapter 4	371
Chapter 5	371
Chapter 6	371

INTRODUCTION

Among the developed nations, cerebrovascular disease (CVD) ranks as one of the top three causes of human death and must therefore be considered a major health hazard for mankind. Due to the elucidation of the risk factors involved, there has been a gradual decrease in the incidence of hemorrhagic CVD, but together with the resultant increases in longevity there has also been a gradual increase in ischemic CVD—a trend which is likely to become a worldwide phenomenon. For this reason, the development of techniques for the prevention and treatment of ischemic diseases of the brain is an issue of extreme importance for all of mankind.

Not only is normal brain function crucial to the individual, but it is worth emphasizing that the brains of world leaders play pivotal roles in current and future world events. The appearance of CVD, the concomitant loss of functions, and the decrease or complete halt in productivity thus have wide-ranging implications for the individual, for his family and for society at large. By the same token, the development of methods to prevent and treat this disease has importance not only for individual patients and their families, but also for the nations within which they work.

The essential nature of ischemic cerebrovascular disease can be described as necrosis of brain tissue due to decreased cerebral blood flow caused by stenosis or occlusion of cervical and/or intracranial arteries. Necrosis produces functional deficits in those parts of the brain and leads either to survival is an impaired condition or to death. While this pathology of CVD is, of course, common knowledge in medicine, it remains true that there is a considerable degree of uncertainty concerning the nature of the gradual intracerebral changes which occur following an ischemic attack. Among several fundamental questions which remain unanswered, the following should be mentioned: What level of reduction of cerebral blood flow and how prolonged a duration of occlusion will result in damage to brain tissue? What differences in these parameters exist in cases of focal ischemia and in cases of global ischemia? With regard to recirculation following ischemia, it must be said that, with the exception of morphological findings using the electron microscope, current research is little more than groping in the dark concerning neurophysiological and neurochemical results.

In the light of these uncertainties, it is evident that accurate evaluation of

the therapeutic effects of various drugs is simply not possible. Moreover, there are significant individual differences in the capacity for developing collateral pathways—a fact which makes evaluation of the prognosis following onset equally difficult. Due to further problems posed by changes in various components of circulating blood, age, blood pressure, associated disorders of the cardiac, pulmonary and respiratory systems, diabetes, and varying degrees of arteriosclerosis, it is evident that the effect of ischemia on brain cells is an extremely complex issue.

What kinds of medical therapy are currently in use for conditions of cerebral ischemia? First of all, with regard to prevention, gradually more favorable results have been obtained by means of dietary measures and the administration of drugs such as aspirin and warfarin to prevent arteriosclerosis and to prevent and/or treat hypertension.

Unfortunately, with regard to the therapeutic steps taken during the acute stage following the onset of ischemic CVD, whatever measures have been employed, the results have been little better than those following the natural course of the disease. Logically, it is easy to imagine that, by means of surgical treatment or the administration of hemolytic agents, vascular occlusions could be removed and efforts then made to increase cerebral blood flow. Such therapy, however, has been found to cause an increase in cerebral edema and cerebral hemorrhage, and for this reason attempts to induce vascular recirculation during the acute stage are now thought to be inappropriate.

Surgical therapy is therefore also thought to be fruitless during the acute stage.

With regard to treatments currently in use for ischemic CVD, only two courses of action are open—neither of which is likely to lead to full recovery. Either the brain tissue which has been affected in the acute stage is considered beyond recovery and the patient is sent for rehabilitation with the neuronal deficits or, alternatively, by-pass surgery can be performed in order to allow for some slight recovery of the brain tissue in the penumbra of the focus.

Serious thought, as a matter of human compassion, should certainly be given to the problems of prevention of ischemic CVD and functional recovery through rehabilitation, but the most important questions concern the development of therapeutic techniques for the acute stage of the disease. Specifically, in order to prevent the rapid deterioration of the patient's cerebral condition and reduce the number of acute deaths, which are known to be a function of the interval from onset, it is essential to develop some form of therapy that can be instituted as early as possible in the acute stage. That therapy, whatever it may be, would be of extreme importance and would constitute the first positive step forward in the treatment of ischemic cerebrovascular disease. During that period, while rapid deterioration of brain cells is being prevented, it would then be possible either to undertake vascular reconstruction or to allow for spontaneous increase in cerebral blood flow due to the emergence of collateral pathways.

The most difficult and frustrating task for the neurosurgeon is to be forced simply to observe the progression of cerebral infarction following onset and to be unable to take positive action. Similar to dealing with a house on fire, the most important step would be to take preventive measures at a very early stage in the event. From our own animal studies we have found that when cerebral flow is reduced to 40% of its normal level for a period of 3 hours, the morphology of brain cells is drastically changed and the cells are phagocytosed by leucocytes 24 hours later. Needless to say, despite the fact that there is total occlusion of capillaries and small vessels, leucocytes manage to destroy the infarcted brain tissue. Once the brain has entered such a condition, it is already too late to take therapeutic steps.

My own interest in and study of the ischemic brain began with an attempt to prolong the permissible time of temporary vascular occlusion for radical surgery on ruptured cerebral aneurysms—and indeed this quest has become a major lifework for me. At that time, an energetic young man, my classmate Akira Watanabe, entered the department of surgery of our college and began investigating hypothermic anesthesia in dogs. I turned my attention to the question of the permissible time for cerebral vascular occlusion using various degrees of hypothermia and soon learned how very difficult it is to reduce cerebral blood flow to zero. Eventually, I found that cerebral flow could be halted by means of thoracotomy and occlusion of all the ascending arteries to the neck, but this

experimental model proved to be extremely laborious!

Finding that 30 minutes of vascular occlusion could be done using hypothermic anesthesia at 27°C, I performed my first aneurysm surgery using hypothermia on May 27th, 1961 and over the following years until 1969, I operated on many such cases. Considerable time however was needed for the lowering and subsequent raising of the patient's body temperature and, moreover, during that procedure complications such as cardiac arrest and skin burns were not uncommon. Throughout this period I pondered in the back of my mind whether or not there might be alternative means for prolonging the permissible occlusion time of cerebral vessels.

A fundamental turning point in our surgical technique came in 1969 when I experienced a case of ruptured cerebral aneurysm with severe cardiac complications. The anesthesiologist suggested that hypothermia alone would be fatal and since I had operated on some 300 aneurysm cases by then, I was confident that a successful operation could be done at normothermia. Craniotomy and dissection of the aneurysm were begun, but before actually reaching the aneurysm, there was a major re-rupture and intracerebral structures could no longer be distinguished or the aneurysm treated. Temporary occlusion of feeding and draining arteries of the aneurysm therefore became inevitable and the total occlusion time exceeded 50 minutes. Since cerebral necrosis occurs in about three minutes in medical common sense, there was no reason to expect favorable

results after such a prolonged occlusion. Expecting severe postoperative sequelae, I went to the patient's bed on the following morning and called her name. To my great surprise, we found her to be in a normal state of consciousness and to be without paresis.

My first thought was that this was surely a case of divine intervention, but the scientist in me soon returned and the entire staff was convened to examine what kinds of treatment the patient had received before, during and after the operation. At this point, I recalled that, in order to reduce the cerebral volume and enlarge the surgical field, 1,000cc of 20% hypertonic mannitol solution had been administered by *i.v.* drip in such a manner that it was completed near the end of craniotomy. It was thus apparent that the mannitol may have been the factor which allowed for the prolonged occlusion of cerebral vessels without producing sequelae.

I asked Assistant Professor Takashi Yoshimoto, who was then a young M.D., if he would investigate the apparent capability of mannitol to suppress cerebral infarction, and in this way a long series of animal experiments were initiated. In order to clarify the effects of drugs such as mannitol, it was first necessary to establish an experimental animal model in which infarctic foci of the same size could be produced consistently at the same site in the brain. Furthermore, the severity of these foci would have to be controllable. Although research into the effects of mannitol was to begin with the development of such an ideal infarction model, animal models using various

species and countless techniques did meet our expectations. Eventually, Dr. Yoshimoto went to Taiwan, where native Taiwanese monkeys were inexpensive enough to pursue such research to develop a model, but he returned despondent without success.

Upon hearing his bad news, I concluded that rigorous animal studies on the effects of drugs on brain infarction might in fact be impossible and I regretfully called a halt to the research project. But just two months after having abandoned hope, Dr. Yoshimoto strode into my office with four formalin-fixed dog brains in hand and announced: "I've done it!" When I asked what he had done, he proceeded to show me infarctic foci of similar size in the anterior thalamus of all four brains cut coronally through the optic chiasma.

As delighted as we both were, it was soon found that even when the four trunk arteries were visible when a unilateral temporal approach was used without doing damage of the temporal lobe, the incidence of anterior thalamic infarction was considerably lower than the initial indications of Dr. Yoshimoto's first four dogs. At that point, Dr. Tetsuya Sakamoto suggested that a deep electrode stereotactically inserted into the anterior thalamus for the purpose of monitoring brain electrical activity would allow for confirmation of the infarction produced by means of occlusion of the four trunk arteries. It was then found experimentally that an ideal focus of infarction could be produced in virtually 100% of the animals using that technique. Subsequent work was then devoted to