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A brief review of Dr F Gotoh's contribution to neuroscience: research in the field of cerebral blood flow and stroke

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Abstract. Professor Emeritus Fumio Gotoh began and continues his remarkable career in medicine at Keio University. Since his graduation from medical school there in 1951, Dr. Gotoh has devoted himself to neurology, especially in the enigmatic field of stroke science. He is most renown for his groundbreaking research and leadership in the study of cerebral blood flow and metabolism. Beginning with his doctoral thesis paper in 1959 entitled "Effects of blood pressure on cerebral circulation," our article briefly delineates how Prof. Gotoh has paved the path for current and future discoveries in modern medicine. Although wholly difficult to sum up Dr. Gotoh's extensive career in such a short article, we have attempted to chronologically list and furthermore to describe his numerous works. Herein we describe his expansion to the international arena with his contributions at Wayne State University as well as his novel cerebral blood gas monitoring techniques now used in modified fashion throughout the world. From his CO_2-based investigations in animals to his study of the autonomic nervous system's role in human cerebrovascular control, we remark on Dr. Gotoh's accomplishments without the use of functional imaging. Yet despite the basic science theme of his research, he has always kept them clinically correlated to entities such as Cheyne-Stokes phenomenon and Shy-Drager syndrome. Prof. Gotoh has been asked to head some of the most influential stroke societies and was the second president of the International Stroke Society. In conjunction with leading authorities, he developed a quantifiable, evidence-based stroke scale which was introduced in the International Journal of Stroke in 2001. Today despite his retirement, Dr. Gotoh continues his work in cerebral blood flow and metabolism. (Keio J Med 50 (2): 72–80, June 2001)

Key words: Cerebral blood flow, CO_2 reactivity, Autonomic nervous system, Nitric Oxide, Stroke scale

Professor Emeritus Fumio Gotoh of Keio University was born on March 9, 1926 in Tokyo, Japan. He began his medical education at Keio University where he graduated in March of 1951. After a brief internship at the First National Hospital in Tokyo, he started his esteemed career in academia in the department of internal medicine at Keio University Hospital. There he had the opportunity to train under Professor K. Ohmori and Professor T. Aizawa.

Dr. Gotoh's devotion to the art of medicine was exemplified by his attention to both his patients as well as his students. Word of his expertise spread rapidly, especially in the budding field of stroke research. In 1959, Keio University honored him with a degree in medical science partly as a result of his groundbreaking article[1] entitled "Effects of blood pressure on cerebral circulation." So influential was this article that it was published in both a Japanese and an English journal.

That same year, Dr. Gotoh left to study abroad at Wayne State University in Michigan, USA. There he joined the chairman of the department of neurology, Dr. J.S. Meyer, to study cerebral circulation and metabolism. Dr. Gotoh was prolific in both research and publications, elevating him to an associate professorship at that prestigious institution.

By 1969, he had returned home to Keio University as an assistant professor of internal medicine and continued his work centered in neurology with special emphasis on cerebral blood flow autoregulation especially due to arterial CO_2 fluctuations. Soon thereafter, he developed a device to continuously record human blood gasses at his laboratory. In 1970, Dr. Fumio Gotoh initiated a new era at Keio University by estab-

lishing the Department of Neurology and becoming its first Chair.

He quickly advanced to become an associate professor in 1971 and gained the title of ''Professor of Neurology'' in 1972. Because of his stature amongst the world's leading experts, he was asked to serve as chairperson of the International Meeting of Cerebral Flow and Metabolism held in Tokyo in 1979. Following multiple contributions to the field, Dr. Gotoh was named Professor Emeritus in 1991 and became the third president of the Japanese Stroke Society as well as the second president of the Japanese Society of Cerebral Blood Flow, serving from 1991 to 1998. Despite his numerous responsibilities, Professor Gotoh tirelessly leads the International Stroke Society as its second president from 1996 to 2000.

Despite his retirement, he continues his lifelong dedication to neuroscience. He is an inspiration and leader to those of us in medicine and certainly a hero to those of us in the pursuit of neurological studies. It is hard to truly convey in words how instrumental Dr. Gotoh has been. It is better to allow his over 220 published works speak for themselves. His primary articles are listed in the reference.[1–163]

Professor Gotoh's research career can best be divided into four periods.

1959–1969: Cerebral Blood Flow Studies at Wayne State University

Dr. Gotoh began his studies by inventing a novel method of continuously monitoring the oxygen & carbon dioxide tension within the cerebral vasculature.[4,5] With this instrument, he demonstrated that hypocapnic arterial constriction resulted in decreased flow and anoxic ischaemia using concurrent measurements of cortical blood flow, pO_2, pCO_2, pH, as well as EEG.[2–6]

Although at the time carbon dioxide was generally thought to have the most potent action on cerebral vasculature, no mechanism of action was immediately apparent.[164,165] These difficulties related to the inability to differentiate carbon dioxide's effects from associated changes of bicarbonate concentration. It was Prof. Gotoh who theorized that carbon dioxide must act directly on the arteriolar smooth muscle. He showed that a large dose of acetazolamide was able to inhibit the vasomotor action of carbon dioxide.[3,12]

The next phase of his research involved comparing gaseous transport rates across brain tissue. Specifically, he compared oxygen and inert nitrogen in living and dead cat brains. The speed at which living brains transmitted these gases was more rapid than dead tissue and blood capillaries were believed to be responsible for the difference.

Later, carbon dioxide was applied directly and externally to the cerebral cortex resulting in vasodilation, which could be prevented by preemptive administration by IV acetazolamide.[3,12] This strongly suggested the vasodilatory action of extravascular carbon dioxide, a product of cerebral metabolism. Carbonic anhydrase enhances the reaction $CO_2 + H_2 = H^+ + HCO3^-$.[12] As Dr. Gotoh had already demonstrated the neutralizing effect of acetazolamide on $HCO3^-$, another chemical mediator was required to explain the effect. H^+ was found to be less potent than CO_2[9] because it does not readily permeate through the cell membrane. CO_2, without an associated charge, is able to more rapidly lower intracellular pH. This lead to the conclusion that the final common pathway for CO_2 vasomotor action is the change of intracellular H^+ in arteriolar smooth muscle (Fig. 1).[163]

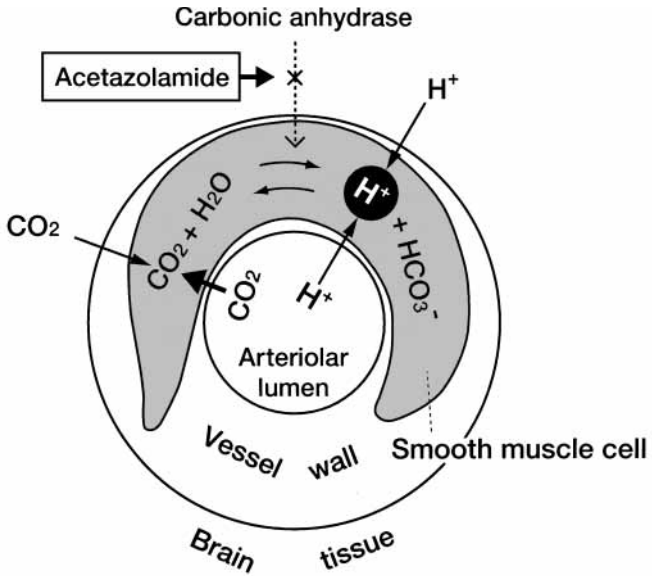

Fig. 1 Cerebral vasodilator action of CO_2 (PCO_2 electrode theory).[163]

Prof. Gotoh felt his research could be extrapolated to include human brain tissue and soon modified his continuous blood gas recorder to monitor humans. He repeated his experiments on humans and verified his findings.[16,17,19,21,22,29,30,35] In 1965, he showed that EEG slowing with hyperventilation was induced by reduction of cerebral jugular venous oxygen tension (JpO_2). This slowing occurred at JpO_2 of 21.0 ± 1.8 mmHg. Of the total decrease of JpO_2, 73% was due to reduction of blood flow and 27% was secondary to the Bohr effect.[16]

Continuing his novel monitoring techniques, Dr. Gotoh developed ways to continuously check sodium, and potassium ion activities in monkeys.[15] Utilizing the Fick principle, 2.5% molecular hydrogen gas, and a

Teflon-coated hydrogen electrode, he found a new way to evaluate cerebral blood flow (CBF).[23,24,27] Using his technical skills, he revealed the results of pH, oxygen tension, and carbon dioxide alterations in human volunteers and patients with seizures, altered mental status, or cerebrovascular disease.

In addition, he studied metabolic activity during periods of arousal and stimulation.[12,31] The subsequent decrement in JpO_2, increment in pCO_2, and fall in pH suggested that metabolism is increased but no appreciable change in blood flow results after arousal from the drowsy state. Dr. Gotoh and his fellow researchers found that increase in CBF was delayed approximately 20 seconds for cutaneous pinpricks, 60 s for auditory stimulation or arousal, and 240 s for photic stimulation. Increased cerebral metabolism from increased mental activity had only been described once before by Kety.

The changes went far to explain the reactive hyperemia resulting from carbon dioxide, a metabolic byproduct. This coupling of cerebral metabolism & blood flow is important in the cerebral circulatory homeostasis in both man and animals. Along with these studies, Prof. Gotoh worked on Cheyne-Stokes respiration using polygraphic recordings.[36] He concluded that it was a neurogenically-mediated mechanism, which results from depression of the respiratory center. Periods of apnea ensue with a delayed rise in $PaCO_2$, which normally incites the respiratory center.

1970–1988: Cerebral Blood Flow Autoregulation

After an encounter in 1970 with a patient who had Shy-Drager syndrome, Prof. Gotoh began to investigate the importance of the autonomic nervous system (ANS) in regulating CBF. Until this period, the ANS was thought, most notably by Lassen & Sokoloff,[162–164] to play a minor role in CBF regulation. Dr. Gotoh recognized, however, that episodic syncope associated with orthostatic hypotension in Shy-Drager was most likely due to dysautoregulation. Using this patient as a model, global and regional CBF was determined by using N_2O & ^{133}Xe injections in conjunction with continuous cerebral blood gas measurements. The results were as follows:[39] a. Loss of autoregulation coincided with abnormality in the ANS. b. The degree of impairment was dependent on the extent of the ANS dysfunction. c. CBF response to CO_2 was spared despite total dysautoregulation.

This data was presented at the 5th International Symposium of Cerebral Blood Flow and Metabolism in Rome in 1971.[39] These findings stressed the participation of the ANS in CBF regulation. Following Dr. Gotoh's revolutionary work, many researchers produced data to verify his theories. He revealed that the chemical (CO_2) & neurogenic (ANS) modalities operated by independent pathways to exert control on the CBF.

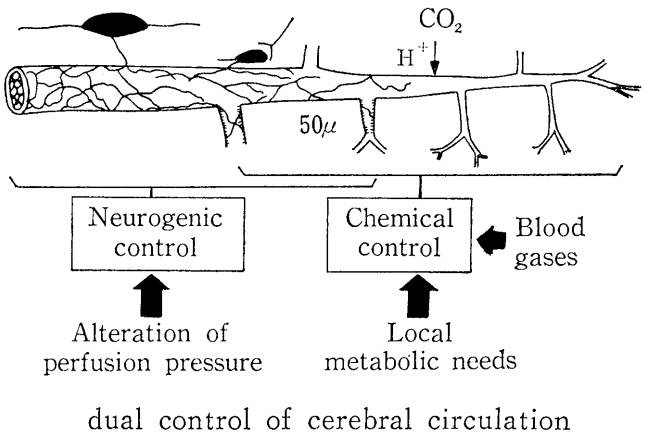

Fig. 2 Dual control of cerebral artery.[163]

This paradigm was cemented by photography of pial arteries 15 to 200 microns in diameter during concurrent hyperventilation of 5% CO_2 with iatrogenic induction of hypotension (by blood withdrawal).

Although blood pressure fluctuations had more pronounced effects on arteries greater than 50 microns, the converse was true for CO_2 alterations. There was greater response in arteries less than 50 microns to CO_2 inhalation or hyperventilation.[44] This elegant demonstration by Dr. Gotoh is illustrated in Fig. 2.[163] He also showed that the ANS was also important in cat CBF regulation.

Pial artery studies were continued using bipolar platinum electrodes and high sensitive preamplifiers to detect action potentials.[56] Induction of hypotension by blood withdrawal was shown to change the potentials across the membrane.[59] These recordings lent evidence to Prof. Gotoh's concepts of ANS-CBF interactions.[59]

With every answer, however, came more questions. These findings only sparked more interest in CBF maintenance.

He began studying the adrenergic & cholinergic systems separately. Furthermore, he discovered that every neurotransmitter, such as VIP, DA, and cGRP, was a candidate for further research. Through his research he uncovered derangements related to the ANS in the mechanisms associated with migraines.

1985–Present: Endothelial Contribution to CBF-Importance of Nitric Oxide

It was Furchgott[167,168] who first took steps to dispel the mystery of endothelial role in vasodilatation of the peripheral vessels.[94,104] Prof. Gotoh expanded on this research by implementing ultraviolet ray damage on

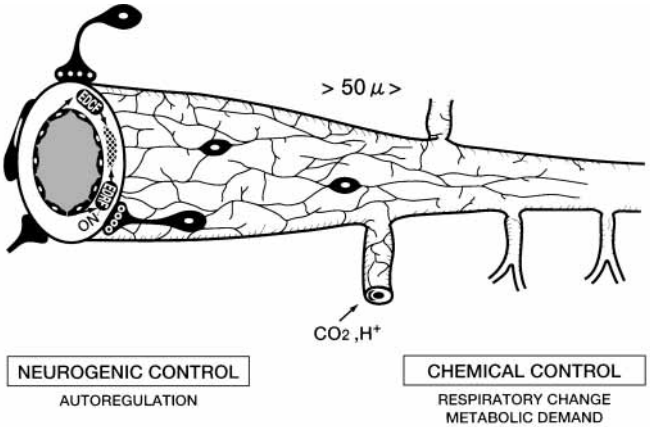

Fig. 3 Endothelial control of cerebral artery (F Gotoh, 1990).

NO: Nitric Oxide.

endothelium, which impaired neurogenic (ANS) control of CBF. Despite this, chemical (CO_2) modulation remained intact.[104]

Following the discovery of nitric oxide endovascularly by Monchada *et al.*,[169,170] Prof. Gotoh discovered its effect on the cerebral circulation for the first time.[155] Later, Dr. Gotoh uncovered the relative contribution of nitric oxide to CBF autoregulation.[156,157] Some researchers had dismissed the role of CO_2 in CBF regulation and claimed that vasodilation was exclusively derived from nitric oxide concentration. Dr. Gotoh, however, showed that nitric oxide and CO_2 exert their control on arterial flow through two independent pathways, because the CO_2 response remained intact even after the inhibition of nitric oxide.[156]

Even after his retirement, he continues to investigate factors such as nitric oxide with regard to cerebrovascular regulation (Fig. 3). During his investigations, he stumbled upon the role of platelets and the vicious cycle, which can be induced by platelet aggregation.[14,127,128] This is one mechanism to explain the progression of microvascular bed deterioration.

1996–Present: Stroke Scale Development

Although there are numerous stroke scales available with varying complexities, clinical dilemma arise because none are able to quantify the severity of cerebral infarction and its residua. Together with other members of the stroke scale subcommittee of the Japan Stroke Society, Prof. Gotoh has taken initiative to develop a weighted scale, which transcends simply documenting neurologic deficits, level of consciousness, and psychological states but which will stratify patients into risk categories, treatment algorithms, and prognostic groups.[158]

This task is an arduous one. The clinical signs and symptoms of stroke are multifarious which makes it hard to formulate quantifiable measures. Together, they have developed novel scales by use of conjoint analysis to calculate the relative weight of each item.[158] The subcommittee headed by Dr. Gotoh published their quantifiable stroke scale in the official journal of the Japan Stroke Society,[159,160] the Japanese Journal of Stroke. Subsequently, he organized the International Workshop on the Stroke Scale in July of 2000,[161] inviting many of the leading experts in the clinimetrics & scales from around the world. At the forefront of stroke science, Prof. Gotoh and workshop attendants discussed the current scales available as well as the need for a reliable, evidence-based, and quantifiable stroke scale applicable globally. Included in this workshop was discussion for the need for international cooperative studies, which continued at the International Conference of the International Stroke Society in Melbourne, which took place in November of 2000.

Dr. Gotoh and his colleagues' work culminated in submission of stroke scales to the International Journal of Stroke in 2001.[162] This ends the last chapter of the book, which is still being written as Professor Emeritus Fumio Gotoh of Keio University continues to be at the leading edge of neurological advancements. His contributions both past, present, and future are deeply appreciated.

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