Special Lecture*

My Study and Thought on Internal Medicine

Experience through the Autonomic Nerve Research

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My research work on the autonomic nervous system is derived from the life work of my beloved teacher, Professor Ken Kuré and its systematic progress has been inseparably interwoven with his work through the history of about 60 years altogether.

Professor Ken Kuré, a born research worker and a great scholar, was extremely strict on his pupils. As one of his students, I was also instructed and trained by him rigorously. At first, there was a time when I was merely a passive worker reading medical literature and assisting his experiment in obedience to his order. During the years of my work with him, however, wisdom required for research life flew into me abundantly without my knowledge.

After graduating from the University of Tokyo Faculty of Medicine in 1907, Professor Kuré studied in Germany and Austria. Professor H. E. Hering, who subsequently discovered "Blutdruckzügler", was his teacher at University of Prague. This precious experience no doubt contributed to his great success as an investigator. After returning to Japan, Professor Kuré became interested in the mechanism of right ventricular hypertrophy and dilatation in patients with beriberi, a common disease of Japan at that time. Under the working hypothesis that paralysis of the diaphragmatic nerve due to beriberi poison is responsible for such change, he started the studies on the innervation of the diaphragmatic nerve using monkeys. Maintenance of diaphragmatic tension by the sympathetic nerve was thus discovered. This led him to his life long study on the autonomic nervous system. Further studies included the autonomic innervation of voluntary muscles, etiology of Dystrophia Musculorum Progressiva, and finally the spinal parasympathetic nerve. At the foundation of this series of studies, a plan of classifying the autonomic nervous system into sympathetic and parasympathetic nerves persisted in a dual approach of morphology and function. In his concept of the autonomic nervous system, sympathetic

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nerve fibers were explained according to the theory of Langley and Gaskell. Preganglionic fibers consist of medullated fibers of small diameter, whereas postganglionic fibers are unmedullated fibers.

According to his working hypothesis, both preganglionic and postganglionic parasympathetic nerve fibers are medullated fibers with small diameter. This was based on the observation on the morphology and function of known peripheral autonomic nervous system with parasympathetic function (for example, pelvic nerve, ciliary body nerve, and chorda tympani).

In 1946, I was appointed Professor of Medicine, heading one of the Department of Internal Medicine full of traditions at the University of Tokyo Faculty of Medicine. Upon deep self reflexion and deliberation on future work, I have made up my mind to advance in the study of internal medicine, in face of thorough self-criticism in the light of pathologic anatomy. This attitude has become another pillar in my academic life, in addition to the pillar of autonomic nerve research already established. In this lecture, my basic thought and attitude on the research work on autonomic nervous system will be described, along with the lessons from my respected teachers and seniors and my own experience throughout the research life.

After the decease of Professor Kuré, I have continued in the research work on the autonomic nervous system on my own. Part of the criteria of the morphological classification of the autonomic nerve fibers advanced by Professor Kuré did not

Fig. 1

satisfy my searching mind at this stage. In the vagus nerve, one of the major representatives of the parasympathetic nerves, the application of this principle of Professor Kuré encountered some difficulty. While medullated nerve fibers with small diameter occupied a major portion of the vagus nerve superior to the jugular ganglion and ganglion nodosa (Fig. 1, a), medullated fibers became rare below these ganglia and non-medullated fibers occupied the majority (Fig. 1, b).

In this nerve, preganglionic fibers probably consist of medullated fibers with small diameter but postganglionic fibers are apparently non-medullated. This is an

apparent contradiction with the theory of Professor Kuré maintaining that both pre- and postganglionic parasympathetic fibers are small medullated fibers. Such paradox was explained by the histochemical method of classification of the autonomic nerves we subsequently adopted. My work on the autonomic nervous system thus gradually found its own original direction after these studies on the vagus nerve.

Under the recognition of limitations of the criteria of classification of the autonomic nerves based merely on the thickness of the fibers and presence or absence of medullary sheath, I felt the necessity of introducing the neurochemical transmission theory (Lewi, Dale) which rapidly rose into popularity at that time. Through understanding the nerve cells and nerve fibers neurochemically and neuroenzymologically, I attempted to grasp the nervous system from the morphological and functional standpoint. From such viewpoint, the nervous system, especially the sympathetic and parasympathetic nervous system was reexamined. Subsequent studies on the regulation of various internal organs especially the endocrine glands were also based on the same principle. As for the composition of the autonomic nerve, individual autonomic nerves in the periphery are not of single component, but composed of mixture of the sympathetic and parasympathetic nerve fibers. According to the individual autonomic nerve, either one of the two shows a predominance and the other is recessive.

Subsequent studies on the autonomic nerve are based on this principle. From that time through the present day, so-called nervistic approach attempting the overall grasp of the phenomena of living body through purely neurological standpoint from the cerebrum to the periphery was held on one hand, while a purely biochemical or humoral approach of fine analysis of the living organism has been held on the other. In my investigation, I have tried to view both of these two approaches equally from

Fig. 2

the borderline, to understand the activity of various internal organs from the neurochemical or neurohumoral standpoint. As part of the studies on the vagus nerve, presence of sympathetic component among the overwhelmingly predominant parasympathetic nerve was demonstrated through physiological experiment in the form of cardiac accelerator nerve (Fig. 2), and through the detection of the presence of sympathetic nerve cells with specific MAO activity by the morphological means (Fig. 3). A series of studies on the circulatory regulation and mechanism of reflex

Fig. 3. MAO-nuclear positive nerve cells in vagus nerve.

were thus conducted as shown in the Table (abbreviated). In the studies on the regulation of various endocrine glands, overall studies were conducted from the standpoint of neurohumoral control. Regulation of the secretion of insulin from the pancreas, thyroid hormone, and hormones of the adrenal cortex and medulla by the peripheral autonomic nerves and central nervous system such as hypothalamus and the limbic system (posterior orbital surface, amygdaloid nucleus, and hippocampus) was thus studied. Besides, the classification of the autonomic nervous system was advanced by neurochemical and enzymological means. In order to classify the autonomic nervous system into cholinergic and adrenergic nerves, acetylcholine and its degrading enzyme, acetylcholine esterase on one hand and noradrenaline and its degrading enzyme, monoamine oxidase on the other were stained histochemically through the steps of staining technic shown in the Table (abbreviated). The autonomic nervous system was thus classified from the center to the periphery and innervation of various organs was systematically studied.

It should be especially noted in these studies, that the functional classification of the autonomic nervous system through histochemical and enzymological method should be scrutinized methodologically as to the specificity and reliability. In the interpretation of the limited information, we should not stop at drawing conclusions from the findings obtained by a new method but further try to understand the whole picture on the basis of informations accumulated so far, for overall interpretation. Based on the above described working hypothesis and concept, studies were conducted from the neurohumoral viewpoint, with emphasis on ChE and MAO activities. During the process of this investigation, presence of nerve cells with specific findings was demonstrated among the nerve cells with positive MAO activity in the staining by Takamatsu's method. In these nerve cells, not only the protoplasm, but also the nucleus gave apparently positive reaction to MAO. Such findings have never been

Fig. 4

- a. MAO-nuclear positive nerve cells in stellate ganglion.
- b. Ciliar body ganglion MAO-activity negative.

reported in the literature. After careful consideration on the significance of such finding, we have tentatively named these as MAO-nuclear positive nerve cells, and attempted to elucidate the nature of these cells. As the result, these nuclear-positive cells were found in nerve cells in which the sympathetic nature has been established (Fig. 4, a, b). Thus the MAO-nuclear positive nerve cells appear to express the adrenergic nerve cells intensely according to our conclusion. While these new informations were being added, the nervous system was classified from the center to the periphery, and various endocrine organs were also divided into cholinergic and adrenergic varieties. Thus the autonomic nervous system throughout the body was systematically classified to prepare a map successfully. Comparison of this information together with the conventional classification of the autonomic nervous system along with a new interpretation has led us one step forward in the classification of the autonomic nervous system. In 1962, Hillarp, Falck and their associates beautifully demonstrated the actual structure of adrenergic nerve with an excellent method.

After careful studies in the comparison of MAO-nuclear positive nerve cells specifically representing adrenergic property according to our work with that of adrenergic nerve cells shown by Hillarp, Flack and others, we came to a conclusion that these two are almost identical. The MAO-nuclear positive cells we discovered thus definitely represent adrenergic nerve cells. It goes without saying that advanced methodology contributes a great deal to the progress of science. However, this is still insufficient because thought, insight, and judgement are required in the course of research work in order to obtain a true progress.

Even in the studies by workers in the old age based on classic and simple methods, excellent insights, directions, and interpretations piercing through the modern era may already be found. Through my own research experience, this is my most profound impression. Some of the excellent investigations to date had already been clearly predicted and founded in outlines by distinguished workers almost 50 years ago.