NATIONAL ACADEMY OF SCIENCES

GEORGE BRAMPTON KOELLE
1918—1997

A Biographical Memoir by
ROBERT E. FORSTER

Any opinions expressed in this memoir are those of the author and do not necessarily reflect the views of the National Academy of Sciences.

Biographical Memoir

Jules Schick Photography

GEORGE BRAMPTON KOELLE

October 8, 1918–February 1, 1997

BY ROBERT E. FORSTER

GEORGE BRAMPTON KOELLE was born on October 8, 1918, in Philadelphia, graduated from West Philadelphia High School in 1935, and entered the Philadelphia School of Pharmacy and Science (now the University of the Sciences) from which he graduated in 1939, majoring in biology. He was admitted to the Department of Pharmacology at the School of Medicine of the University of Pennsylvania in 1939 as the first graduate student of A. N. Richards, then chair, while he also worked as an instructor in the School of Pharmacy.

The U. S. Army was at that time concerned about the effects of nerve gases (fluorophosphate compounds) and possible protective agents, because it was known that the Germans possessed large stores of these toxic materials. Richards was a consultant to the Chemical Warfare Service at Edgewood, Maryland, and it was probably at his insistence that Koelle joined the Army as a private in 1942 and was assigned to its Medical Administrative Corps at Edgewood, an extremely fortuitous circumstance for him. Lewis S. Goodman and Alfred Gilman from the department of pharmacology at Yale, whose monumental medical pharmacology text had first appeared in 1941, were already at Edgewood and working on the fluorophosphates and mustard gas. Koelle went to work under Major Gilman, and they showed that the primary

action of di-isopropylfluorophosphate was to inhibit acetylcholine esterase (ACHE); their publications were accepted for his Ph.D. thesis at Penn. This was an exciting period for Koelle. He had a superb senior colleague and an important topic on which he spent the rest of his career.

A second fortuitous circumstance occurred after leaving the Armed Services. Koelle was accepted at Johns Hopkins School of Medicine. (Before Hopkins, he had applied to the University of Pennsylvania and had been turned down by the dean because of his predoctoral education.) During medical school he obtained a fellowship in ophthalmology at the Wilmer Institute and worked with Jonas Friedenwald, who was an outstanding ophthalmic pathologist interested in histochemical techniques. Together they developed a method to stain ACHE in microscopic sections, enabling Koelle to study neurotransmitters for the rest of his life.

After finishing medical school in 1950, Koelle took a position as assistant professor in pharmacology at the College of Physicians and Surgeons, Columbia University—the same year he was 32 years old and was awarded the prestigious John J. Abel Prize. In 1952 he was recruited by Julius H. Comroe as a professor in the Department of Physiology and Pharmacology in the Graduate School of Medicine (GSM) at the University of Pennsylvania. The GSM provided organized instruction in the specialties to medical school graduates, and was completely separate from the School of Medicine. It had its own hospital, built by the University of Pennsylvania in about 1914 with funds from the sale of the Polyclinic Hospital, which had been acquired by the City of Philadelphia by right of eminent domain to build the Benjamin Franklin Parkway. However, a competing method of training specialists arose in which groups of prominent specialists, specialty boards, supervised a preceptor-type clinical training outside

the university under an accredited specialist and gave an examination. The latter type of postgraduate training gradually won out and is the accepted training today.

Its original purpose gone, the GSM was very active after World War II refreshing physicians who had been in the Armed Services. After this flood of students disappeared, the GSM trained foreign physicians, but for a number of reasons the university decided to eliminate the GSM as a separate unit. Julius Comroe's interest was in teaching basic science to physicians, and when he realized the change in political climate in 1957, he left to found the Cardiovascular Research Institute at the School of Medicine of the University of California, San Francisco; George Koelle became chair of the Department of Physiology and Pharmacology in the GSM, and later the dean. He was a good administrator and the provost, who was not given to kind words, said he was the best that GSM had had.

In 1959 Carl Schmidt stepped down as chair of pharmacology in the School of Medicine, and Koelle was appointed his successor, relinquishing the deanship of the GSM and absorbing the Department of Pharmacology of the GSM into that of the School of Medicine. Koelle remained Elmer Bobst Professor and chair of pharmacology in the School of Medicine until he stepped down in 1981, but remained active as a Distinguished Professor until he became emeritus in 1989. While dean of the GSM, he had established the Isaac Ott Professorship in Physiology from several bequests to the GSM, which supports an endowed chair in the Department of Physiology in the School of Medicine.

Koelle was married to Ethol Shields and then to Winifred Jean Angenent, who received her M.D. from Columbia and worked with him in pharmacology, coauthoring a number of papers. They had three sons.

Koelle's scientific career was quite focused on neurotransmitters in the sympathetic and parasympathetic nervous systems. Acetylcholinesterase (ACHE) is a neurohumoral transmitter found in the parasympathetic nervous systems and in the somatic nerves to skeletal muscle. ACHE is released in minute vesicles (quanta) by the presynaptic nerve endings and diffuses across 100 angstroms of synaptic cleft to the postsynaptic membrane in milliseconds, thereby exciting it. Nerve impulses occur at rates from several to hundreds per second. The neurotransmitter from one impulse must be destroyed before the next impulse can occur, in periods as short as milliseconds. ACHE is an enzyme that hydrolyzes acetylcholine (ACH) this rapidly and, where found, is presumptive evidence of the location of ACH. It is not possible to stain ACH itself because it is hydrolyzed by nonspecific enzymes in minutes and would be lost in the tissue staining. The original technique of Koelle and Friedenwald involved exposure of a tissue section to thio analogues of acetyl, benzoyl, and butyl choline. The enzyme hydrolyzes the substrate, liberates thiocholine as a mercaptide, which is then replaced by cupric sulfide, resulting in a black precipitate that localizes the choline esterase to microscopic dimensions.

The method did not distinguish between the nonspecific choline esterase, found in liver and plasma, and the specific choline esterase, found in the nervous system; so Koelle went on to do a thorough study of the activity of the enzymes on different substrates and on their sensitivity to fluorophosphate inhibition, for which he was awarded the 1950 John J. Abel Prize by the Society for Pharmacology and Experimental Therapeutics. He found that 10^{-6} M di-isopropylfluorophosphate (DFP) almost completely inhibited the nonspecific esterase in 30 minutes while the specific esterase was only reduced 60 percent, which enabled him to stain for specific esterase alone. Butyrylthiocholine is hydrolyzed

by nonspecific esterase and not by specific esterase, so it can be used to stain for the former. Therefore Koelle could separate the enzymes histochemically, but another possible artifact of localization had to be disposed of, the diffusion of the enzyme after sectioning. This also was studied and it was found that 28 percent Na_2SO_4 would precipitate the enzyme, thereby preventing it from diffusing.

Armed with a technique that could differentiate specific and nonspecific choline esterase on a microscopic scale, while they could not be measured on tissue samples grossly, and prevent in vitro diffusion of the enzyme, Koelle launched into a study of the distribution of the two types of enzymes throughout the body, mainly in the cat. He found that specific choline esterase was in the axone terminations of the parasympathetic system, preganglionic synapse of the sympathetic and the motor end plate of striated muscle, while the nonspecific enzyme was found in the liver, plasma, smooth muscle, and glia. This showed that ACH is the preganglionic transmitter, even in the sympathetic nervous system, and he also found that recently synthesized ACHE was stored beneath the postganglionic membrane.

Koelle did not limit his research to this technique but also used biochemical and cellular biological approaches to study the distribution, function, inhibitions, and regeneration of ACHE in human and other animal species. His lifelong association with the enzyme led to its being called "Koelle esterase" at Penn. In the later part of his career he concentrated upon the degradation and synthesis of ACHE, using the superior cervical ganglion, after either preganglionic section or DFP inhibition. Glycyl-glutamine acted as a neurotropic factor to maintain or increase the level of ACHE, and he showed this was not acting on the polymerization of the enzyme but on its synthesis.

He continued developing histochemical techniques (for example, using lead and gold methods for ACHE). He was basically interested in neurotransmission and so studied sympathetic transmitters and metabolism as well as the parasympathetic, developing a histochemical stain for monoamine oxidases and investigated epinephrine metabolism with it. Koelle was always cognizant of the clinical implications of his work, accentuated perhaps by his close personal association with clinician specialists teaching in the Graduate School of Medicine. He experimented with DFP as a therapeutic agent in myasthenia gravis and megacolon.

Koelle was a fine teacher, magnificent lecturer and raconteur, and could deliver a lecture filled with details without notes. He received teaching awards at Penn, and was frequently asked to lecture elsewhere in the United States and abroad. Because of his distinguished research he attracted colleagues and students from around the world to work with him in Philadelphia and in turn was invited to give at least 21 distinguished lectures abroad.

He published more that 100 peer-reviewed papers, more than 60 reviews and book chapters, including the sections on neurohumoral transmission, ACH, and ACHE in the third edition of Goodman and Gilman's pharmacology text. He was appointed visiting professor at more than 10 foreign medical schools, including the University of Lausanne, where he was a Guggenheim fellow; Pahlavi University in Iran; and at the Laboratoire de Neurobiologie, École Normale Supérieure, Paris. In addition, he was invited to lecture at more than 20 U.S. medical schools. Koelle was a member of many societies of pharmacology and toxicology in the United States and abroad. He was awarded honorary degrees from the University of Zürich and the College of Pharmacy and Science in Philadelphia and was elected to the National Academy of

Sciences in 1972. In 1989 he became emeritus, received the Torald Sallman Award for Lifetime Achievement, and a lectureship was established in his name by the Mid-Atlantic Pharmacological Society.

His interests were not limited to science; he was active in the Shakespeare Society of Philadelphia and was a Master Beech Smith in the Sons of the Copper Beeches, a branch of the Baker Street Irregulars of New York, an unusual organization that met to consider inconsistencies in Sir Arthur Conan Doyle's hero, Sherlock Holmes. Drawing on his professional expertise, he wrote an article, "The Poisons of the Canon," for the society (*Leaves from the Copper Beeches,* pp. 91-96. Narberth, Pa.: Livingston Publishing Co., 1959).

George B. Koelle was a heavy smoker, and eventually it took its toll. He was mourned by his family, his university colleagues, and a multitude for whom he was a warm and extremely loyal friend.

SELECTED BIBLIOGRAPHY

1946

With A. Gilman. The relationship between cholinesterase inhibition and the pharmacological action of di-isopropyl fluorophosphate (DFP). *J. Pharmacol. Exp. Ther.* 87:421-434.

With A. Gilman. The chronic toxicity of di-isopropyl fluorophosphate (DFP) in dogs, monkeys and rats. *J. Pharmacol. Exp. Ther.* 87:435-448.

With J. H. Comroe, J. Todd, G. D. Gammon, I. H. Leopold, O. Bodansky, and A. Gilman. The effect of di-isopropyl fluorophosphate upon patients with myasthenia gravis. *Am. J. Med. Sci.* 212:641-651.

1949

With J. S. Friedenwald. A histochemical method for localizing cholinesterase activity. *Proc. Soc. Exp. Biol. Med.* 70:617-622.

1950

With J. S. Friedenwald. The histochemical localization of cholinesterase in ocular tissues. *Am. J. Ophthalmol.* 33:253-256.

The histochemical differentiation of types of cholinesterases and their localizations in tissues of the cat. *J. Pharmacol. Exp. Ther.* 100:158-179

With E. S. Koelle and J. S. Friedenwald. The effect of inhibition of specific and non-specific cholinesterase on the motility of the isolated ileum. *J. Pharmacol. Exp. Ther.* 100:180-191.

1951

The elimination of enzymatic diffusion artifacts in the histochemical localization of cholinesterases, and a survey of their cellular distributions. *J. Pharmacol. Exp. Ther.* 103:153-171.

1952

With W. J. Angenent. The destruction of epinephrine by the DOPA-oxidase system of ocular tissue. *Science* 116:543-544.

1953

With K. Kamijo and R. B. Hiatt. Congenital megacolon. A comparison of the spastic and hypertrophied segments with respect to cholinesterase activities and sensitivities to acetylcholine, DFP and barium ion. *Gastroenterology* 24:273-285.

1955

With W. B. Shelley and S. B. Cohen. Histochemical demonstration of monoamine oxidase in human skin. *J. Invest. Dermatol.* 24:561-565.

1959

With W. A. Koelle. The localization of external or functional acetylcholinesterase at the synapse of autonomic ganglia. *J. Pharmacol. Exp. Ther.* 126:1-8.

1965

With C. Foroglou-Kerameos. Electron microscopic localization of cholinesterases in a sympathetic ganglion by a gold-thioacetic method. *Life Sci.* 4:417-424.

With B. Csillik. The histochemistry of the adrenergic and the cholinergic autonomic innervation apparatus as represented by the rat iris. *Acta Histochem.* 22:360-363.

1967

With R. Davis. Electron microscopic localization of acetyl cholinesterase and non-specific cholinesterase at the neuromuscular junction by the gold thiocholine and gold-thioacetic methods. *J. Cell. Biol.* 24:157-171.

1976

With W. A. Koelle and E. G. Smyrl. Effects of persistent selective suppression of ganglionic butyrylcholinesterase on steady state and regenerating levels of acetylcholinesterase: Implications regarding function of butyrylcholinesterase and regulation of protein synthesis. *Proc. Natl. Acad. Sci. U. S. A.* 73:2936-2938.

1984

With E. Uchida. Histochemical investigation of criteria for the distinction between monoamine oxidase A and B in various species. *J. Histochem. Cytochem.* 32:667-673.

1985

With U. J. Sanville and S. J. Wall. Glycyl-L-glutamine, a precursor, and glycyl-L-glutamic acid, a neurotropic factor for maintenance of acetylcholinesterase and butyrylcholinesterase in the preganglionically denervated superior cervical ganglion of the cat. *Proc. Natl. Acad. Sci. U. S. A.* 82:5213-5217.

1990

With M. S. Han. Effects of glycyl-glutamine and methylprednisolone on the maintenance of acetylcholinesterase of transected rat sciatic nerves. *Proc. Natl. Acad. Sci. U. S. A.* 87:9495-9497.