Postprint: Virology Research by Renowned Chinese Pediatric Expert Professor Zhong Shifan

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Abstract

Zhong Shifan (1901-1987), a native of Xiamen, Fujian, was a pioneer of modern clinical pediatrics in China and also an expert in virology. This article primarily introduces his role and influence on the development of virology in China.

Full Text

Preamble

Abstract: Zhong Shifan (1901–1987), a native of Xiamen, Fujian Province, was a pioneer in modern clinical pediatrics in China and an expert in virology. This paper primarily introduces his role and influence in the development of virology in China.

Keywords: Zhong Shifan; Virology; Pediatrics; Peking Union Medical College

Introduction

After graduating from Peking Union Medical College in 1930, Zhong Shifan worked successively at the college itself, Nanjing Central Hospital, Changsha Central Hospital, Guiyang Central Hospital, Guangzhou Central Hospital, Lingnan University Medical College, Pok Oi Hospital, Yau Chi Hospital, and Zhongshan Medical College. He devoted his entire life to pediatric clinical practice and medical education, establishing himself as a renowned pediatric clinician in China. Simultaneously, he founded a clinical virology laboratory to conduct virus research, making him a distinguished virologist as well. This article focuses specifically on his contributions to virology.

1. Biography of Professor Zhong Shifan

Born on May 2, 1901, into an impoverished farming family in Xiamen, Fujian, Zhong Shifan was able to pursue his education only through the financial

support of his fifth uncle, Zhong Guangwen, who dealt in traditional Chinese medicine. Physically frail as a child, Zhong followed his uncle' s advice to study medicine. From 1922 to 1930, he attended Peking Union Medical College, earning his Doctor of Medicine degree from the State University of New York. Upon graduation in July 1930, he remained at Peking Union Medical College Hospital as a pediatrician until 1935. In August 1934, he married Liao Yueqin, a fellow Fujian native and graduate of the nursing program at Peking Union Medical College. They later had two children: their son Zhong Nanshan and daughter Zhong Qianjun.

In September 1938, Zhong served as Chief of Pediatrics and Deputy Chief of Internal Medicine at the Changsha Temporary Central Hospital, while also holding a professorship in pediatrics at Xiangya Medical College. From September 1938 to July 1944, he was Director of Guiyang Central Hospital, concurrently serving as Professor of Pediatrics and Deputy Chief of Internal Medicine. In November 1945, he won a government scholarship to study in the United States for one year. After completing his studies, he returned to China in July 1946 and moved with Guangzhou Central Hospital from Guiyang to Guangzhou, assuming the roles of hospital director, Chief of Pediatrics, Professor of Pediatrics at Lingnan University Medical College, and Chief of Pediatrics at Yau Chi Hospital.

In 1947, the Nationalist government awarded Zhong Shifan the "Meritorious Service to the Nation" certificate and medal in recognition of his extraordinary efforts in maintaining the integrity of Guiyang Central Hospital during the War of Resistance Against Japanese Aggression. In 1949, he received a stipend from the World Health Organization and was appointed as a WHO consultant. Following the liberation of Guangzhou in 1949, the Central Hospital was placed under military control. Zhong continued working there for a period before stepping down from administrative duties, retaining only his positions as Professor of Pediatrics at Lingnan University Medical College, Chief of Pediatrics at Pok Oi Hospital, and Consultant for Pediatrics at Yau Chi Hospital. Beginning in May 1951, he served as a pediatric consultant at Guangzhou Workers' Hospital. In May 1952, he became a member of the provincial and municipal epidemic prevention committee in Dongguan, Guangdong, helping to prepare for anti-biological warfare efforts. Proficient in both English and German, Zhong served as a member of the Chinese Medical Association' s Pediatric Society for seven consecutive terms and as Director of the Guangdong Branch of the Chinese Medical Association' s Pediatric Society for seven terms. He also served on the editorial board of the *Chinese Journal of Pediatrics* and as a member of the Fourth Guangdong Provincial Committee of the Chinese People' s Political Consultative Conference. Zhong dedicated 55 years of continuous service to his profession, only retiring on August 1, 1985, at the age of 85 due to illness.

2. Contributions to Virology and Academic Characteristics

A native of Fujian deeply influenced by the core culture of South China, Zhong Shifan received a traditional Chinese education in his youth before pursuing

modern scientific training at China' s most prestigious medical institution, Peking Union Medical College. His academic characteristics can be summarized as follows: pragmatic, rigorous, resilient, inclusive, adept at inheriting tradition, courageous in innovation, and emphasizing both fundamental skills and clinical thinking ability.

2.1 Contributions to Virology Research

Throughout his lifelong dedication to pediatrics, Zhong Shifan was simultaneously a virologist. His qualities of perseverance, relentless pursuit, ability to inherit tradition, and courage to innovate were particularly evident in his virology research.

Even as a student at Peking Union Medical College, he developed a keen interest in pathogenic microbiology. After graduation, while serving as a resident physician at Peking Union Medical College Hospital, he conducted research on rapid typing and identification of pneumococcus. He discovered that when pneumococcus was cultured on agar plates containing specific antipneumococcal antiserum, a precipitation ring formed around colonies of the same serotype, indicating inhibited bacterial growth. He recognized this as a specific antigen-antibody reaction. This method enhanced the specificity and reliability of pneumococcus identification, significantly improving experimental diagnostics while reducing identification time. It also provided a better means for treating pneumococcal infections (primarily pneumonia) with type-specific antiserum. Methodologically, this diagnostic technique represents what is now widely used in clinical diagnostics and experimental research as the immunodiffusion technique.

2.2 Pioneering Research in Viral Isolation Methods

Between 1945 and 1946, Zhong Shifan received a Rockefeller Fellowship to pursue advanced studies in the United States, where he conducted virology research at the Pediatric Research Institute of the University of Cincinnati College of Medicine. Virology was then a nascent science, and little was known about the biological characteristics of viruses. Zhong investigated the survival relationship between bacteria and viruses, discovering that bacteria could protect Western equine encephalomyelitis virus. This was the first observation that when bacteria and viruses were mixed together, bacterial proliferation through oxygen consumption protected the virus from oxygen inactivation. This finding earned the admiration of renowned American virologist A.B. Sabin (later inventor of the polio attenuated live vaccine and Nobel laureate), who considered it an important discovery. H.A. Howe, a virologist at Johns Hopkins University, also regarded this as a significant contribution. The paper was evaluated by A.A. Weech, Director of the Pediatric Research Institute at the University of Cincinnati, as an outstanding piece of work.

At that time, research on viral infectious diseases was in its infancy, with the greatest obstacle being the lack of effective methods for viral isolation. Viruses

causing human disease did not necessarily cause illness in laboratory animals. Some required extraordinary methods to induce infection in animal models. For example, isolating poliovirus required filtering infected material through microporous filters that blocked bacteria but allowed the much smaller viral pathogens to pass through, followed by inoculation into the spinal cords of susceptible monkeys to confirm pathogenicity. To establish a pathogen, the isolated virus had to be serially passaged in susceptible animals across generations, consistently producing the same disease and pathological changes. However, many suspected viral diseases could not be confirmed as viral infections using laboratory animals, as many viruses parasitize only humans or produce symptoms only in human infections, while infected animals remain asymptomatic. Moreover, using large animals such as monkeys, cats, dogs, rabbits, and ferrets for virus isolation required substantial financial and human resources, limiting such research to well-equipped laboratories and preventing widespread application in daily clinical diagnosis.

In the late 1930s, Japanese encephalitis virus (hereinafter referred to as JEV) was successfully isolated by intracerebral inoculation in mice, opening new avenues for the diagnosis and research of such viral diseases. Since breeding and raising mice was much easier and more cost-effective than using larger laboratory animals, experimental diagnosis of Japanese encephalitis could be widely applied in clinical practice. Research also revealed that newborn mice within a few days of birth could develop encephalitis and die from JEV inoculation via intraperitoneal or subcutaneous routes, not just intracerebral injection. However, after this neonatal period, only intracerebral inoculation could successfully infect mice. In late 1940, researchers isolated a new virus from the excretions of paralyzed pediatric patients after processing and inoculating it into suckling mice that had not yet been weaned. This virus was named Coxsackie virus, but mice beyond this age became insensitive to infection.

The phenomenon that JEV and Coxsackie virus propagation in mice was limited by the age of the animals inspired Zhong Shifan: if JEV were directly inoculated into mouse embryos, could it also grow and propagate? If so, could intrauterine inoculation in mice become a new experimental method for isolating viruses that could not be isolated using adult mice? In 1946, when Zhong Shifan became Chief of Pediatrics at Lingnan University, he began breeding mice at his home in Lingnan University' s Kangyuan. His son, Zhong Nanshan, served as his caretaker. Following the institutional reorganization in 1953 that established South China Medical College (the predecessor of Zhongshan Medical College), Zhong received support from college president Ke Lin to establish a laboratory on the top floor of the Medical College' s Red Building. Using mice for experiments, he developed techniques for inoculating JEV into fetal mice. Each pregnant mouse could be inoculated with a maximum of two fetal mice per session, with each fetus receiving 0.03 ml of inoculum. Even with such a small volume, the procedure involved some uncertainty regarding the inoculation site since it was performed without cesarean section. The inoculated fetal mice often died immediately or were disabled by the trauma. Five to six days after inoculation,

before the mother gave birth naturally, she was sacrificed and the fetuses were examined via cesarean section. All fetuses inoculated with JEV were dead, while those injected with saline as controls showed mixed survival.

The critical question was whether the fetal mice died from JEV propagation or simply from injection trauma. This could not be determined visually. The embryos had to be ground up to prepare a suspension, which was then inoculated intracerebrally into three-week-old mice. If the experimental animals developed disease and died within days, this proved the presence of virus in the inoculum. But how could one distinguish between residual virus from the original inoculation versus virus that had replicated in the fetal mice? This required detection using median lethal dose titration. Through step-by-step experimental refinement, Zhong confirmed that the amount of JEV in inoculated fetal mice was tens to hundreds of times greater than the dose used for inoculation, thereby validating his hypothesis: JEV replicated extensively in mouse embryos, theoretically supporting the use of mouse fetuses as experimental animals for virus isolation. In 1958, Zhong published his experimental results in a paper titled "Preliminary Study on Using Mice as Animals for Virus Isolation" in the annual report of Zhongshan Medical College, and later presented the findings at the 6th Annual Meeting of the Chinese Medical Association' s Pediatric Branch.

In 1959, Zhong Shifan recruited his first cohort of graduate students and guided them in continuing virology research. Under his mentorship, graduate student Shen Jieping and colleagues performed median lethal dose titrations separately on the heads and trunks of JEV-inoculated mouse embryos, demonstrating that entire embryonic tissues could effectively support JEV growth and replication. However, just as Zhong was planning to use mouse embryos to isolate pathogens from clinically suspected viral diseases, the Cultural Revolution began. The virology laboratory was shut down, personnel were sent to rural areas, and Zhong was forced to abandon his exploration of diagnostic methods for viral diseases—a profound regret. Nevertheless, he never relinquished this unfinished work. In the 1980s, despite being physically incapacitated by illness, Zhong even moved time-sensitive virology experiments into his home for observation.

After more than half a century of development, clinical virology has evolved into a vast discipline with numerous subfields. Yet Zhong Shifan' s early explorations in etiological diagnostic methods for viral diseases, like his clinical investigations into disease causes in pediatrics, fully demonstrated his rigorous scientific spirit and foresight.

3. Zhong Shifan' s Influence on Pediatrics in Lingnan

Before Zhong Shifan' s arrival at Lingnan University Medical College, the most prominent pediatric expert in South China was Liang Langhao at National Sun Yat-sen University. In 1946, at the invitation of Li Ting'an, an alumnus of Peking Union Medical College and Dean of Lingnan University Medical College, Zhong came to Guangzhou to serve as Director of Guangzhou Central Hospital and

Professor and Chief of Pediatrics at Lingnan University Medical College. This marked the beginning of five decades of dedicated work. In 1946, he initiated pediatric academic exchange activities, conducting three lectures annually with approximately a dozen participants each time—the genesis of pediatric academic exchange in Guangdong Province. In 1950, the Guangdong Provincial Branch of the Pediatric Society was established in Guangzhou, with Zhong serving as its first Director until 1985.

In 1953, following the merger of Lingnan University Medical College, National Sun Yat-sen University Medical College, and Guanghua Medical College to form Zhongshan Medical College, Zhong Shifan became Director of the Pediatrics Teaching and Research Section, overseeing all medical, educational, and research activities across Zhongshan Medical College' s affiliated hospitals. He emphasized fundamental skills training for students, stressed the importance of medical record writing, and chaired weekly discussions on difficult cases. He established a laboratory within the pediatric ward, requiring all clinicians to be capable of performing common diagnostic tests themselves. For patients under their care, doctors were expected to thoroughly understand the three major routine tests and not blindly trust others' laboratory results while neglecting clinical judgment. For fatal cases, he required attending physicians to pursue autopsies whenever possible. In the later period of the Cultural Revolution, he compiled his lifetime of learning into the book *Differential Diagnosis of Pediatric Diseases*, enabling pediatricians to quickly identify relevant diseases and differential diagnoses based on clinical symptoms and signs without relying on complex specialized equipment, thereby allowing sick children to receive better and more timely treatment. The book was enthusiastically received by readers and reprinted multiple times. He transplanted the grand ward rounds and the "three basics, three strictness" approach from Peking Union Medical College to South China, establishing a systematic and standardized pediatric medical education and research system that trained numerous medical talents. After liberation, he supervised several graduate students, including Shen Jieping, Wu Ziliang, He Qinglan, and Liao Qingkui, who inherited Zhong' s academic philosophy and style, made outstanding contributions in their respective pediatric specialties, became authoritative experts, and served as standing committee members of the Chinese Medical Association' s Pediatric Society or directors of provincial pediatric societies. Under Zhong Shifan' s leadership, modern pediatrics grew and flourished in South China, becoming one of the three major centers of pediatrics nationwide and exerting profound influence on pediatrics across South China and the entire country.

The foregoing discussion represents only a small fraction of Zhong Shifan' s lifetime contributions. As an influential medical scientist and educator, Zhong Shifan merits further in-depth research. A scholar well-versed in both Chinese and Western learning, with keen insight and active thinking, his arduous explorations and pioneering work in virology laid a solid foundation for future generations. By absorbing the strengths of various schools of thought, he shaped the distinctive characteristics of Lingnan pediatrics—adept at learning, innovative,

emphasizing exchange, patient-centered, and committed to service quality—an influence that persists to this day.

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Additional colleagues who worked in pediatrics under Zhong Shifan's leadership, including Ye Bide, Guan Xiji, Zhu Changguo, Chen Shumei, and Li Wenyi, all possessed considerable capacity for academic research and talent cultivation, holding important positions in the National Pediatric Society.

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