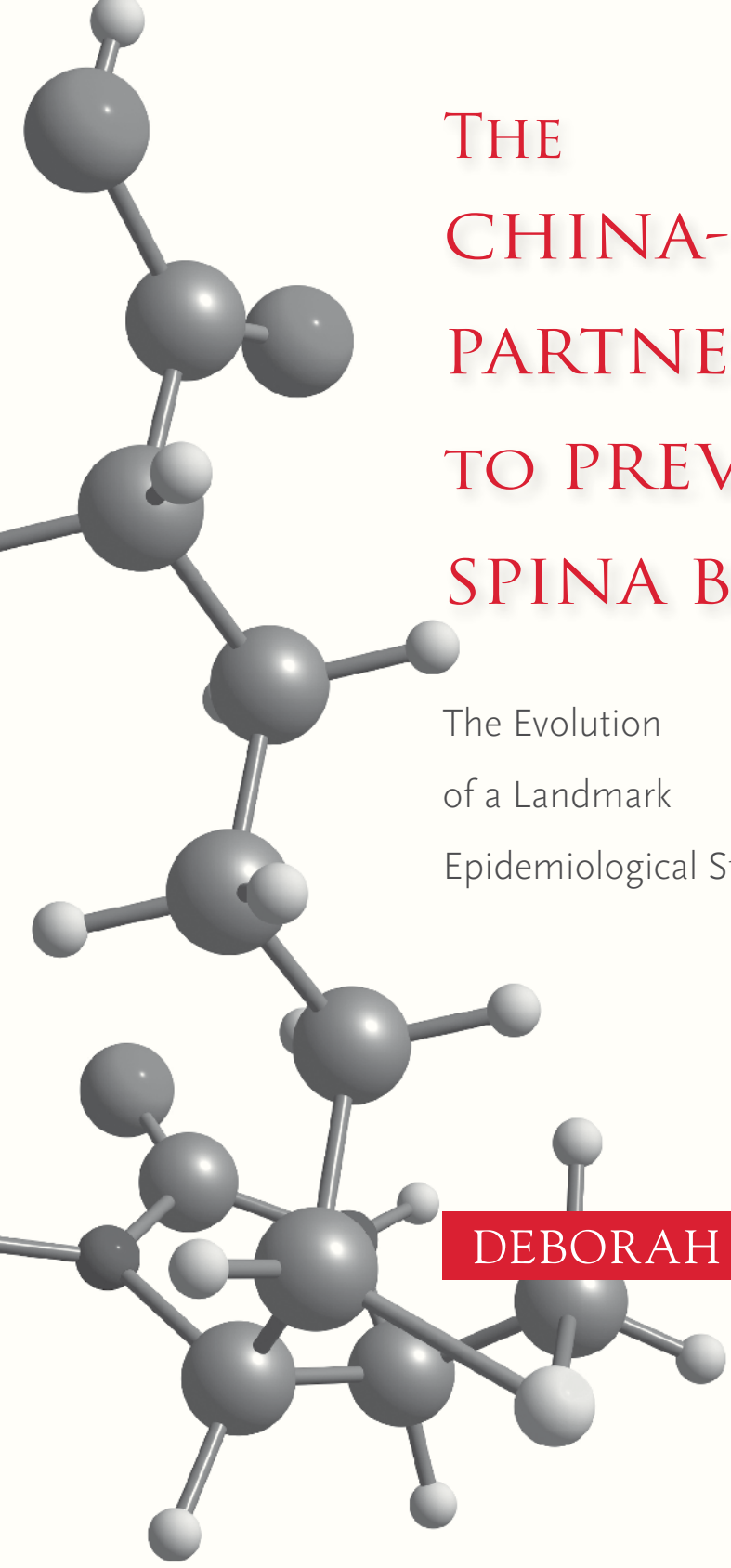

The China-US Partnership to Prevent Spina Bifida

The Evolution of a Landmark Epidemiological Study

Deborah Kowal

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To my husband, Rick Goodman, and the legions

who safeguard the public's health in every land

To my brother, Garry Kowal, and the many families

that experience the challenges of a birth defect

Contents

Acknowledgments

The limited space in which these acknowledgments appear in no way reflects the unlimited generosity of those who agreed to be interviewed and to share expertise and materials.

Li Zhu, Robert J. Berry, Godfrey Oakley, and J. David Erickson spent hours being interviewed and days responding to follow-up questions. These key leaders of the Project shared not only the things that went right but also the things that went wrong. They believe that the lessons they and their colleagues learned could help other researchers faced with the practical responsibilities of designing studies, juggling administrative challenges, standardizing data collection, training and managing field-workers, and working across international borders and cultures. They additionally read through early drafts of the manuscript, offering valuable corrections and additions.

Their colleagues, current and former, from the US Centers for Disease Control and Prevention cleared their calendars, patiently giving answers about the science and dusting off reminiscences of their personal stories from this long study. Brian McCarthy shared colorful tales and poignant anecdotes. Jacqueline Gindler, busy raising three daughters, squeezed her interviews into several small pockets of her precious personal time. Cynthia Moore described the hours invested in poring over thousands of photographs taken for surveillance of birth defects. Elaine Gunter explained the details of her work on outdated equipment in the chilled Beijing laboratory. All of them lauded the commitment, hard work, and intelligence of the Chinese colleagues with whom they worked.

Joseph Mulinare played a pivotal support role back in Atlanta, as did Irene Yen on-site in Beijing. Both were generous in expressing their admiration of their colleagues in carrying a good share of the workload for the Project. Robert Delaney and Anthony Fowler, in charge of the many

details for administrative and financial support, related their gratitude for being given a chance to be a part of the complex and innovative activities. And I feel fortunate to have spent a quiet couple of hours with the late Stephen Thacker. An advocate for people with spina bifida and their families, Cathy Hartnett described how she rallied political support for dedicating federal funds to the Project; these many years later she continued to sound like an enthusiastic lobbyist for the cause. Gail Henderson provided perspective based on her considerable experience with China's health care structure, beginning well before the start of the Project.

In China, that nation's godmother of perinatal health, Yan Renying, and her colleague Qu Chuanyan stepped away from their clinical duties to remember how the Shunyi County parents suffered too many miscarriages and stillbirths, which led to this collaborative effort for finding a way to prevent some of those losses in other families. The lead administrators at the former Beijing Medical University (BMU), Peng Ruicong and Wang Debing, conveyed their personal as well as professional commitment to preventing neural tube defects. Several researchers based in the Project office at BMU added important details on their contributions, which spanned a decade and more: Li Song, Wang Hong, Zhao Ping, Hong Shi-Xin, Chen Xin, Ji Xiaocheng, and Zheng Junchi. Keeping the BMU office and staff running smoothly were Guan Yubei, Bi Li, and Lu Hongyu, each of whom were proud to have played a part.

Li Tianlin, who mentored the young Li Zhu in Gansu Province, and who had so much to teach others, talked about all he had learned from the experience and from the other epidemiologists on both sides of the ocean. Former students Zhu Huiping and Hao Ling described what they had learned through their active participation in the Project and what now, as professors, they teach their own students.

In the counties and cities serving as Project sites, local officials and healthcare supervisors proved to be thoughtful interviewees—[in alphabetical order] Chen Hua, Chen Xingya, Du Weiyan, Fan Baling, Fan Fusheng, Liu Xuehai, Mu Huiyuan, Pan Yujuan, Tong Qiaoling, Wang Zhiqiang, Xiong Zhiaoxia, Zhang Bolan, and Zhang Menglan—who spoke with enthusiasm and pride, remembering the many friends they made and have kept.

Given the nature of communication, especially across different languages and cultures, it is possible that some comments I have included

in this book may contain errors or may have been taken out of the interviewees' intended context. Most of the Chinese people who so generously agreed to be interviewed spoke to me through an interpreter. I apologize for any misunderstandings that may have arisen from the interpreted interviews. Any attributional errors, omissions, or misstatements are unintentional.

Liu JingJing served as both a congenial interpreter and a guide through the introductory formalities of interviews as well as the perils of the banquet table.

I also want to acknowledge the funding from the National Center for Maternal and Infant Health, Beijing, that helped make this work possible.

Several outside readers helped improve the manuscript, giving insightful comments. Penelope Prime brought considerable expertise about multiple aspects of China. She encouraged publication of this account, saying China scholars outside the field of public health could find it helpful and interesting. Kenneth Hindman, a clear thinker and writer, played both roles in his guidance. Kate Anderson sat with me one sunny summer afternoon, suggesting visual images I could create in word pictures. Paula Rouse identified areas where her interest flagged, keeping me from straying too far into verbal doldrums. Mary Ann Oakley, who lived through the Project vicariously, being married to Godfrey, gave me good advice on keeping the text relevant and dynamic. I thank Katie Baer for her mentorship over the years. I thank Kelly Cleland, Mary Sherman, and Christina Devuono for their careful reading and attention to wordsmithing. At Vanderbilt University Press, Joell Smith-Borne and Peg Duthie provided thorough and thoughtful editorial attention. Capping off my appreciation, I thank Michael Ames, director at Vanderbilt University Press, who advocated for publication and then deftly strengthened my manuscript, removing redundancies and diversions and challenging me to better capture the meat and the essence of the story and its lessons.

Preface

My brother was born with a hole in his heart. It was larger than a nickel, smaller than a quarter. Within the dimensions of a heart—a child's heart, at that—the rift was immense. Situated in the wall between the two largest chambers, called ventricles, the term for the defect is ventricular septal defect (VSD). A repair was inconceivable when my brother was born; the technology had not been developed. He survived with substantial limitations, and as other children romped and rode bicycles, his role was as a spectator. Other people's stories are different from that of my family's, but many of them experience the consequences of a birth defect. Some lose pregnancies early when a deformity renders a fetus unviable. Some mourn the loss of an infant. Others bring home a baby with an impairment, as my parents did. Some impairments cause a direct disability that stems from problems like weakness or malfunction or absence of a vital part of the anatomy. Other disabilities are indirect. They can be social, creating anxieties or separateness, affecting both the person with the birth defect as well as his or her loved ones. Yet others may arise from side effects of the "fixes" applied to a specific defect, such as the stroke-inducing blood clot formed on the rough scar tissue left decades earlier by my brother's heart surgery to close the hole.

What does make others' stories similar to that of my brother's lies in the roots of birth defects. Many of them begin early after fertilization, around the time of the mother's first missed period. Over the next several weeks, such a fragile time, developing organ systems are vulnerable. An exposure of some type, a toxin maybe, can disrupt development. So can an absence of a vital building block, such as a vitamin.

Through history, flaws in the neural tube forming the spinal cord and brain have been among the most common birth defects, appearing all over the globe and most heavily falling on the poor. The fates of infants born

with spina bifida or related neural tube defects (NTDs) varied, and still do, according to the severity of the impairment and the resources available to treat the impairments or manage the associated disabilities. Affluent nations such as the United States can marshal high-priced surgical, medical, and physical therapy to help infants with spina bifida survive and eventually lead productive lives as adults. In poorer nations, the lack of these therapeutic services doomed these infants to early death, although many did not even survive the nine months in their mothers' wombs.

In the late 1970s and early 1980s, families in China's Shunyi County were found to suffer a high risk of pregnancy loss and early infant death. An epidemiologic assessment revealed causes typically found throughout low-resource nations, but one stood out. One-third of the deaths were due to birth defects, primarily NTDs. The rate of NTDs in Shunyi County revealed an epidemic that likely reflected what was occurring in other parts of China. I was asked to help write the report on the Shunyi County assessment, and I worked with the Chinese epidemiologist Li Zhu while he was a visiting scientist at the US Centers for Disease Control in 1989.[1] In the report, one sentence hinted at what was to become a landmark study: "We are planning to conduct clinical trials on periconceptional nutrition to decrease the incidence of neural tube defects."[2] The term "periconceptional"—meaning "around [*peri*] the time the egg is fertilized [*conception*]"—refers to the month before conception through early in the pregnancy, when the embryo forms and develops.

The plan for a clinical trial led to the China-US Collaborative Project for Neural Tube Defect Prevention, a name that belies the drama and adventure the international team would encounter. The results of this China-US collaboration (also known simply as "the Project") were reported in articles in prestigious medical journals. But scientific articles cannot reveal the sociopolitical tensions, the lessons learned from mistakes and hurdles, or the repeated negotiations at all levels. Diplomacy generally eschews describing the challenges of working within the rules and expectations of each nation's respective institutions and governments or of guarding against adversarial officials who have the power and inclination to derail programs, policies, and treasuries. The uprisings get shunted to the news, and the background finagling for resources gets its hearing only in the back corridors of the workplace. As circumstances beyond their

control repeatedly unraveled their plans and preparations, the research team eventually prevailed, recruiting a quarter of a million women, and consequently a quarter of a million babies, to test whether a simple vitamin taken just before and after fertilization could save pregnancies and babies and stop a profound NTD epidemic in northern China.

This behind-the-scenes case study offers lessons for today's public health professional in managing global health projects, organizing communities, and collaborating on epidemiological studies or surveillance. Moreover, with the escalating cost of conducting research in Western nations, China as well as other developing countries offer more affordable opportunities. These nations, which confront many of the same public health challenges as we do in the United States, are eager to create partnerships with Western public health entities. Yet mutual advantages alone do not smooth the rocky terrain of merging different cultural and policy precepts.

Today it is estimated that the global rate of NTDs has decreased as much as 70 percent, thanks to nose-to-the-grindstone researchers, including the British, Hungarian, Chinese, and American epidemiologists mentioned in this account. There is evidence that some heart defects, including the VSD with which my brother was born, may be prevented by a woman taking folic acid beginning before the time of fertilization. My brother's heart condition was not prevented, but still, he was lucky. His VSD was sutured closed in his early adolescence. But I wonder. If medical science had advanced more rapidly, could his medical problems, too, have been prevented by a vitamin?

There are many lenses through which to view this case history, and I invite the reader to bring his or her particular lens to this text. My intention has been to view the issues, including the nonepidemiological (social, cultural, political, financial, etc.), through the lens of those who faced them. Trained and experienced as old-fashioned field epidemiologists, these shoe-leather researchers investigated health problems as they exist in peoples' lives, looking at what can be a complex interplay between behaviors and environment and social conditions. As James A. Trostle writes, "Society and culture are fixed in the very center of the epidemiologic categories of person, place, and time."[3] It seems reasonable to apply these categories broadly, beyond the evidence of investigations

and disease causation and patterns. The conditions revealed within person, place, and time can inform communication and education, community intervention, collaboration, and more. *Person*—who were these collaborators, and what were the actions that helped them work with others successfully, even if not always so smoothly? *Place*—how did the researchers work within the cultural and policy contexts of China and, at a remove, those of the United States, to gain acceptance, approval, and cooperation? *Time*—it is said that "timing is everything": when was timing an opportunity, when was it a barrier, and how did the research team influence timing in its favor?

I offer up examples from the China-US Collaborative Project, but intend them to represent simply that—examples of what can appear with the kaleidoscopic turn of person, place, and time. Every project will make its own turn of the kaleidoscope. Upon close inspection, even the seemingly immutable precepts of research ethics have required rethinking in applying the specifics: upon the fiftieth anniversary (2013) of the Helsinki Declaration for research involving human subjects, an eighth version of the policy was released[4] and critiqued,[5] having been revised yet again to meet the challenges of changing technologies and understandings.

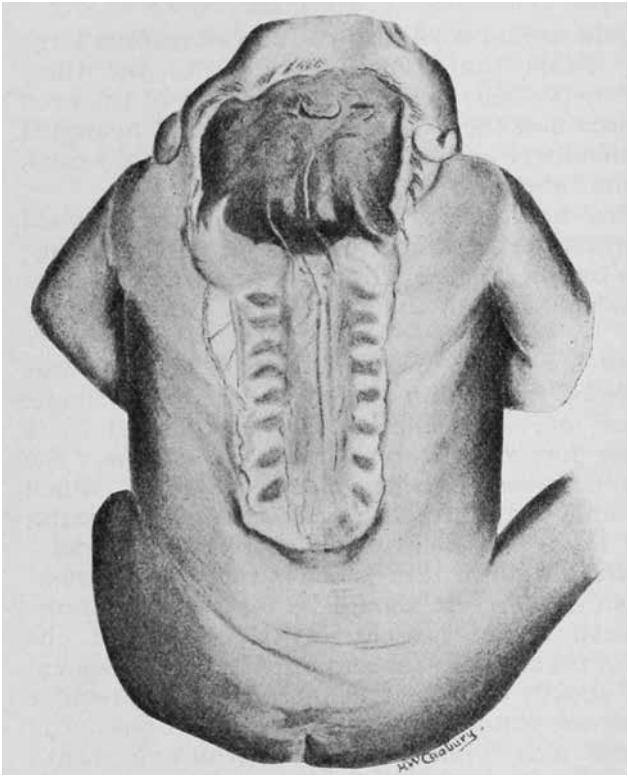
The China-US Partnership to Prevent Spina Bifida is the story of how American and Chinese epidemiologists together built critical evidence to show that folic acid supplementation can prevent NTDs. I interviewed more than forty researchers and administrators, in the United States at the Centers for Disease Control and Prevention (CDC) and in China at the former Beijing Medical University and the local communities' bureaus of health.[6] In getting to know these individuals, I found much to recommend in Elizabeth Etheridge's description of the CDC's officers in the Epidemic Intelligence Service. Her words could apply to other members of the Project team as well: she writes of the officers' "mix of scientific talent and missionary spirit which makes them believe, often correctly, that they can make the world a better place."[7]

Three decades ago, with China's doors newly opened to the West, US researchers walked through those doors, not really having a clear idea of what they might find. Early on, events at Tiananmen Square confirmed their fears of working with a totalitarian regime. In turn, Chinese researchers knew little about Americans. In their remembered

history, the Chinese people tended to suffer at the hands of foreigners, who inflicted brutality, massacres, and inhumane medical "experimentation" on them.

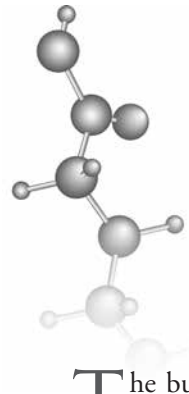
It would not have been surprising if suspicion had prevailed. Nevertheless, the researchers formed a genuine collaboration. What does genuine collaboration look like? William Foege, senior fellow in the Global Health Program of the Bill and Melinda Gates Foundation and former director of the CDC, writes that it is "the give-and-take of human beings who are so dedicated to a mission they will set aside the politics of organizations, share the difficulties, and invent solutions together."[8] In the rough-and-tumble of fieldwork, the Project team learned how to navigate personal, local, and institutional strife. They focused on building key infrastructure and key alliances; they built trust and team cohesion and motivations. The Project also benefited from the personalities of the colorful researchers, from the politics of the banquet table, and from the dogged labors of a small army of field-workers who needed training, monitoring, and cheerleading.

The Project's outcome, that most neural tube defects are folic-acid preventable, will be no surprise. But the process by which that outcome was reached . . . now there is the story, and I let the researchers tell their tale.



Craniorrhachischisis Totalis. There is a small amount of brain substance present and a few shreds of nervous tissue in the spinal grove. From William Michael Late Coplin's *Manual of Pathology: Including Bacteriology, the Technic of Postmortems, and Methods of Pathologic Research*, 4th ed. Philadelphia: P. Blakiston's Son & Co., 1905. Pg. 842. Courtesy of HathiTrust.

The politics aside, this should be done.
—Yan Renying



CHAPTER 1

Looking for Gold

The bus bumped along potholed roads. Near Beijing, the traffic had been heavy with masses of men and women riding bicycles, accompanied by the tinny bleat of bicycle bells. Outside the city limits, the traffic thinned markedly. Most of the passengers on the small bus glanced out the windows from time to time, but they were primarily interested in the strangers riding with them to Shunyi County, one of Beijing's suburbs. An observer would have quickly seen differences among the dozen or so passengers. In May 1983, before China began to rival the moneyed United States, the Chinese wore their poverty: skinny men and women cinched their belts around their waists to hold up threadbare clothes. In contrast, the Americans, even the modest visitors on the bus, wore the affluence of their country, then the world's shopping mall for consumer goods.

Godfrey Oakley, chief of the Birth Defects Branch at the US Centers for Disease Control (CDC), leaned forward as he spoke, his voice full of energy and volume, his speech laden with expletives, and his hands busy with gestures.[1] Next to him, the reserved Yan Renying, professor of obstetrics and director of clinical teaching at the eminent Beijing Medical University (BMU), sat with her back straight and her shoulders squared. As they shared the hard bus seat, both Oakley and Yan Renying tried to conform to what little they knew of each other's cultural etiquettes. As they talked, this mismatched couple embarked upon a journey that would grow beyond the two-hour bus ride from Beijing to Shunyi County—beyond the awkward conversation between two people who knew so little of each other but sensed that they would come to ask so much of each other.

What prompted this unlikely partnership between Oakley and Yan Renying? Babies. The two physicians had spent their careers trying to discover why so many babies were born with handicapping or killing

deformities. In China, birth defects were afflicting anywhere from 800,000 to 1.2 million infants annually.[2] In the United States, birth defects were an underlying or contributing cause of almost one-quarter of infant deaths when Oakley and Yan Renying together puzzled over their mutual concern.[3] One of the most common birth defects left babies' spines or brains incomplete. Doctors called the spinal deformity "spina bifida," and they called the brain deformity "anencephaly." Spina bifida and anencephaly were part of a constellation of congenital conditions called neural tube defects (NTDs). These big words meant little to mothers and fathers in China. A severely afflicted infant would be called *guai tai*—roughly translated as "monster baby"—a name that described how deformity greatly affected its appearance.[4]

All babies with anencephaly died. Children with spina bifida who survived their infancy endured a range of problems, from a poor gait to paralysis to early death. In the early 1980s, when Oakley and his team first traveled to China, spina bifida and other NTDs annually killed or paralyzed between three hundred thousand and four hundred thousand babies across the globe.[5] In China, about 100,000 infants were born with spina bifida or anencephaly each year.[6] In the United States, where the death rate from NTDs was one-tenth of that in China, fewer couples faced the traumatic loss of a fetus or newborn. However, of the US-born infants that survived "the first twenty-four hours of life with the most common form of NTD—spina bifida, 75 percent will have varying degrees of paralysis from permanent damage to the spinal cord and spinal nerves, and 20 percent will have moderate or severe mental retardation."[7] What happened during early childhood is suggested by a study from Dublin, Ireland, showing that of those NTD-affected infants born alive between 1976 and 1987, 60 percent died before age five. Of those who survived to age five, having undergone a mean of five surgeries since birth, more than half lived with severe disability and another quarter with less severe forms of disability.[8]

Oakley and Yan Renying found themselves on the same bus that day because they were attending the first European-Chinese Conference on Perinatal Surveillance. Perinatal surveillance is the set of tools for investigating health problems from pregnancy through the first month after birth—the time when the potential for life can be so frighteningly fragile.

The scientists attending the meeting were tracking not only the health problems but also the threats contributing to the problems.

For spina bifida and other NTDs, the threats were taking root at the beginning of pregnancy and perhaps even before then. Before many women know that they are pregnant, circumstances have already determined the outcome of their pregnancies. A substantial part of the difficulty in preventing spina bifida and other NTDs is that the neural tube develops within a month after conception. The multiplying cells are not yet a baby, not yet a fetus. At the point of discovery that the period is late, the growing cluster is an embryo. Even within this short span of time, the embryo has undergone a significant journey. When the father's sperm fertilized the mother's egg, the two together formed the zygote, which split into two cells, then four, then eight. This mass of doubling cells traveled through the mother's fallopian tubes for six days, and finally settled into her womb.

At this stage, the embryo resembles a flat disk, not a human, but it carries out the vital task of forming the cell layers that will develop into the major organs needed to sustain life. Soon the shape of the disk shifts from two dimensions to three. A primitive groove forms and deepens, and the ridges at the sides grow higher. With the deepening and the pushing up of tissue, the sides of the groove gradually connect together, starting high in what will become a neck and then extending upward and downward, eventually forming a long tube. Because this tube is made of nerve cells, it is called the neural tube.

By the end of the third week, the embryo's heart begins to beat. So small, the size of a grain of rice, the embryo seems in danger of being crushed by the weight of the mother's tissues. But that is not the risk. The risk lies in those invisible things to which the growing embryonic cells are exposed, or not exposed, during this period of exquisite sensitivity. By the end of the fourth week, the long neural tube closes to form the spinal cord and, at the top end of the tube, the immature brain. Occasionally, the neural tube does not close, and the fetus sustains any of an array of defects. These are aptly named neural tube defects. As with many objective medical terms, however, the name "neural tube defect" describes only the anatomical problem, not the many related physical, mental, social, emotional, and life-altering or life-denying problems associated with the condition.

When the top end of the neural tube fails to develop into a brain, the result is anencephaly. The Chinese say the afflicted infant, often lacking the frontal bones of the skull, resembles a frog in shape. Anencephaly usually ends in a stillbirth, although some infants are born alive, sometimes appearing beautifully normal and then dying within a few days because no brain is present to coordinate the life-sustaining functions of organs. When the tube opens somewhere below the level of the brain, the result is spina bifida. In "closed" forms of spina bifida, the vulnerable spinal cord may be covered by only a thin layer of meninges or dimpled skin instead of protective bony vertebrae. "Open" forms of spina bifida do not have even these paltry coverings, and the naked brain or spinal cord extrudes from the body. In rural areas of northern China at the time, the death rate for open spina bifida was 100 percent.[9]

One of the two main reasons infants with open spina bifida die is from infection entering the open lesion on the back. The other main reason they die is that almost all the infants develop hydrocephalus. In the hydrocephalus associated with spina bifida, cerebrospinal fluid—the fluid that cushions and protects the brain—cannot exit the brain cavity. The way out is blocked. If the blockage is not removed, fluid pressure builds, gradually squeezing the brain against the skull and causing brain cells to die, which leads to mental retardation and then death. Some forms of the less severe, closed spina bifida may cause no detectable problems until an event, an injury perhaps, discloses the vulnerable anatomy. Other forms leave the individual weak or paralyzed. If the lesion is high up on the spinal cord, the child usually requires a wheelchair. If the lesion is lower down on the spinal cord, the child may one day walk, but experience other problems with bladder and bowel control. In spina bifida *occulta*, an invisible lesion delays walking and creates gait disturbances and pain. Some individuals with the milder disabilities may live for years. At least, that has been the case in the United States, where medical technology keeps babies from dying of infection inside the open neural structures, where surgical techniques bring as much repair and wholeness as possible, and where rehabilitative services support the disabled. Most people with spina bifida need treatment for bladder and skin infections, to which they are more susceptible, and many need surgeries to close the opening that exposes neural tissues, to place and replace shunts for hydrocephalus, to

untether the spinal cord, and to manage problems with the hips, feet, or spine. These fixes are expensive. Beyond these treatment costs lie expenses for braces and wheelchairs, for catheters inserted as often as six times a day to empty the bladder, for diapers and bowel management programs along with adaptive bathroom equipment, and for the rigid routine to maintain skin integrity. Beyond the cost in dollars is an emotional toll on both the individuals affected by spina bifida and their parents; they are sometimes depressed, often feeling isolated, and always working hard to get through a day.

Medical advances and rehabilitative services, however, were not available in China in the late twentieth century (and are not available today, three decades later, for many Chinese families). The nation was not rich enough, its generally available medical technology not advanced enough, and its resource-poor families not supported enough to care for such disabled babies and children. The parents, frightened and heartbroken, did not have the means to prevent the dangers of infection or overcome the physical impairments. And being poor, they lived in enclaves with no health providers trained in the complex medical needs of severely affected infants and children. When Oakley visited China, the nation was still feeling the consequences of public health strategies initiated by Chairman Mao Zedong. Many academically credentialed physicians had been replaced by minimally trained "barefoot doctors." Although the focus on the most basic level of primary care reduced problems such as infectious diseases, the shift in how monies were allocated left the higher-level tertiary care services underfunded. The medical system was left unable to provide sufficient infrastructure in technology, medical education, research, and personnel to address chronic ailments and impairments.[10] With care and treatment falling desperately short, and with physiology precluding cure because nerve tissue cannot be repaired or replaced, something had to be done to *prevent* babies from developing NTDs in the first place—to find what stopped the neural tube from zipping shut during its delicate development.

During the 1960s and 1970s, researchers were beginning to gather a body of evidence about the causes of birth defects. They suspected that some NTDs might be due to genetic abnormalities, but it would be three decades before the human genome project would produce enough