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Unlocking Secrets of Inflammatory Bowel Disease: A Sino-American Partnership between Specialty Medical Societies

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IN a recent article in *Science & Diplomacy*, Daryl Copeland wrote, "Science diplomacy is relevant, effective, and potentially transformational."[1] Indeed, international cooperative science works if there is opportunity, supportive science, and a mutual commitment to overcome barriers. This paper describes how two specialty medical societies recognized an unprecedented opportunity to shed light on a scientific enigma through shared initiatives.

Opportunity

The People's Republic of China is undergoing a social transition as personal wealth increases. Chinese citizens, especially those in urban areas, are adopting lifestyles typical of Western populations, while those in rural areas retain more traditional habits. This dichotomy provides a special opportunity to study the impacts of Westernization on environmentally related diseases. We are particularly interested in how changes in diet and the intestinal microbiome might relate to an

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increased incidence of autoimmune disorders such as inflammatory bowel disease (IBD).

The annual incidence of IBD is rising in China following a pattern that occurred in the United States in the 1950s and in Japan several decades later.[2, 3] Recognizing this trend, the American Gastroenterological Association (AGA) created a China task force—co-chaired by the senior author, John I. Allen, and Chung Owyang of the University of Michigan—to explore research opportunities along with the Chinese Society of Gastroenterology (CSG). With help from Chinese-born American research leaders, the AGA and CSG signed a three-year memorandum of cooperation in September 2014. We now are developing Sino-American partnerships to enhance digestive science education and training, with a special focus on IBD. This paper describes the potential opportunities realized by national specialty medical societies in both countries and how these organizations might overcome cultural and logistical barriers to success.

Science

IBD is phenotypically characterized by chronic ulcerative colitis and Crohn's disease (CD). Both are chronic inflammatory conditions of the bowel that develop when an environmental trigger initiates an overly aggressive immune response in a genetically susceptible individual who has intestinal microbial dysbiosis.[4] Until recently, IBD was considered a disease of Caucasian, Northern European populations, and most etiologic theories were genetically based. In the 1970s, however, genetic predisposition was shown to be only part of the story by the rising incidence of IBD and other autoimmune diseases in East Asia (Japan, Korea) and India.[5, 6, 7] We suspected this trend was mediated through changes in the intestinal microbiome.

The human microbiome comprises approximately 10^{14} microbes, including bacteria, fungi, and viruses, and accounts for roughly one kilogram of the average adult's body weight.[8] Until the advent of affordable next-generation nucleotide sequencing, the microbiome was difficult to study because of the vast diversity of microbial composition. Between 2001 and 2011, however, the cost of sequencing one million nucleotide bases decreased from US$10,000 to US$0.10, so enormous community surveys such as MetaHIT and the Human Microbiome Project were conducted and yielded a composition and molecular profile of a healthy microbiome. Microbiome DNA (genome) and RNA (transcriptome) sequencing were combined with emerging bioinformatics and statistical tools, allowing researchers to correlate disease incidence with microbial dysbiosis. Now, researchers are in a unique position to investigate the contribution of microbial dysbiosis to human disease in a population undergoing rapid social and dietary changes, such as the Chinese. Changes in diet, especially adoption of a Western diet, affect the composition of the human microbiome and its interaction with the mucosal immune system.[9] This interaction can include disruptions that lead to diseases such as IBD.

The rising incidence of IBD in China is well documented. In particular, estimates of CD incidence from 1950 to the early 2000s were derived from hospital-based reports and thought to be 0.848 per 100,000 people.[10] New data from the Asia-Pacific Crohn's and Colitis Epidemiologic Study group[11] and three large regional studies in northern China (Daqing),[12] central China (Wuhan),[13] and southern China (Guangdong), respectively, report total IBD incidence from 0.58 to 3.44 per 100,000.[14] While still lower than the reported U.S. and Western European incidence (6.39 to 29.3 per 100,000 people), the rapid increase resembles that noted in the United States during the 1950s.[15]

Having noted the opportunity and scientific questions, along with the availability of necessary and affordable technologies, we are poised to shed further light on IBD's etiology. In seeking such an outcome, however, we must first identify possible barriers to success and ways our mutual medical societies can overcome these barriers.

China's Healthcare System: New Opportunities for Medical Diplomacy

The Chinese healthcare system has experienced profound changes over the past sixty-five years, going through four distinct phases: government owned and operated (1949–1983); market driven (1983–2002); modest health insurance coverage (2003–2008); and affordable basic healthcare for all (2009–present). China's government emphasizes healthcare as a social priority, so the most recent reform of 2009 included an initial US$120 billion stimulus.

Healthcare expenditures more than doubled in the five-year period between 2006 and 2011, from US$156 to US$357 billion (close to 5 percent of GDP), and are projected to reach US$1 trillion by 2020, fueled by overall economic expansion and personal income growth. An expanding middle class (474 million in 2012) is demanding access to advanced medical technology. To address strain in care delivery, a downside of rapid expansion, the Chinese government invested more than US$230 billion from 2009 to 2011 to expand care options and widen insurance coverage from 43 percent of the population in 2006 to 95 percent in 2011.

In 2012, the central government further expanded options by encouraging privatization, allowing physicians to develop practices independent of their public hospital commitments. This policy helped increase international investments in China in technology and therapeutics and provided a legal infrastructure for international partnerships.[16] Thanks in part to these partnerships, domestic Chinese companies now can test new products on a larger scale. For example, global pharmaceutical companies have shown vastly increased interest in the Chinese market, and the government's current five-year plan identifies biotechnology as one of seven strategically prioritized industries. In the gastrointestinal and IBD space, there has been an expanded use of newer pharmaceutical options, especially biologic agents, and medical devices such as high-definition endoscopes and

ancillary endoscopic products. To date, these expanded options tend to be focused in urban areas.

In 2013, the Chinese market for pharmaceuticals was almost US$87 billion, ranked third globally behind Japan (US$94 billion) and the United States (US$339 billion). Since 2006, thirteen of the top twenty pharmaceutical companies have established research and development centers in China, and several have announced major manufacturing investments. Over the fifteen-year period from 1995 to 2010, China's share of pharmaceutical industry output increased nearly sevenfold, to 18.3 percent. During this same period, the U.S. share remained stagnant at 26 percent. China's ten largest multinational pharmaceutical players now field a total sales force numbering more than twenty-five thousand, even as they have downsized sales forces in the United States and Europe. This reduction appears to be a response to the current situation where numerous branded medications are losing their patent protection and fewer new medications are being introduced.[17, 18, 19]

Endoscopy is an important technology for physicians treating IBD patients. China's endoscopic devices market is undergoing rapid growth, with an estimated value of US$376 million in 2014, up 27.4 percent from US$295 million in 2010. Increasing interest from private-sector investors has now made China the world's second largest source of venture capital for inventions involving medical technology. The broader medical device sector has taken notice. In April, 2015, Boston Scientific, one of the largest manufacturers of ancillary equipment used in endoscopy, entered into a strategic alliance with China's Frankenman Medical Equipment Company to improve access to the emerging Chinese device market. The partnership is expected to expand physician and patient access to minimally invasive endoscopic technologies in China, and sets a precedent for other companies, such as Pentax, Olympus, and Medtronic, seeking to enter the Chinese market.

Over the past decade, China has invested in clinical research, and its infrastructure provides the possibility of an international collaboration to study IBD. As demonstrated through previous Chinese large-scale epidemiologic efforts targeting the HIV and SARS viruses, healthcare infrastructure can facilitate meaningful data collection, analysis, and large-scale interventions.[20, 21]

From 2007 to 2012, China increased its biomedical research funding by 313 percent, from US$2 billion to US$8.4 billion.[22] As part of this expansion, the government established the National Clinical Research Centers program in 2012, whereby centers provide a network to spearhead large-scale clinical studies.[23] As an example, the National Clinical Research Center for Digestive Diseases, based at Changhai Hospital, recently launched an ambitious gastric-cancer-risk screening study with at least twenty thousand patients and more than fifty hospitals participating over the one-year study period. With this newfound research capability, efforts to characterize environmental exposures and interactions with

host factors in IBD might be feasible. China could likewise join an international consortium of health centers in clinical trials of novel therapeutic or surgical interventions, providing valuable contributions toward the creation of new clinical knowledge.

Remaining Barriers

Challenges to international collaboration remain, especially related to data sharing, ongoing disparities in healthcare access, institutional hurdles in developing physician-scientists, publication fraud, and the lack of China's infrastructural depth within specialty medical societies.

With respect to data sharing, despite the efforts outlined earlier, the Chinese framework is not well developed, resulting in significant deficits in data collection methods, organization, and storage. The lack of core infrastructure, such as readily available deep sequencing, hinders the potential for complex, large-scale, population-based analyses needed for the epidemiologic studies we are contemplating. In addition, a relative lack of cooperation among hospital systems and provinces prevents the pursuit of many types of cooperative trials common in the United States. Finally, clinical experience and knowledge about IBD remains isolated and insufficient for the emerging disease burden and for identifying appropriate patients for clinical research. Of note, the AGA is developing a "train the trainer" educational effort with the CSG to further IBD clinical care.

Another obstacle to international experimentation involves the absence of specific Chinese legal and policy structures for sharing biological samples and genetic information across borders. Issued in 2012 and slated to replace the 1998 interim measures, China's 2013 Draft Ordinance on Human Genetic Materials represents the country's latest effort to regulate the collection of human genetic material and the approval process for collaboration. The Draft Ordinance contains reasonable elements, including an ethics committee requirement and a clause for informed patient consent. However, the policies depend on individualized agreements and licenses rather than creating a collaborative space for research.

Although China is now second in the world in the number of biomedical research articles published—behind only the United States and having recently surpassed Japan, the United Kingdom, Germany, Italy, Canada, and Spain—several organizations have questioned whether research integrity has kept pace. In 2012, the National Academy of Sciences published a study of retractions accounting for nation of origin. The study authors purport that in medical journal articles in the PubMed database, China and India combined had a higher number of papers that were retracted due to plagiarism compared to the United States, despite the fact that U.S. researchers had a far higher total number of articles published. The study also found that China led the world in retractions due to duplication—that is, the

same papers being published in multiple journals. On retractions linked to fraud, China ranked fourth, behind the United States, Germany, and Japan.

Although scientific fraud is a global concern, there might be particular aspects that render China especially susceptible. A recent editorial in *The Lancet* proposed that a root cause of scientific fraud in China could be an evaluation system that relies heavily on research output.[24] Publication pressure hangs over Chinese investigators because promotions are closely connected with publications in journals with high impact factors. Conversely, punishment for being caught engaging in medical research misconduct is considered by some to be lenient.

Finally, other challenges center on physician training and professional organizations. Chinese physicians have a limited tradition of medicine as a profession and only recently have formed independent professional societies. Established in 1980, the CSG does not even have a formal office staff. Administrative duties fall to the personal staff of the CSG's current leaders or even to pharmaceutical or industry partners. By comparison, the AGA, founded in 1897, is the oldest medical society in the United States, with a membership exceeding 16,000 and a 106-person national office staff based in Bethesda, Maryland.

Overcoming Barriers: The Future

Despite the administrative challenges outlined here, the CSG is recognized by the Chinese government as the country's official gastroenterology society and is a natural partner for the AGA. Although lacking a formal staff, the CSG is governed by a ninety-five-member national committee representing each province and municipality directly under the Chinese central government. Every three to four years, general elections are held to select a leadership group consisting of a chair, designate chair, three vice chairs, a secretary, and a vice secretary. The current leadership team, serving from 2014 to 2016, is providing a multiyear platform for international cooperation. This is the case despite the lack of a CSG national office and the involvement of industry in planning, which can create additional layers of complexity and sometimes cause delays in program planning and execution. Altogether, the CSG, although a relatively new entity, represents a stable, constructive partner for future IBD-related collaborations in China.

The memorandum of cooperation signed in 2014 between the AGA and CSG represents a significant step to promote international collaboration, and a gesture that demonstrates how specialty medical societies might promote international science and diplomacy. This memorandum sets the groundwork for official collaborations, including Chinese participation in Digestive Disease Week, the largest international conference of physicians, researchers and academics in gastroenterology, and the CSG's annual conference in China.

Preliminary discussions between the CSG and AGA have focused on ways to overcome some of the already noted barriers to cooperation. On this count, the AGA

has initiated a plan to provide focused advice about manuscript preparation and submission, including education about fraud and auditing authorship responsibility. The AGA is also discussing ways to become a valued intermediary for young Chinese scientists seeking to connect with U.S.-based academic programs with the ultimate aim of improving China's clinical research infrastructure. A number of academic medical centers are establishing core research and clinical laboratory facilities in China, a development that should help Chinese institutions build infrastructure and better utilize resource-intensive technology and knowledge. We are investigating whether data sharing and handling of biological samples are best coordinated at the society (AGA) level or at the level of an individual academic medical center.

Historically, Sino-American collaboration in gastroenterology focused primarily on endoscopic technology. The AGA-CSG collaboration focuses more on expanding clinical expertise in IBD and gaining basic scientific insights that will translate into improved care in both China and Western countries. There are few other obvious opportunities comparable to what has emerged with the changing social and dietary habits in China to study complex clinical conditions. An ancient Chinese aphorism goes, "Stones from one mountain can be used to polish the jade of another". Collaborative efforts have the potential to strengthen the AGA and CSG alike, creating space for a shared effort among physicians and scientists seeking to improve human health. We hope this example will successfully demonstrate how medical societies can contribute to science and diplomacy. SD

Endnotes

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