Research Report

China's Hookworms*

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ABSTRACT *Huang zhong bing*, the "yellow puffy disease" caused by parasitic hookworms living in the human small intestine, was common throughout pre-liberation China. Hookworms contributed significantly to the nation's reputation as the sick man of Asia. However, even today China has the world's greatest number of cases of human hookworm infection. From estimates based on diagnostic surveys obtained during the early 1990s on over one million patients, there are approximately 194 million Chinese infected with hookworm. Most of these infections occur among the rural poor in the south and south-west. Even more recent data obtained in 1997 and 1998 indicate that hookworm remains a major public health problem in Hainan, Sichuan and Yunnan provinces. Populations of the elderly and middle-aged women are emerging as the groups now at greatest risk for acquiring hookworm. New evidence indicates that in addition to threatening health, hookworms also contribute significantly to economic under-development. Hookworms are a living reminder of China's often-forgotten rural southern poverty and a rapidly growing urban–rural inequality; they are an impediment to China's future economic growth.

With sustained annual economic growth rates of 7 to 8 per cent and the recent announcements that it will host the 2008 Olympics and join the World Trade Organization, it is difficult to remember a time when China was known as the "sick man of Asia." However, during the first-half of the 20th century, China was plagued with devastating poverty, disease and malnutrition, and was considered among the most unhealthful nations in the world. Significantly contributing to its "sick man" reputation was China's astonishing rates of endemic infections with parasitic worms or "helminths." The majority of the population of pre-Liberation China harboured in their intestines a menagerie of roundworms, whipworms, hookworms and tapeworms. It was so common to find individuals simultaneously infected with Ascaris roundworms, Necator hookworms and Trichuris whipworms, that Harold Brown, the late Professor of Parasitology at Columbia College of Physicians and Surgeons, referred to the three types of worms together as "The Unholy Trinity." Children were

* This article is dedicated to the life and work of Professor Frank F. Richards who retired from the Yale University faculty in 2001. In his position as Director of the MacArthur Center for Molecular Parasitology, Frank pioneered the establishment of numerous joint biomedical research projects between Chinese and American scientists, and helped to found the Morgan-Tan Institute of Molecular Genetics on the campus of Fudan University in Shanghai.

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typically the worst-off, because of their innate predisposition to acquiring large numbers of the Trinity. Some of the less fortunate harboured hundreds of these helminths. Occasionally the resulting mass of worms would entangle in a hideous, writhing, Medusa-like structure that killed the child by obstructing or perforating the intestine. More commonly, helminth-infected Chinese children experienced physical growth-stunting and intellectual and cognitive retardation. Observing children in Shanghai, W.A. Scott described,

> … scurvy-headed children, lice-ridden children, children with inflamed red eyes, children with bleeding gums, children with distended stomachs and spindly arms and legs, children with horrible sores on which flies feasted, children having a bowel movement which, after much strain, would eject only tapeworms.[1]

Throughout rural pre-Liberation China, hookworms wreaked particular devastation. Hookworms are one-centimetre-long helminth parasites that are equipped either with teeth or cutting plates that permit them to attach to the inner wall of the human small intestine. The hookworm tears at the small blood vessels contained within the intestinal wall and then ingests the released blood. By this means as few as ten hookworms can remove up to one half-teaspoon of blood per day. Individuals with moderate and heavy hookworm infections suffer from two major effects caused by the of chronic blood loss. First, blood loss results in iron-deficiency leading to deficits in intelligence, motivation and cognitive development, as well as anemia. Secondly, it results in the loss of protein leading to malnutrition that is similar to what is typically seen in kwashiorkor in which the upper and lower extremities would swell with edema fluid. When hookworm occurs during childhood, the deficits in iron and protein contribute to physical growth stunting. Infected individuals often acquired a sallow complexion so that chronic infection was known in China as *huang zhong bing* or "the yellow puffy disease," or *lan huang bing*, "the lazy yellow disease," referring to the extreme lassitude and fatigue that results from hookworm anemia.

In the 1940s, a Rockefeller Foundation-sponsored commission led by Dr K. Chang studied hookworm infection in rural Sichuan. Here they observed hookworm infection in almost 100 per cent of the population. The commission noted that both major species of hookworm, *Ancylostoma duodenale* and *Necator americanus*, were present. Chang's written account of a patient is not unusual:

> Hookworm Case No. 508 (Langchung Series). Li by name, male, a farmer aged 26, came to our field clinic on 19 August 1941, for treatment of Lan Hwang Ping (lazy yellow disease). The patient was very weak, extremely anemic, exceedingly pale, expressionless, the voice was low … he was exceedingly edematous all over the body; there was extreme edema of the lower extremities, his legs were very puffy and heavy, and he could not walk with ease. The scrotum and tip of the penis were also extremely edematous. In order to collect hookworm specimens, after having been

1. W.A. Scott, "China revisited by an old China hand," *Eastern Horizon*, Vol. 5, No. 6 (1966), pp. 34–40.

given carbon tetrachloride and magnesium sulphate he was asked to defecate into an earthen jar. One day after defecation he tried to stand up but was so weak that he fell. All of us were astonished and fortunately he recovered after a few minutes. Fecal examination showed … hookworm, 45,400 eggs per cc of feces. A total of 637 worms, of which 602 were *Ancylostoma duodenale* and 35 were *Necator americanus* were collected from the patient.[2]

The Rockefeller commission found that hookworm in Sichuan afflicted entire families who were connected to the farming and cultivation of certain crops such as corn and sweet potato. This is in contrast to the findings of an earlier China hookworm commission sent to Jiangsu and Guangdong in eastern and south-eastern China respectively, which attributed hookworm to the cultivation of mulberry trees used in sericulture for the silkworm industry.[3] In each province, however, both commissions linked transmission of hookworm infection to the ancient agricultural practice of using human faeces as "nightsoil" in order to fertilize crops. Hookworms living in human intestines deposit their eggs into the intestinal contents, so that the faeces of an infected patient may contain hundreds of thousands of hookworm eggs. The eggs develop and hatch when faeces containing them are deposited through defecation on soil that contains adequate moisture, warmth and shade. The soil and climate of south China's agriculturally rich provinces are perfectly suited for hookworm egg and larval development. Microscopic hookworm larvae that hatch from the eggs develop and moult before they are ready to infect another human within about a week following the deposition of faeces on the soil. Human transmission results when the larvae either actively penetrate the skin, usually through the feet and hands, or in some cases when the larvae are swallowed.

For centuries, hookworm plagued the poor rural areas of southern and south-western China either because of the practice of indiscriminate defecation or, more commonly, because Chinese farmers relied on human waste for fertilizer. Even Mao's economic reforms during the first Five-Year Plan following the 1949 Liberation or the Great Leap Forward in 1958 could not diminish the farmer's absolute dependence on nightsoil. This is not to say the policies of the People's Republic of China had no beneficial effect on reducing parasitic disease in China. During the Great Leap, hundreds of thousands of peasants were mobilized in order to combat schistosomiasis, a water-borne parasitic infection caused by the blood fluke *Schistosoma japonicum* and transmitted by tiny snails lining the irrigation canals and drainage basins of the Chang (Yangtze) River. To interrupt schistosomiasis transmission, an aggressive effort was launched to eliminate snails over a region around the Chang comprising

2. K. Chang *et al.*, *Studies on Hookworm Disease in Szechwan Province, West China*, American Journal of Hygiene Monograph Series, No. 19, pp. 1–152 (Baltimore: The Johns Hopkins Press, 1949).

3. W.W. Cort, J.B. Grant and N.R. Stoll, *Researches on Hookworm in China*, embodying the results of the work of the China Hookworm Commission, June 1923 to November 1924, parts 1–15, American Journal of Hygiene Monograph Series, No. 7 (Baltimore: The Johns Hopkins Press, 1926), pp. 1–398.

thousands of millions of square metres. This was often accomplished by the back-breaking task of burying snails in mounds of damp earth and dirt,[4] or even picking up snails individually with sticks, frequently in the southern heat and humidity of "China's furnace." In so doing, the number of cases of human schistosomiasis was substantially reduced from tens of millions to today's estimates of less than 750,000.[5] Mao's success against schistosomiasis during the Great Leap Forward prompted him to compose his now famous poem "Farewell to the God of the Plague," in which he celebrated victory over the snail. More than anyone, Mao must have been aware of how Katayama Fever, an incapacitating illness that results from acute schistosomiasis, thwarted his ambition to reunify China in 1950 when this infection devastated his PLA Third Field Army in Fujian and Zhejiang. Acute schistosomiasis may have been responsible for aborting a planned amphibious military assault on Taiwan. During the Cold War *Schistosoma japonicum* became known as "the fluke that saved Formosa."[6]

Similar heroic efforts were responsible for the near eradication of lymphatic filariasis (LF), a mosquito-transmitted helminth infection in south China. LF can result in a disfiguring condition known as elephantiasis in which the patient's scrotum or lower limbs become grotesquely distorted. China became the first Asian nation to control its LF problem by mandating the supplementation of its nation's dietary salt supply with an anti-parasitic drug during the 1980s. Ironically, the natural history and transmission of LF was first described in Fujian at the end of the 19th century.

Magnitude of China's Hookworm Problem

China's successes in controlling LF and achieving more than a ten-fold reduction in schistosomiasis during 50 years of CCP control since 1949 are considered monumental public health successes. However over this same period, the prevalence and intensity of human hookworm infection remained largely unchanged. The lack of progress in solving modern China's hookworm problem became starkly evident following a nationwide survey of human intestinal parasites. From 1988 to 1992 the Chinese Ministry of Health in association with provincial and national institutes of parasitic diseases, as well as local anti-epidemic field stations, conducted faecal examinations of 1,477,742 individuals living in 2,848 study sites in 726 counties.[7] A major goal of the faecal examina-

4. J.S. Horn, *Away with all Pests, an English Surgeon in People's China 1954–1969* (New York & London: Monthly Review Press, 1969), pp. 94–106.

5. P.J. Hotez *et al.*, "Emerging and reemerging helminthiases and the public health of China," *Emerging Infectious Diseases*, Vol. 3, No. 3 (1997), pp. 303–310.

6. E.E. Rice, *Mao's Way* (Berkeley: University of California Press, 1972), pp. 149–150.

7. Hotez *et al.*, "Emerging and reemerging helminthiases"; L.Q. Xu *et al.*, "Soil-transmitted helminthiases: nationwide survey in China," *Bulletin of the World Health Organization*, Vol. 73, No. 4 (1995), pp. 507–513; S.H. Yu *et al.*, "Special report, nationwide survey of human parasites in China," *Southeast Asian Journal of Tropical Medicine and Public Health*, Vol. 25, No. 1 (1994), pp. 4–10.

Table 1: **China's Helminth Infections Based on the Nation-wide Parasite Survey**

Helminth infection	*Estimated number of cases*
Ascariasis (large roundworm infection)	531 million
Trichuriasis (whipworm infection)	212 million
Hookworm infection (Necatoriasis & Ancylostomiasis)	194 million
Clonorchiasis (oriental liver fluke infection)	4 million
Fasciolopsiasis (intestinal fluke infection)	2 million
Taeniasis (pork and beef tapeworm infection)	1 million
Schistosomiasis (blood fluke infection)	1 million

Note:
Numbers derived from data obtained during China's nation-wide parasite survey of 1,477,742 individuals between 1988 and 1992.

tions was to detect the presence of helminth eggs, the signature of infection with the Unholy Trinity. The Chinese nation-wide survey became one of the largest medical studies ever conducted. It found that an impressive percentage of China's population is infected with helminths (Table 1). Approximately 17 per cent were shown to harbour hookworms, indicating that by 1992 there were an estimated 194 million cases of hookworm in China. Based on measured determinations of daily blood loss caused by individual hookworms, the overall yearly blood loss resulting from China's hookworm burden was equivalent to the amount of blood donated by more than 80 million individuals, or more than one million blood donors every week![8]

It came as little surprise that the nation-wide survey identified hookworm as a public health threat in the same agriculturally rich provinces along the Yangtze that were identified prior to the Liberation as hookworm problem sites in south and south-west China. The survey found that 40 per cent of Sichuan and 20 per cent of Jiangsu were infected with

8. Laboratory investigations conducted during the 1960s revealed that each Ancylostoma hookworm causes the daily blood loss of 0.2 ml (cc), while each Necator hookworm causes the loss of about 0.03 ml (cc) per day. Necator is the predominant Chinese hookworm south of the Yangtze River (e.g. Hainan, Yunnan and southern parts of Sichuan provinces), while Ancylostoma predominates further north (e.g. Anhui, and northern parts of Jiangsu and Sichuan provinces). The total blood loss resulting from hookworm infections is calculated on the basis of knowing the predominant species in a given regions and the average numbers of hookworms per individual, either measured directly or estimated on the basis of quantitative faecal egg counts. For instance in 1998, we found that Necator was the exclusive hookworm in the Hainan village of Xiulongkan (population of 792). It was determined that 60% of Xiulongkan was infected with Necator and that each of the infected villagers harboured a mean faecal hookworm egg count of 1,453 eggs per gram of faeces (N.S. Gandhi *et al.*, "Epidemiology of *Nectar americanus* hookworm infections in Xiulongkan village, Hainan province, China: high prevalence and intensity among middle-aged and elderly residents," *Journal of Parasitology*, No. 87 (2001), pp. 739–743). This corresponds to the presence of 39 hookworms in the average intestine of a Xiulongkan villager. With each hookworm causing 0.03 ml of blood loss per day, the total annual blood loss in the entire village is equivalent to 200 litres for a year.

hookworm.[9] Approximately one-quarter of the hookworm infections were moderate or heavy enough to result in clinically significant effects. The tropical South China Sea island province of Hainan exhibited the greatest hookworm prevalence, with approximately 60 per cent rates of infection. Hainan alone loses an estimated one million litres of blood annually from hookworm infections.

Hookworm among China's Elderly

In 1994 my laboratory began working with the national Institute of Parasitic Diseases of the Chinese Academy of Preventive Medicine in Shanghai in order to apply modern biotechnology to the study of China's hookworm problem.[10] Our collaboration focused both on laboratory investigations in Shanghai in order to work towards developing a new anti-hookworm vaccine,[11] as well as fieldwork conducted in 1997 and 1998 in south China's traditional hookworm belt in order to identify the human populations at greatest risk for acquiring infection.[12] It was surprising to find that the middle-aged and elderly now comprise the age

Table 2: **Prevalence of Human Hookworm Infection in Selected Provinces 1997–1998**

Province	*No. patients*	*Prevalence*	*Age group highest prevalence*
Anhui	488	33%	41–50 y.o.
Hainan	631	60%	> 40 y.o.
Jiangsu	876	12%	> 50 y.o.
Sichuan	520	67%	> 65 y.o.
Yunnan	766	37%	> 60 y.o.

9. Xu *et al.*, "Soil-transmitted helminthiases."

10. Hotez *et al.*, "Emerging and reemerging helminthiases"; P.J. Hotez, "Hookworm infection in China today," *Yale–China Review*, Vol. 3, No. 2 (1995), pp. 2–3.

11. P. Hotez *et al.*, "Experimental approaches to the development of recombinant hookworm vaccine," *Immunological Reviews*, No. 171 (1999), pp. 163–171; S Liu *et al.*, "Hookworm burden reductions in BALB/c mice vaccinated with Ancylostoma secreted protein 1 (ASP-1) from *Ancylostoma duodenale*, *A. caninum*, and *Necator americanus*," *Vaccine*, No. 18 (2000), pp. 1096–1102.

12. Gandhi *et al.*, "Epidemiology of *Necator americanus* hookworm infections"; Z. Lili *et al.*, "Epidemiology of human geohelminth infections (ascariasis, trichuriasis and necatoriasis) in Lushui and Puer counties, Yunnan province, China," *Southeast Asian Journal of Tropical Medicine and Public Health*, Vol. 31, No. 3 (2000), pp. 448–453; C.H. Liu *et al.*, "Epidemiology of human hookworm infections among adult villages in Hejiang and Santai counties, Sichuan province, China," *Acta Tropica*, No. 73 (1999), pp. 243–49; F.H. Sun *et al.*, "Epidemiology of human intestina nematode infections in Wujiang and Pizhou counties, Jiangsu province, China," *Southeast Asian Journal of Tropical Medicine and Public Health*, Vol. 29, No. 3 (1998), pp. 605–610; Y. Wang *et al.*, "Epidemiology of human ancylostomiasis among rural villages in Nanlin county (Zhongzhou village), Anhui province, China. Age-associated prevalence, intensity, and hookworm species identification," *Southeast Asian Journal of Tropical Medicine and Public Health*, Vol. 30, No. 4 (1999), pp. 692–97.

group with the highest rate of hookworm. In Hainan, for instance, the prevalence and intensity of hookworm rises in an almost linear manner as a function of age, so that individuals over the age of 60 years have the highest rates of infection (Table 2). We regularly encountered elderly individuals in Hainan with strikingly high rates of hookworm infection and clinical disease. The observation that the middle-aged and elderly populations over the age of 50 constituted the most infected population extended to every village examined in Anhui, Hainan, Jiangsu, Sichuan and Yunnan.

More detailed studies in Hainan revealed that middle-aged and elderly women acquired the heaviest hookworm infections.[13] In these Hainan villages almost all of the women over the age of 40 are infected with hookworm; these women suffer from the heaviest infections with the greatest numbers of worms. Both the prevalence as well as the intensity of hookworm infection exhibits a linear relationship with age, so that the peak proportion of infected individuals occurs in the eldest age categories. Together, age and gender account for 30 per cent of the variation in hookworm infection intensity, with age alone responsible for 27 per cent of this variation.[14] Wearing of shoes and other traditional barrier protections against skin-penetrating hookworm larvae in the soil did not decrease the risk of acquiring hookworm. The possible explanations for why hookworm targets female geriatric populations in south China are now under investigation. This will include determining whether susceptibility to hookworm occurs because of some unique relationship between the ageing human host and her hookworm parasite, or whether it occurs because of behaviour, occupational exposure or some other socio-economic basis.

The observation that hookworm is predominantly a disease among China's middle-aged and elderly has important implications for the nation's rapidly changing demographics. China, like much of the developing world, is anticipated to experience rapid expansion of its geriatric population. China's population is ageing rapidly. For example, it took over a century for France's elderly population to double from 7 to 14 per cent of its population, whereas China is expected to double the equivalent population within 25 years.[15] By the year 2020 it is estimated that 11 per cent of China's population will be over the age of 65.[16] The rapid increase in the number of elderly in the hookworm-endemic regions of Anhui, Hainan, Sichuan, Yunnan and elsewhere in south China may create a new population susceptible to hookworm. Over the next decade hookworms could flourish in the intestines of this new greying Chinese population.

13. Gandhi *et al.*, "Epidemiology of *Necator americanus* hookworm infections"; J. Bethony *et al.*, "Emerging patterns of hookworm infection: influence of aging on the intensity of Necator infection in Hainan province, People's Republic of China," *Clinical Infectious Diseases* (forthcoming).

14. Bethony *et al.*, "Emerging patterns in hookworm infection."

15. P.G. Peterson, "A graying world," *Harvard International Review*, Vol. 23, No. 3 (2001), pp. 66–70.

16. The World Bank, *Financing Health Care*, China 2020 Series (Washington, DC: The World Bank, 1997), p. 4.

Hookworm and Poverty

Like many tropical infectious diseases, hookworm is linked to poverty and economic underdevelopment. Probably more than any other single factor, including sanitation, administering anti-parasitic drugs, wearing barrier protection and health education, economic development has done the most to control or eradicate hookworm among the industrialized nations. While it is widely assumed that Rockefeller Foundation-sponsored interventions were responsible for eradicating hookworm, malaria and yellow fever from the southern United States during the early 20th century, almost certainly it was the overall economic development of the new South that finally chased away the hookworms and the disease-carrying mosquitoes. Similar economic reforms that transformed South Korea during the 1960s and 1970s helped to eradicate the Unholy Trinity from this region.

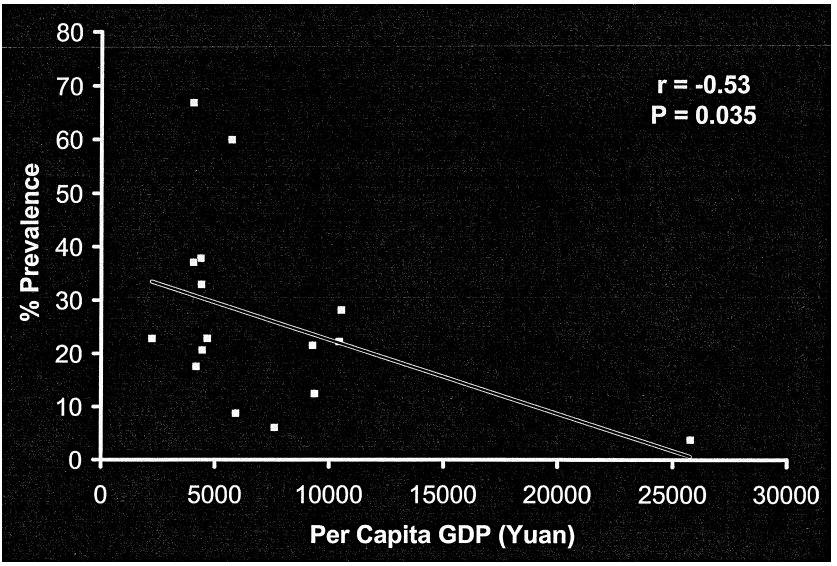
Because the decade of the 1990s has been one of the most productive periods in China's modern economic history, it was of interest to determine how China's transition to a modern economy affected its hookworm problem. Using the World Bank's international poverty standard of $1.00 per day, some estimates indicate that the number of rural poor in China has decreased from 260 million in 1990 to 106 million in 1998, or from one-third to less than one-tenth of the population.[17] Most of the decrease in hookworm among China's rural poor has taken place either in the eastern provinces or in the cities along its Pacific rim. Cities such as Shanghai, Hangzhou and Fuzhou have experienced unprecedented prosperity and annual economic growth rates of 7 to 8 per cent. As a result, they rival Hong Kong as new centres of trade and commerce in Asia. A World Bank analysis suggests that rural poverty will continue to diminish along China's coast and eastern provinces, leaving much of the residual poverty to China's mountainous regions and the provinces of West China. The depth of poverty in the western provinces is now more severe than the rest of China.[18]

The eastern province of Jiangsu exemplifies how rural poverty reduction translates into reduced endemic hookworm. Since the mid-1990s, Jiangsu has benefited from spillover economic development that began in nearby Shanghai. In 1997, hookworm was found in 12.5 per cent of a village population compared to almost double that rate almost ten years previously (Table 2). In contrast, the prevalence (and intensity) rates in the traditionally poor hookworm-endemic regions of west China, such as in Sichuan and Yunnan, remained the same in 1997 and 1998, or even increased, since hookworm was examined there during the nation-wide survey. Hainan also still suffers from high rates of endemic hookworm. Despite its extreme poverty, hookworm is not endemic in the north-west (Qinghai, Xinjiang and Tibet) because its cold and dry conditions are unfavourable for parasite transmission.

17. The World Bank, *China, Overcoming Rural Poverty*, a World Bank Country Study (Washington, DC: The World Bank, 2001), pp. 1–14.

18. *Ibid.*; J. Levin, "China's divisive development," *Harvard International Review*, Vol. 23, No. 3 (2001), pp. 40–42.

Figure 1: **Hookworm Prevalence in Endemic Regions of China as Function of Per Capita GDP**



Note:
Hookworm prevalence figures were obtained from the nation-wide parasite survey completed in 1992, except for updated figures for Sichuan, Yunnan, Jiangsu and Anhui provinces. Per capita GDP data were obtained from Donald S. Benwick, *The State of China Atlas* (Harmondsworth: Penguin Reference, 1999), pp. 94–101.

Figure 1 shows that hookworm infection is linked to the economic development of the region. The poorest provinces, as measured by per capita GDP, have the highest prevalence rates of hookworm. Although the relationship between hookworm and poverty is solid and substantive, it is not yet possible to ascertain whether poverty creates conditions that are favourable for hookworm transmission, as it almost certainly does, or whether hookworm itself also contributes to low human economic productivity. Without sufficient data it is not yet possible to prove that endemic hookworm not only functions as a marker for poverty, but that it also directly drags down economic growth. However, a new analysis that endemic malaria was responsible for a five-fold reduction in economic growth in Italy and Spain prior to the Second World War[19] suggests that similar trends might some day be identified for hookworm.

In China, hookworm is now a showcase for a growing divide between the newer wealthy urban regions in the east and poor rural areas in the south-west. During the last decade China's urban-based development schemes have favoured eastern urban industry and foreign investment over the promotion of western agriculture.[20] Hookworm can therefore be

19. J.L. Gallup and J.D. Sachs, "The economic burden of malaria," *American Journal of Tropical Medicine and Hygiene*, Vol. 64, Nos. 1, 2 (2001), pp. 85–96.
20. Levin, "China's divisive development."

expected to remain endemic among the estimated 21 million rural poor who live in the western provinces of Sichuan, Yunnan, Guizhou and Guangxi. These include ethnic minority groups that may account for large populations of the absolute poor who live in the region. Hookworm will also continue to occur among the residual 5.7 and 3.2 million who live in hookworm-endemic regions of central (including Hainan) and south-eastern China, respectively.[21] Together these 29 million rural poor represent the Chinese population that will remain at the very highest risk from hookworm infection. Over the next decade, the extent of China's hookworm problem is anticipated to reflect a balance between the rapidly diminishing numbers of China's rural poor in the east, high rates of rural poverty in the west, and an expanding geriatric population in both regions. Greying populations living in Sichuan, Yunnan, Guizhou, Guangxi and Hainan will suffer the most from endemic hookworm.

New Solutions for China's Hookworm Problem

The Chinese government has made impressive strides since the Liberation in leading efforts to control or eradicate schistosomiasis and LF, but there is still only incremental progress in the control of human hookworm infection in the south and south-west. The unusually intimate relationship between hookworm and rural poverty in these regions has thwarted all government control efforts short of aggressive economic development. Even sanitation and use of anti-parasitic drugs have largely failed, presumably because the parasite has adapted so well to humans living under the unique conditions created by rural tropical and subtropical poverty, including the continued reliance on human nightsoil or the practice of indiscriminate defecation.

One solution to China's hookworm problem might arise through new applications of biotechnology. An example of the promise of biotechnology is a new joint effort between American and Chinese scientists to genetically engineer a recombinant anti-hookworm vaccine.[22] Development of an anti-hookworm vaccine that prevents establishment of the parasite in its human host would be a major breakthrough for hookworm control. Vaccination might be the most effective near-term control measure until economic development in China's rural south-west catches up with the urban industrialized development in the east. A hookworm vaccine could also become an important instrument to help reduce poverty in the west. Because the rural poor living in west China also suffer from high rates of many other infectious diseases including measles,[23] a hookworm vaccine might be used in combination with other low-cost public health interventions designed to reduce poverty. These include the Expanded Programme on Immunization (EPI), hepatitis B immunization, maternal immunization against tetanus, oral rehydration,

21. The World Bank, *China, Overcoming Rural Poverty*.

22. Hotez *et al.*, "Experimental approaches to the development of recombinant hookworm vaccine"; Liu *et al.*, "Hookworm burden reductions in BALB/c mice."

23. The World Bank, *Financing Health Care*, China 2020 Series (Washington, DC: The World Bank, 1997), p. 29.

and iodized salt, vitamin A and iron supplements.[24] The World Bank lists hookworm along with eleven other major conditions, such as tuberculosis, diarrhoeal disease, EPI-preventable diseases, lower respiratory infections, and nutritional conditions that are identified almost entirely with poverty.[25] Together, these conditions accounted for 23 per cent of China's disease burden in 1990.[26]

Human clinical trials for testing the effectiveness of a recombinant hookworm vaccine are on the horizon. A major hurdle for developing an anti-hookworm vaccine for China's rural poor, however, will be the enormous costs associated with its production and clinical development. The hookworm vaccine will be likely to be a sophisticated product that requires one or more genetically engineered proteins. This will create a situation in which a public sector "orphan" vaccine for the poorest of the poor will be far more expensive than traditional childhood vaccines.[27] The development of orphan vaccines for tropical infectious diseases such as malaria and tuberculosis will also face similar economic hurdles. Therefore the future of hookworm and other orphan vaccines may ultimately depend more on establishing innovative financing schemes than it will on overcoming technical obstacles in the laboratory.

An Opportunity for Sino-American Vaccine Diplomacy

In addition to improving health and reducing poverty, a Sino-American bilateral initiative for the purposes of developing a hookworm vaccine could have implications for strengthening diplomatic ties between the two nations. There is a brief but interesting history of employing vaccines as instruments of foreign policy.[28] This includes the development of the oral polio vaccine, which resulted only after unprecedented co-operation between Soviet and American scientists during the late 1950s. The eradication of smallpox by a mass vaccination campaign is another legacy of Soviet-American Cold War diplomacy.

A Sino-American initiative to combat hookworm could become the latest example of vaccine diplomacy between two superpowers. It is ironic that the April 2001 collision between an American Navy EP-3 electronic reconnaissance plane and a Chinese F-8 fighter forced the landing of the former plane on to a runway in Lingshui, Hainan, just a few miles from a hookworm-endemic area.[29] An initiative to build a hookworm vaccine or to create a new vaccine research institute could help to ease tense Sino-American relations, just as similar efforts to combat polio and smallpox were instrumental in diminishing potential conflict with the Soviets. Such an initiative would build on an existing

24. The World Bank, *China, Overcoming Rural Poverty*, p. 139.
25. The World Bank, *Financing Health Care*.
26. *Ibid.* p. 38.
27. P.J. Hotez, "Vaccines as instruments of foreign policy," *EMBO Reports*, Vol. 2, No. 10 (2001), pp. 862–68.
28. *Ibid.*; P.J. Hotez, "Vaccine diplomacy," *Foreign Policy*, May/June 2001, pp. 68–69.
29. P.J. Hotez, "The other Hainan, plane crash is least of Hainan's problems," *The (Stamford) Advocate* (op-ed), 10 April 2001, p. A17.

joint effort to discover vaccine antigens suitable for pre-clinical testing,[30] followed by field trials in Sichuan, Yunnan, Guizhou, Guangxi or Hainan. Ultimately, Chinese manufacturers could assume responsibility for producing a low-cost, public-sector hookworm vaccine suitable for distribution in impoverished rural areas. China is currently the world's largest producer of vaccines, almost all of which are used within the country. Because the human hookworm vaccine would be used for the poorest of the poor, it is unlikely to be of commercial interest to one of the traditional large pharmaceutical manufacturers. However, new vaccines being designed for developing countries, such as those to combat malaria, tuberculosis, leishmaniasis and hookworm, might still be produced and developed so that it brings in a modest amount of revenue. A Chinese-manufactured hookworm vaccine could become one of its most prestigious exports, and a new source of national pride.

Appendix: **Hookworm in China**

Province Autonomous Region Municipality	*% Prevalence 1993*	*% Prevalence 1997–2000*	*GDP/ person 1997 yuan*	*Human. develop. index*	*Rural urban*
Beijing	0.0		16,735	2	0.33
Tianjin	0.4		13,796	3	0.51
Hebei	0.3		6,079	12	4.12
Shanxi	0.02		4,736	14	2.39
Inner Mongolia	0.09		4,691	22	1.29
Liaoning	0.03		8,525	7	0.89
Jilin	0.0		5,504	13	1.11
Heilongjiang	0.0		7,243	10	0.89
Shanghai	3.8		25,750	1	0.20
Jiangsu	21.8	12.5	9,344	6	2.41
Zhejiang	28.2		10,515	5	2.05
Anhui	33.4	33	4,390	19	3.06
Fujian	21.6		9,258	8	3.52
Jiangxi	17.6		4,155	23	3.33
Shandong	6.1		7,590	9	1.83
Henan	20.7		4,430	16	5.02
Hubei	8.8		5,899	17	1.96
Hunan	22.9		4,643	20	3.18
Guangdong	22.3		10,428	4	2.23
Guangxi	37.9		4,356	18	4.27
Hainan	60.9	60.0	5,698	11	3.09
Sichuan	40.9	66.9	4,029	21	2.53
Guizhou	22.9		2,215	29	2.43
Yunnan	19.3	37.1	4,042	26	4.85
Xizang (Tibet)	0.4		3,194	30	3.21

30. Hotez *et al.*, "Experimental approaches to the development of recombinant hookworm vaccine"; Liu *et al.*, "Hookworm burden reductions in BALB/c mice."

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Shaanxi	0.01	3,707	25	2.81
Gansu	0.01	3,137	27	3.88
Qinghai	0.0	4,066	28	2.60
Ningxia	0.4	4,025	24	2.44
Xinjiang	0.3	5,904	15	1.67
Total	17.2			

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