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Five-year impact of repeated praziquantel treatment on subclinical morbidity due to *Schistosoma japonicum* in China

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Abstract

We report the 5-year impact (1996–2001) of repeated praziquantel chemotherapy on subclinical morbidity related to *Schistosoma japonicum* infection. We repeated stool examinations and hepatosplenic ultrasonography in a cohort of 120 individuals living on an island with endemic infection in Dongting Lake, China. Prevalence of schistosome infection fell by 43% and intensity (geometric mean eggs per gram) declined by 80% over the 5 years. However, transmission persisted at a dangerously high rate of 13% per year for re-infection or new infection in the cohort. The prevalence of left-lobe enlargement and dilated portal vein fell significantly ($P < 0.01$) to about half initial levels although a few patients progressed during the study period. At study endpoint, infection was nearly twice as common if the portal vein was dilated (23% versus 13%, respectively), but this association was not statistically significant ($P > 0.05$). However, endpoint infection was even more strongly associated with left-lobe enlargement (57% versus 15%, $P < 0.01$). The proportions of subjects with improved parenchymal and periportal fibrosis were much higher than the proportions of subjects that progressed ($P < 0.05$). Reduction of prevalence and intensity of infection, and improvement of subclinical morbidity, were benefits of repeated treatments. Further research is needed to understand why some patients developed fibrosis despite substantial reductions in egg counts and to evaluate the functional importance of residual subclinical morbidity after chemotherapy-based control in the lake and marshland area of China.

Keywords: schistosomiasis, *Schistosoma japonicum*, re-infection, morbidity, chemotherapy, praziquantel, ultrasonography, China

Introduction

Schistosoma japonicum causes the most severe pathology of the 3 major schistosome species infecting humans (CHEN & MOTT, 1988). Despite great strides for controlling schistosomiasis over the past 4 decades in the People's Republic of China, infection still affects about one million people in this country, with most patients being concentrated in the lake and marshland regions (CHEN & FENG, 1999; LI *et al.*, 2000a, 2000b; YUAN *et al.*, 2000). Historically, the disease had a devastating effect on the public health of people in endemic areas. Chronically infected patients developed liver fibrosis with portal hypertension, frequently resulting in life-threatening upper-gastrointestinal haemorrhage. Today, infection persists and some people still get severe disease, although less commonly than before. Effects on economic production, learning capacity and childhood growth remain major problems (LI *et al.*, 1993; MCGARVEY *et al.*, 1993; NOKES *et al.*, 1999).

Praziquantel remains the drug of choice for treatment of established *S. japonicum* infection although artemether and artesunate are known to have useful prophylactic effects against recent *S. japonicum* infection (XIAO *et al.*, 2000; ROSS *et al.*, 2001). Praziquantel is safe and can be administered orally in a single dose. Thus, it has become the basis of the major control strategy for schistosomiasis in endemic areas through community-based chemotherapy programmes. Parasitological cure rates achieved by praziquantel in China are still 80–90% (LI *et al.*, 2000a, 2000b; YU *et al.*, 2001) and there is no evidence of resistance in China although this drug has been used widely to control schistosomiasis for more than 15 years. Clinical morbidity attributable to *S. japonicum* infection can be reduced and prevented by use of periodic chemotherapy (WIEST *et al.*, 1991; OHMAE *et al.*, 1992; OLVEDA *et al.*, 1996; ROSS *et al.*, 1998). However, the long-term public health importance of chemotherapy on subclinical *S. japonicum* morbidity, detected by ultrasonography, remains unclear (LI *et al.*, 2000a, 2000b; CAI *et al.*, 1997).

Usually, more than half of the chronic cases of schistosomiasis are asymptomatic, and many clinical symptoms and signs related to *S. japonicum* infection are non-specific. Ultrasonography is a safe and rapid tool and it has been proposed as an approach to examine hepatic fibrosis induced by *Schistosoma* infection since the 1970s (HATZ, 2001). Most studies have reported decreases in portal vein enlargement and in echogenic bands after effective treatment (HOMEIDA *et al.*, 1988; DOEHRING *et al.*, 1989; MOTT *et al.*, 1992; WIEST *et al.*, 1993; BOISIER *et al.*, 1998; LI *et al.*, 2000a, 2000b). Recently, we reported subclinical changes in a community cohort in Dongting Lake exposed to endemic *S. japonicum* infection from before praziquantel treatment to 2 years after therapy (LI *et al.*, 2000a, 2000b). Here we describe the 5-year impact of repeated chemotherapy on endemic *S. japonicum* infection and associated subclinical morbidity in the same longitudinal cohort of 120 residents in the Dongting Lake region of China.

Materials and Methods

Study area

This study involved 5 villages on 2 islands (Qingshan and Niangashan) in the Dongting Lake, Hunan Province, China. This is a moderately endemic area for schistosomiasis but is not endemic for malaria. Control programmes including praziquantel chemotherapy for humans were established in the 1990s. However, due to uncontrolled infection sources, re-infection after drug therapy is frequent and the overall prevalence of infection for humans in the 2 islands remains stubbornly at 15–20% (LI *et al.*, 1997; ROSS *et al.*, 1998).

Study design

Full details of the longitudinal study design are described by LI *et al.* (1999). In brief, we screened 72% ($n = 1909$) of the residents of the study area for active schistosome infection by stool examination, and for

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continuing water exposure or past infection by questionnaire. A total of 250 individuals (160 subjects from Qingshan and 90 from Niangashan) were currently exposed and had past or present infection. They were selected for a 5-year longitudinal study in 1996. All 250 subjects, whether found infected ($n = 75$) or not ($n = 175$) at baseline stool examination, received a single dose (40 mg/kg) of praziquantel (Shin Poong Pharmaceutical Co., Ltd, Seoul, South Korea) and ultrasound assessment at the beginning of the study. Seven weeks after treatment, the stool examination was repeated and those still positive ($n = 13$) were re-treated. Thus, all egg-positive subjects were cured at the start of study.

Two years post-treatment the study subjects initially selected had further parasitological and ultrasound assessment and were again offered a single dose (40 mg/kg) of praziquantel treatment. Unfortunately, soon after that the islands suffered greatly as a result of major flooding of the Yangtze River and Dongting Lake in August 1998. The residents of Niangashan abandoned the island to rebuild houses near a small township close to the shore of Dongting Lake. Because these island residents moved out of our study area and substantially changed their occupations with much less water exposure, they were excluded from this study. Thus our follow-up examinations in 2000 and 2001 were restricted to those living on Qingshan island for the next 3 years.

In May 2000, 131 subjects still living on the larger island (Qingshan) were again offered a single dose of praziquantel. In June 2001, 5 years after the start of the study, 120 of these residents (original $n = 160$) provided complete data for 3 treatments and 3 parasitological and ultrasound assessments. In addition, current alcohol intake (none, occasionally, frequently, daily and intoxicated at times) and water exposure (none, 1–2 times/month, 1–2 times/week) in the previous 2 months were recorded by a questionnaire.

Infection assessment

Each subject was asked to provide 2 stool samples for parasitological examination in 1996, 1998 and 2001. For each stool sample, three 41·7-mg Kato–Katz thick smears were prepared; thus every subject had 6 smears for each assessment. The presence of *S. japonicum* eggs was confirmed independently by 2 microscopists from Hunan Institute of Parasitic Diseases, China.

Ultrasound measurements

All ultrasound measurements were conducted on subjects in 1996, 1998 and 2001 by the same experienced observer to reduce measurement bias that could arise with different technicians at multiple time-points. The examiner was blinded to all other results and was unaware of the underlying study hypotheses. The equipment used was a portable ultrasonograph (Sonolayer L SAL-33B; Toshiba, Tokyo, Japan). Measurements, classifications, standard positions and views followed the WHO standards established in Cairo in 1990 (see Cairo protocol by JENKINS & HATZ, 1992). Photographs and a description of the parenchymal fibrosis stages for schistosomiasis japonica that have been used in China for many years can be found in ROSS *et al.* (2001) and are defined as:

stage I fibrosis, focal echodense areas scattered within the liver parenchyma with absence of definite borders;
stage II fibrosis, stronger light bands forming a 'fish-scale' pattern, and a few focal echodense areas >20 mm in diameter;
stage III fibrosis, echodense bands forming a contiguous network, multiple focal echodense areas >20 mm in diameter and masses with central fibrosis.

Periportal fibrosis was also based on the same standards: the average of the out-to-out measurements of 3 periportal branches of the portal vein were used for recording purposes: I = 3–5 mm, II = 6–7 mm, III > 7 mm. 'Enlargement of spleen' was defined as >100 mm.

Statistical analysis

Statistical software (SPSS, Inc., Chicago, IL, USA) was used for data processing and analysis. Infection intensity (eggs per gram of faeces; epg) among the infected sub-groups was expressed as geometric means (± geometric SD). Relative frequencies were compared by the χ^2 test, or McNemar's test for paired analyses. Differences with a P value <0·05 were considered statistically significant. Cohort data analysis compared results for 1996 and 2001. Subclinical data of this study before (1996) and 2-years post-treatment (1998) were recently published (LI *et al.*, 2000a, 2000b).

Ethical considerations

This study was approved by the medical ethics committees of Hunan Province in China, the University of Queensland and Queensland Institute of Medical Research in Australia. Treatment once every 2 years for schistosomiasis control in endemic areas like those involved in this study is recommended by the Chinese National Control Programme (LI *et al.*, 1999).

Results

Among the 120 cohort individuals studied in 2001, 79·2% were male, 85% were adults (aged >20 years) and the mean age was 39 ± 13·1 years (range 9–65 years). Overall, 91% ($n = 109$) had had water contact in the previous 2 months; 25·7% of these recently exposed subjects reported contact with lake water weekly due to work activities. Few cohort members reported frequent alcohol intake (only 6 subjects) so we could not explore its influence on liver disease in this cohort.

The initial prevalence and intensity (mean ± SD) of *S. japonicum* infection among the infected patients in the cohort in 1996 was 25·8% ($n = 31$) and 295 ± 3·4 epg, respectively. Two years after the first treatment in 1996 the prevalence and intensity of infection (1998) were 20·8% and 95 ± 5·6 epg, respectively. At the end of the study in 2001, the prevalence and intensity in the cohort were 14·2% and 58 ± 2·4 epg. Overall, 28·1% ($n = 25$) of 89 non-infected subjects at the commencement of the study got a new infection during the 5 years; 37·0% ($n = 17$) of 46 subjects initially infected in 1996 or 1998 were re-infected before 2001 (Figure). Of 17 infected individuals in 2001, 10 subjects had not previously been detected as infected in 1996 and 1998. The yearly incidence of new infection plus re-infection remained dangerously high (13%). Compared with the 1996 baseline data, the human prevalence fell 43% and geometric mean intensity of infection fell 80% owing to chemotherapy applied 3 times over 5 years.

Parenchymal abnormalities

Parenchymal fibrosis (stage II or III) was detected by ultrasound in 38·3% of the cohort (46/120) in 1996 and this prevalence declined to 29·2% ($n = 35$) by 2001 (Table 1), a substantial but not significant fall ($P > 0·05$). We observed the evolution of parenchymal features of subjects from 1996 to 2001 and found that fibrosis staging after treatment did not change in 68·3% ($n = 82$) of individuals; however, 11 of those with stage I or II progressed (10%, 11/105) and 27 of the 46 patients with stage II or III improved (59%, 27/46) (Table 2). Stage II and III parenchymal fibrosis in 2001 was not related to current infection status ($P > 0·05$). However, the evolution of parenchymal fibrosis was strongly associated with current infection; 55% (6/11) of those with progressive fibrosis had current infection, in contrast to only 12·5% (11/88) of others ($P < 0·01$).

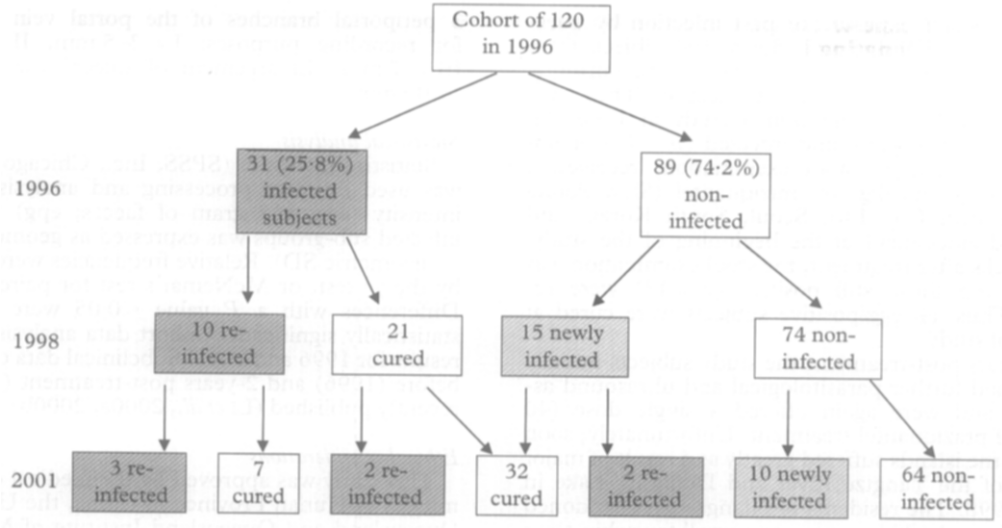

Figure. Infection, new infection and re-infection with *Schistosoma japonicum* in a cohort of 120 subjects in 1996, 1998 and 2001 from the Dongting Lake region of China. Treatment with praziquantel was given at the start of the study (1996) and in 1998 and 2000.

Table 1. Parenchymal measurement in a cohort of 120 subjects, from the Dongting Lake region, China, in 1996, 1998 and 2001

Parenchyma grading	1996 % (*n*)	1998 % (*n*)	2001 % (*n*)
0	9·2 (11)	11·7 (14)	20·8 (25)
I	52·5 (63)	62·5 (75)	50·0 (60)
II	25·8 (31)	20·8 (25)	20·8 (25)
III	12·5 (15)	5·0 (6)	8·3 (10)

Table 3. Periportal grading of a cohort of 120 subjects in Dongting Lake region, China, in 1996, 1998 and 2001

Fibrosis grading	1996 % (*n*)	1998 % (*n*)	2001 % (*n*)
I[a]	79·2 (95)	87·5 (105)	74·2 (89)
II	19·2 (23)	10·8 (13)	19·2 (23)
III	1·7 (2)	1·7 (2)	6·7 (8)

[a]Grades 0 and I were combined.

Periportal abnormalities

Periportal fibrosis (stage II or III) was found in 20·8% (25/120) of the cohort in 1996, and in 25·8% (31/120) at the end of the study in 2001 ($P > 0·05$) (Table 3); 73·3% ($n = 88$) had no changes in periportal fibrosis. Periportal fibrosis progressed in 17·8% of the subjects (21/118), but 47·8% ($n = 11/23$) identified initially with periportal fibrosis stage II improved by 2001 ($P < 0·01$) (Table 4). The 2 patients with periportal fibrosis stage III in 1996 did not improve during the 5-year study. Another 6 individuals (4/6 without current infection) developed periportal fibrosis stage III. Periportal fibrosis was not related to current infection in 2001 ($P > 0·05$).

Coincidence between parenchymal and periportal grade measured in 2001

Measurement of both parenchymal and periportal fibrosis evaluates overall liver fibrosis. A high coincidence (79·3%) was noted between grading 0 or I of parenchymal and periportal fibrosis in 2001 when the 2 parameters were compared. However, a low coincidence for fibrosis II (57·5%) and III (53%) was evident.

Portal vein dilation and left-lobe and spleen enlargement

A dilated portal vein (≥12 mm inner-wall diameter) in 1996 and 1998 was recorded in 19·2% ($n = 23$) and 12·5% ($n = 15$) of the cohort, respectively; by 2001 the prevalence had fallen to 10·8% ($n = 13$). There was no statistical significance of portal vein dilatation prevalence from 1996 to 2001 ($P > 0·05$). However, of 23 persons who previously had a dilated portal vein at baseline (1996) 35% ($n = 8$) improved by the end of the study; another 3·1% (3/97) progressed to develop a dilated portal vein ($P < 0·05$), with no current infection. Current dilated portal veins were not substantially associated with re-infection ($P > 0·05$); 23% (3/13) of patients with dilated portal vein had infections in 2001 compared to 13% (14/107) of those with no dilated portal vein. Ascites was not detected in any individual in the cohort.

Table 2. Dynamics of parenchyma grading in a cohort of 120 subjects in Dongting Lake region, China, in 1996 and 2001

	Parenchyma grading 2001					
Parenchyma grading 1996	I[a]	II	III	Total (*n*)	Progressed (%)	Improved (%)
I[a]	**64**	6	4	74	10·5	–
II	17	**13**	1	31	3·2	54·8
III	4	6	**5**	15	–	66·7
Total (*n*)	85	25	10	120	($n = 11$)	($n = 27$)

[a]Grades 0 and I were combined.

Table 4. Dynamics of periportal grading in a cohort of 120 subjects in Dongting Lake region, China, in 1996 and 2001

	Periportal grading 2001					
Periportal grading 1996	I[a]	II	III	Total (*n*)	Progressed (%)	Improved (%)
I[a]	**78**	15	2	95	17·9	–
II	11	**8**	4	23	17·4	47·8
III	0	0	**2**	2	–	0
Total (*n*)	89	23	8	120	(*n* = 21)	(*n* = 11)

[a]Grades 0 and I were combined.

Left-lobe enlargement was detected in 24·2% (n = 29) of the cohort in 1996 but this figure was significantly reduced to 11·7% (n = 14) by 2001 ($P < 0·01$). Although 7·7% (7/91) of individuals without left-lobe enlargement in 1996 developed it by 2001, 76% (22/29) of baseline left-lobe enlargement subjects improved ($P < 0·01$). Development of left-lobe enlargement was related to *S. japonicum* infection ($P < 0·01$); 57% (4/7) of patients with left-lobe enlargement had endpoint infection, compared to only 15% (13/84) of those with a normal left lobe.

Splenomegaly occurred in only 5·8% (n = 7) of the cohort in 1996, and 4·2% (n = 5) in 2001 ($P > 0·05$). Of the 7 baseline splenomegaly cases, 5 improved after treatment; the 2 patients with persistent splenomegaly were aged >64 years and were uninfected in 2001. However, 3 subjects (aged >50 years) developed splenomegaly in 2001; 2 were infected only in 1996 and one had an infection in 1998 and a re-infection in 2001.

Discussion

Previous studies have demonstrated that the prevalence and morbidity of schistosomiasis japonica decrease over time after implementation of successful population-based chemotherapy programmes (OLVEDA *et al.*, 1996; ROSS *et al.*, 1998; CHEN & FENG, 1999; YUAN *et al.*, 2000). This success is due to a decrease in average human worm burdens and may also reflect a transmission decline in the number of infected humans contributing eggs into the environment. In our study, prevalence declined by 43·4% (25·8% to 14·6%) and infection intensity fell by 80% (295 epg to 58 epg) following chemotherapy given 3 times over 5 years. Overall, this chemotherapy-based intervention reached the goal of a 40% reduction of infection established for national control by the World Bank–China Schistosomiasis Control Programme (YUAN *et al.*, 2000). The strategy of chemotherapy at 2-year intervals in endemic areas typified by the lake and marshlands in the Dongting Lake region reduces both prevalence and infection intensity, but transmission of infection in this area certainly continues. We found a 13% rate of re-infection or new infection per year in our at-risk cohort. This might be explained by the fact that the transmission of *S. japonicum* is maintained by migrating fishermen living on the lake combined with the existence of non-human reservoirs, especially water buffaloes. Frequent re-infection after treatment blunts the impact of chemotherapy-based control and both people and programme staff become less enthusiastic over time.

Ultrasound is a safe, rapid, non-invasive and relatively inexpensive technique for assessing schistosomiasis-related lesions in individual patients and in community surveys (ABDEL-WAHAB *et al.*, 1990; HATZ, 2001). Moreover, it provides an opportunity to visualize the evolution of pathological lesions after effective treatment. We used this technique to stage fibrosis at the beginning and end of our 5-year study. Left-lobe enlargement and dilated portal vein were considerably less common in the cohort in 2001 than in 1996. Although the prevalences of parenchymal and periportal fibrosis II or worse were not significantly reduced statistically, the percentage of improvement was much greater than that of progression. Parenchymal fibrosis and left-lobe enlargement progressed in association with current infection, but not progression of periportal fibrosis and dilated portal vein. This suggests that left-lobe enlargement and abnormalities of the liver parenchyma in this cohort may be due mainly to granulomatous inflammatory host responses to schistosome eggs trapped in the perisinusoidal spaces of the liver. Given the study design and the examinations undertaken, we cannot completely exclude other pathogenic agents, such as chronic hepatitis B and alcoholic liver disease (LI *et al.*, 2000a).

Improvement of left-lobe enlargement and abnormalities of parenchymal features after chemotherapy is attributable to treatment benefits. It seems that improvement of parenchymal fibrosis was more responsive to treatment than periportal fibrosis. Parenchymal abnormalities are recognized as the most common and distinctive findings for *S. japonicum* infection. It is interesting that co-morbidity with severe parenchymal fibrosis and severe periportal fibrosis was relatively uncommon in this cohort, which might reflect the different pathobiology or host susceptibility for these lesions, or both. A study of *S. japonicum* infections in the Philippines recently described 2 types of liver lesion as detected by Doppler ultrasonography (KARDORFF *et al.*, 1999). The first, a typical periportal fibrosis reduced portal venous blood flow velocity; the second, a fibrous network, anatomically separated from the portal branch, was not associated with changes in portal venous blood flow, but with cholestasis and enzyme changes indicative of liver damage. In our previous study of this Chinese cohort (LI *et al.*, 2000a) we reported that serum concentrations of hyaluronic acid, a glycosaminoglycan mainly synthesized by hepatic stellate cells and taken up and degraded almost exclusively in hepatic sinusoidal endothelial cells, were related to re-infection and severe parenchymal fibrosis but not to periportal fibrosis and dilated portal vein.

The interpretation of ultrasound imaging depends somewhat on the experience of the investigators. Therefore, a protocol for standardizing scan procedures, reducing observer variation for organ measurements and integrating the grading system of fibrosis with other observation of left-lobe and portal vein enlargement, is required to compare results from different settings. As the new standard proposed by World Health Organization to stage ultrasound observations has so far been developed only for assessing pathology induced by *S. haematobium* and *S. mansoni* (HATZ, 2001), we had to use the original (unrevised) WHO Cairo standards (JENKINS & HATZ, 1992).

Only 15% of subjects were aged <20 years in this study because our cohort participants were from a very remote island and younger people migrate out for school and work. This limited our capacity to study

age-related subclinical morbidity. However, severe periportal fibrosis was seen less commonly in patients younger than 36 years old, and parenchymal abnormalities occurred less commonly in patients younger than 20 years old in our previous study (LI *et al.*, 2000a), suggesting long-standing infection is needed to induce the most severe form of liver fibrosis.

Hepatosplenic disease (advanced schistosomiasis) induced by schistosomes is characterized by periportal liver fibrosis, spleen enlargement and congestion, portal vein hypertension, and other serious sequelae. These are the end result of $CD4^+$ T-cell-dependent granuloma formation, caused by live parasite eggs lodged in hepatic portal venules (ROSS *et al.*, 2001). Infection prevalence and intensity do not show a stable correlation with each other in areas that have had regular population treatments, and mean intensity is then the most reliable (but still imperfect) predictor of disease.

Genetic variants among humans have been reported to influence the development of severe disease. In studies on *S. mansoni*, Dessein and his colleagues have identified several genomic regions (5q31–q33, 6q22–q23, 1p21–q23, 6p21–q21) that may be associated with infection intensity or clinical manifestation (MARQUET *et al.*, 1996, 1999; DESSEIN *et al.*, 1999; ZINNJUSTIN *et al.*, 2001). In China, an association between susceptibility to schistosomal hepatic fibrosis and HLA-DR-DQ alleles has been demonstrated (HIRAYAMA *et al.*, 1999; ROSS *et al.*, 2001), reflecting a possible genetic basis for the disease. In our study area, although effective praziquantel treatment had been given to all participants several times, hepatic morbidity still progressed in a few subjects even without recent reinfection. We are not sure whether the patients who progressed are associated with some genetic effect. In addition, a questionnaire we used to collect family history of advanced schistosomiasis (data not shown) revealed that 3 of 15 patients having hepatic fibrosis stage III had records of ascites and significant splenomegaly in their family pedigrees. Whether severe liver fibrosis induced by *S. japonicum* infection is linked to genetic factors is currently under study in the Dongting Lake region. In addition, there is a need to establish more clearly the functional significance and thus the impact of subclinical morbidity in *S. japonicum*, in order to capture the full public health importance of the disease in these endemic settings. It is known there are 3·2 million people still at risk of schistosomiasis in the Dongting Lake region, with an average infection prevalence of 10% (LI *et al.*, 2000b). Applying our endpoint prevalence of parenchymal morbidity (29%) to the infected population just in this region (320 000) we can estimate that 93 000 people would still have subclinical disease despite optimal periodic treatment.

To control schistosomiasis in an endemic area such as Dongting Lake much still needs to be done. First, chemotherapy should be repeated and focused on those with high water exposure after using a questionnaire to determine those most at risk. For instance, the prevalence of human infection and re-infection probably reaches 20–30% at maximum in this area, but another 70% of individuals without infection were also treated. With limited financial resources for schistosomiasis control and potential drug resistance, chemotherapy could be replaced by targeted chemotherapy even when the prevalence is relatively high (>15%). Similarly, the application of molluscicides could focus on the high concentrations ('hot-spots') of snails before the transmission season. Health education as a complementary approach will improve the residents' knowledge and behaviour for self-protection. Ecological measures to reduce such occupational exposure should be a priority in the lake and marshland region of China. As well, anti-fecundity and anti-disease vaccines, once developed and validated, will become important complements of the currently prevailing control strategies. Finally, the genetic basis of residual subclinical morbidity, and its functional impact on public health in the lake and marshland area of China deserve further research.

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Announcement

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE
Chalmers and Christophers Medals 2003

The Chalmers Medal is awarded each year in recognition of research contributing to the knowledge of tropical medicine or tropical hygiene. Only persons of 45 years or under on 1 June of the year of the award shall be eligible.

The Christophers Medal is awarded triennially for work in tropical medicine and hygiene in its broadest sense. Practical and field applications receive special consideration in making the award.

Nominations may be made by any Fellow of the Society, on forms available from Manson House. Completed forms should be sent to the Honorary Secretaries by **30 September 2002**. For full details please refer to the Yearbook.