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Two-year impact of praziquantel treatment for *Schistosoma japonicum* infection in China: re-infection, subclinical disease and fibrosis marker measurements

Y. S. Li[1,2]*, A. C. Sleigh[1], A. G. P. Ross[1], Y. Li[2], G. M. Williams[1], M. Tanner[3] and D. P. McManus[1] *[1]Tropical Health Program, Australian Centre for International and Tropical Health and Nutrition, The Queensland Institute of Medical Research and The University of Queensland, 300 Herston Road, Herston, Brisbane, Queensland 4029, Australia; [2]Hunan Institute of Parasitic Diseases, Huabanqiao Road, Yueyang, Hunan 414000, The People's Republic of China; [3]Swiss Tropical Institute, Socinstrasse 57, P. O. Box Ch-4002, Basel, Switzerland*

Abstract

We studied a community cohort of 193 individuals exposed to endemic *Schistosoma japonicum* infection in the Dongting Lake region of China to assess subclinical morbidity and the 2-year benefit of curative therapy (praziquantel) administered in 1996. Prevalence and intensity of *S. japonicum* infection before treatment were 28% and 192 eggs per gram faeces (epg), respectively. Two years after cure, 22% of the cohort were re-infected, but with a lighter intensity (67 epg). Sixty-four subjects (37%) showed significant improvement in ultrasound parenchyma images after treatment and 51 subjects (54%) showed significant improvement of periportal fibrosis. Left-lobe enlargement also reversed ($P < 0.05$) and splenomegaly reversed in 6 of 8 cases and developed in only 1. Two years post-treatment a dilated portal vein became less frequent, but the decline was not significant (16% vs 11%, $P > 0.05$). The serum levels of laminin and collagen IV associated with re-infection and intensity and hyaluronic acid levels correlated with ultrasound findings ($P < 0.01$). Overall, treatment induced a marked decrease in subclinical hepatosplenic morbidity attributable to *S. japonicum* although low-intensity re-infection after treatment remained relatively frequent. Stratified analysis and logistic models evaluated potential confounding factors for assessment of treatment effects on hepatic fibrosis. *S. japonicum* infection and moderate–heavy alcohol intake interacted: improvement in parenchymal morbidity was impeded among drinkers ($P < 0.05$). Chemotherapy focused on at-risk residents controls prevalent subclinical hepatic fibrosis but re-infection indicates the need for complementary control strategies.

Keywords: *Schistosoma japonicum*, schistosomiasis, morbidity, re-infection, ultrasonography, fibrosis markers, China

Introduction

Schistosoma japonicum causes the most severe pathology of the 3 major schistosome species infecting humans (CHEN & MOTT, 1988; JORDAN *et al.*, 1993). The morbidity prevented by effective control has been studied clinically, but subclinical forms detectable by ultrasound are poorly understood and remain widespread in many endemic areas, even when infection prevalence is low (CAI *et al.*, 1992; MOTT *et al.*, 1992). Several million people are infected with *S. japonicum* in China and the Philippines, and millions more are at risk. The disease has an adverse impact on rural economies and has been the focus of Chinese health programmes for decades (LI *et al.*, 1993; SLEIGH *et al.*, 1998a). Control in some parts of China has made great progress, even before the advent of praziquantel, using integrated ecological approaches sustained over 40 years (SLEIGH *et al.*, 1998b).

Schistosomiasis japonica remains a problem in marshland and mountain endemic areas of 6 Provinces in China (ANONYMOUS, 1997, CHEN & FENG, 1999). Reduction in morbidity is sought by use of periodic chemotherapy because many reports show its positive overall impact on schistosome prevalence, intensity and clinical disease (SLEIGH & MOTT, 1986; SLEIGH *et al.*, 1986; STURROCK *et al.*, 1987; WIEST *et al.*, 1992; BOOTH *et al.*, 1996; OLDS *et al.*, 1996; OLVEDA *et al.*, 1996; LI, Y. S. *et al.*, 1997). But the impact of community-based praziquantel on subclinical *S. japonicum* morbidity in China is not yet known (CAI *et al.*, 1992; ROSS *et al.*, 1998a).

Hepatic fibrosis is the major morbid outcome of chronic infection with *S. japonicum* and many lesions are similar to those caused by *S. mansoni*. The liver pathology is caused by trapped eggs (SLEIGH & MOTT, 1986; JORDAN *et al.*, 1993) and is probably genetically associated (DESSEIN *et al.*, 1999). Besides periportal fibrosis, there are changes in the liver parenchyma which are characteristic of *S. japonicum* infection. On ultrasound and computerized tomography these appear as images thought to result from progressive septal fibrosis and related clusters of calcified eggs (CHEUNG *et al.*, 1996). However, little is known of the natural history of periportal or septal fibrosis due to this parasite, or the hepatic effects of treatment, re-infection, or concurrent damage due to alcohol or hepatitis B virus infection.

Ultrasonography can stage hepatic fibrosis induced by *Schistosoma* infection. Decreases in the thickness of portal vein walls and in echogenic bands have been detected after praziquantel therapy (HOMEIDA *et al.*, 1988; DOEHRING-SCHWERDTFEGER *et al.*, 1989; OHMAE *et al.*, 1992; WIEST *et al.*, 1993; CAI *et al.*, 1997; GERSPACHER-LARA *et al.*, 1997; BOISIER *et al.*, 1998). Assay of serum levels of fibrosis markers may be a useful supplementary tool for monitoring changes in liver fibrosis (SHAHIN *et al.*, 1992; KARDORFF *et al.*, 1997; OBERTI *et al.*, 1997; ESTERRE *et al.*, 1998; RICARD-BLUM *et al.*, 1999).

We assessed the benefit of curing endemic *S. japonicum* infection by evaluating the effect on subclinical morbidity. The data were longitudinal and included repeated parasitological stool examinations, blinded sequential ultrasound findings and serum assay of 3 markers for fibrosis in a community cohort. We document residual subclinical morbidity and changes that occurred after chemotherapeutic cure and re-infection over 2 years. We relate subclinical changes to new and past infection, alcohol intake, hepatitis B, and age.

Materials and Methods

Study area

The 5 study villages (population 2990) are on 2 islands (Qingshan and Niangashan) in Dongting Lake, Hunan Province, China (LI, Y. S. *et al.*, 1997; ROSS *et al.*, 1998a). Local residents, fishermen and buffaloes are the main infection source. Control programmes from 1988 to 1996 included periodic praziquantel treatment for those infected, health education and improved water supplies. Only 10% of the subjects in our cohort had never been treated before this study. Infection persists because of occupational exposure but clinically detectable liver and spleen enlargement has been controlled (BOOTH *et al.*, 1996; ROSS *et al.*, 1998a).

*Author for correspondence: phone +61 7 33620401, fax +61 7 33620104; e-mail yueshenL@qimr.edu.au

Study design

In 1996, we screened the resident population of the study area for active schistosome infection (1 stool, $3 \times 41{\cdot}7$-mg Kato–Katz smears) and for continuing water exposure or past infection (questionnaire). All 250 individuals who were currently exposed and had past or present infection (ROSS *et al.*, 1998a; LI *et al.*, 1999) received ultrasound assessment and then, whether found infected ($n = 75$) or not ($n = 175$) at baseline stool examination, received a single dose of praziquantel (40 mg/kg). Stool examination was repeated 7–8 weeks post-treatment and those still stool-positive ($n = 13$) were retreated, re-examined once more, and shown to be egg-negative. Thus all egg-positive subjects were cured in 1996 at the start of the study. In 1998, 2 years after treatment, 193 (77%) of the 250 subjects initially selected had a final parasitological (2 stools, 6 Kato–Katz smears per person) and ultrasound assessment. This group of 193 persons with ongoing exposure to re-infection constituted a 2-year prospective cohort enabling us to measure the influence of past, initial and re-infection with *S. japonicum* on the post-treatment evolution and regression of hepatic fibrosis.

The 193 cohort subjects were similar to the 250 eligible at baseline for mean age (39·7 vs 39·2 years), sex (males: 78% vs 76%), and initial schistosome infection (prevalence: 30% vs 28%; intensity: 204 vs 192 epg). Measurement bias for infection assessment was minimized by employing 2 experienced staff of the Hunan Institute of Parasitic Diseases to prepare and read all faecal smears. They were blinded to all other results. A 10% random sample of all smears was read by a third senior microscopist: concordance exceeded 95%. To assess the influence of potential confounders of treatment effects, we recorded age, sex, reported alcohol intake and past history of anti-schistosomal chemotherapy. To explore the biological correlates of findings we tested 97% of the 193 cohort members for serum fibrosis markers. For 105 of the 193 (random selection from the serum panel) we measured 5 hepatitis B markers.

Ultrasound measurements

Ultrasound measurements were conducted by the same experienced observer before and 2 years after treatment. This person directed abdominal ultrasound services at a large hospital and was blinded to all other results and to the underlying study purpose. The equipment used was a portable ultrasonograph (Sonolayer-L™ SAL-33B; Toshiba, Tokyo, Japan) with a 3·5-MHz sector probe. Standard positions, views, measurements and classifications were according to the CAIRO protocol (JENKINS & HATZ, 1992; CAI *et al.*, 1997).

Serum markers for fibrosis and hepatitis B

Blood (5 mL) was taken at a final assessment in 1998. All sera were separated within 12 h, stored at −20°C, transported on dry ice to the Brisbane laboratory, and aliquoted and stored at −70°C until used. Three serological fibrosis markers were measured using enzyme-linked immunosorbent assays (EIA) for human laminin (LA) and collagen type IV (Fuji Chemical Industries, Tokyo, Japan) and human hyaluronic acid (HA) (Chugai Diagnostics Science, Tokyo, Japan). Values exceeding reference means by >2 SD were considered abnormal; serum levels for LA, HA and collagen IV of 200 ng/mL, 80 ng/mL and 150 ng/mL, respectively, were the upper limits of normal when tested among healthy persons. For assessing hepatitis B virus (HBV) exposure, 5 markers (HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc) were tested by EIA using commercial kits (Nanyan Institute of Biochemical Reagents, Shenzhen, China). Subjects positive for 1 of the 5 markers were considered positive for HBV exposure (LI, Y. *et al.*, 1997).

Statistical analysis

Infection intensity (eggs per gram faeces; epg) among infected sub-groups was expressed as the geometric mean (± geometric SD); for whole populations (including uninfected persons) the (egg count + 1) transformation was used for individual counts before calculating geometric means. Relative frequencies were compared by χ^2 test for independent comparisons, or McNemar's test for paired analyses. Student's *t*-test (paired test when appropriate), or analysis of variance, was used to evaluate differences between or among group means. Non-parametric analysis of variance (Kruskal–Wallis) was used if Bartlett's test showed variances for compared groups were heterogeneous. Stratified analysis was used to assess potential confounding. For all outcomes assessed, the final logistic regression models included cure-of-heavy-infection (endpoint <100 epg), moderate alcohol intake (weekly or more), older age (>35 years) and past recurrent infection (treatment >twice) as explanatory variables. These variables provided the best fit for the outcomes studied. This produced adjusted odds ratio estimates for each variable allowing for the influence of all other variables in the model. For statistical inference *P* values were set at $< 0{\cdot}05$, and relative risk (RR) and odds ratio (OR) estimates were reported with 95% confidence intervals (CI). We distinguish between the magnitude of an effect (ranging from trivial to substantial) and its statistical significance (assessed by *P*-values) (ROTHMAN, 1986). Analysis used EpiInfo and SPSS software.

Ethical consideration

This study was approved by the local body for medical ethics in Hunan Province, China, and by the University of Queensland and the Queensland Institute of Medical Research. Individuals found to be re-infected with *S. japonicum* after 2 years received prompt oral treatment with praziquantel.

Results

S. japonicum *infection*

The initial prevalence of *S. japonicum* infection in the 193 pre-treatment cohort subjects and intensity among those positive were 28% (54/193) and 192 ± 3·5 epg, respectively. Heavy-intensity (epg ≥400) individuals comprised 6·7% ($n = 13$) of the cohort; males had higher prevalence (29·8%) and intensity among positives (212 ± 3·5 epg) than females (21·4%; 116 ± 3·1 epg). Children and adolescents (aged <20 years, $n = 16$) had high prevalence and heavy intensity of infection (62·5%; 316 epg) and infection then declined slowly with age (Fig.). Two years after cure, 22·3% (43/193) were found to be infected again with mean intensity among those positive (67 ± 4·8 epg) one-third the corresponding level at baseline. Males had re-infection more commonly (25·8%, 39/151) and higher intensity among those positive (77 ± 4·8 epg) than females (9·5%, 4/42; 18 ± 2·5 epg).

Children and adolescents had the highest re-infection (37·5%) and incident intensity among those positive (130 ± 10 epg). Only 2·6% ($n = 5$) of the cohort had re-infection intensity ≥400 epg at endpoint. The age pattern of re-infection after treatment was similar to that before (Fig.). Sixteen subjects (29·6%, 16/54) who were infected at baseline became re-infected and 27 (19·4%, 27/139) who had been negative at baseline had new incident infections. For the 16 individuals positive before and 2 years after treatment, mean intensity (160 ± 5·6 epg) at endpoint was much lighter ($P < 0{\cdot}005$, paired *t*-test) than at baseline (389 ± 3·9 epg).

Hepatic parenchymal abnormalities

Compared to 1996, 36·8% (64/174) of subjects improved parenchymal fibrosis in 1998 and 13·5% (23/171) became worse (Table 1). The prevalence of grade II–III in 1996 was 40·9% ($n = 79$) but fell significantly to 28·5% ($n = 55$) by 1998 ($P < 0{\cdot}01$). The prevalence

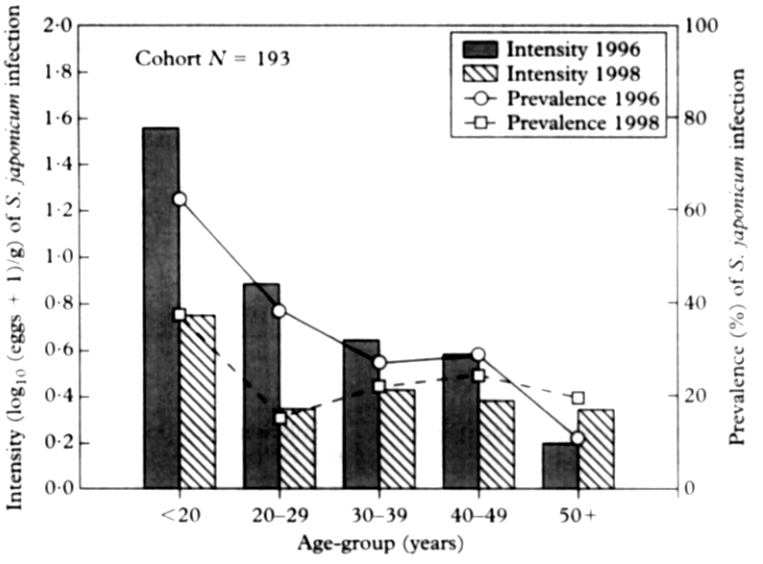

Figure. Cohort prevalence and intensity of infection with *S. japonicum* by age before (1996) and two years (1998) after praziquantel cure.

Table 1. Dynamics of parenchyma grading before and 2 years after treatment for control of schistosomiasis japonica in a cohort of 193 subjects (Dongting Lake region, 1996–98)

Parenchyma grading	Parenchyma grading 1998					Progressed	Reversed
1996	0	I	II	III	Total	(%)	(%)
0	**6**	12	1	0	19	68·4	–
I	16	**71**	8	0	95	8·4	16·8
II	1	31	**23**	2	57	3·5	56·1
III	0	1	15	**6**	22	–	72·7
Total (*N*)	23	115	47	8	**193**	(*n* = 23)	(*n* = 64)

of grade II–III rose steadily as age increased (Table 2). Alcohol intake substantially and significantly impeded post-treatment improvement in grade II–III: 45·6% of heavy drinkers (⩾ weekly) improved in contrast to 70·8% of others ($P < 0.05$). Re-infection impeded improvement of grade II–III although this effect was less than for alcohol and was not significant: 51·2% (22/43) of re-infected improved and 64·7% (97/150) of others ($P > 0.05$).

For reversal of grade II–III, adjusted ORs showed a substantial but not statistically significant positive cure-of-heavy-infection effect (OR = 2·55; 95% CI = 0·67–9·58). Reversal effects were substantial and significantly negative for alcohol (0·29; 0·08–0·91), older age (0·15; 0·03–0·74) and past recurrent infection (0·32; 0·10–0·99). For incidence of grade II–III, the adjusted estimates were not statistically significant but the cure-of-infection effect appeared to be preventive (0·50; 0·05–4·99) and alcohol promotive (1·75; 0·35–8·87); age and past recurrent infection had almost no effect.

Periportal thickness

Periportal thickening was found in 48·7% (*n* = 94) in 1996 and 39·4% (*n* = 76) in 1998 ($P < 0.05$): over the 2 years 54·3% (51/94) improved and 10% (19/190) got worse (Table 3). No one with grade II deteriorated, but 1 of 3 cases with grade III improved. Alcohol, re-infection, past infection, age and HBV had little influence on reversal of grade II–III. For incidence of grade II–III significant associations with explanatory variables were not found; however, OR point estimates for cure-of-heavy-infection (OR = 0·49; 95% CI = 0·04–4·98) suggested it may be preventive whereas older age (1·81;

Table 2. Periportal and parenchyma (grading II–III) changes in 193 subjects by age at baseline and 2 years post treatment for control of schistosomiasis japonica

Age		Periportal (% of II–III)		Parenchyma (% of II–III)	
(years)	*n*	1996	1998	1996	1998
<20	16	6·3	0	6·3	6·3
20–35	58	6·9	3·4	22·4	12·1
36–49	65	24·6	12·3	50·8	30·8
50+	54	33·3	20·4	59·3	50·0

Table 3. Dynamics of periportal thickening measured by ultrasound in 193 cohort subjects from the schistosomiasis japonica-endemic Dongting Lake Region after treatment with praziquantel in 1996

Periportal grading 1996	Periportal grading 1998					Progressed (%)	Reversed (%)
	0	I	II	III	Total		
0	**86**	11	2	0	99	13·1	–
I	24	**25**	6	0	55	12·7	43·6
II	7	19	**10**	0	36	0	72·2
III	0	0	1	**2**	3	–	1/3
Total (N)	117	55	19	2	**193**	($n = 19$)	($n = 51$)

0·33–9·83) and past recurrent infection (7·26; 0·80–65·41) appeared to be promotive.

Portal vein size

A dilated portal vein (DPV) was demonstrated in 16·1% ($n = 31$) and 11·4% ($n = 22$) in 1996 and 1998, respectively ($P > 0·05$). Subjects not re-infected had 8% (12/150) prevalence of DPV in 1998, substantially and significantly less than the prevalence of 23·3% (10/43) among those re-infected ($P < 0·01$). Adjusted ORs for 2-year incidence of DPV showed a substantial and significant preventive effect for cure-of-heavy-infection (OR = 0·17; 95% CI = 0·03–0·83), and moderate but not significant promotive effects for alcohol (1·43; 0·40–5·13), age (1·55; 0·43–5·62) and past recurrent infection (1·55; 0·43–5·52).

Left-lobe and spleen enlargement

Left-lobe enlargement (LLE) was seen in 26·4% ($n = 51$) in 1996 and 19·2% ($n = 37$) in 1998 ($P < 0·05$). Although 15·5% (22/142) of individuals without LLE in 1996 developed it by 1998, 68·6% (35/51) of baseline LLE reversed ($P < 0·05$). Incident LLE among the re-infected (25%) was higher than for those not re-infected (12·7%)($P > 0·05$). A substantial (but not significant) apparent preventive effect was noted for cure-of-heavy-infection (OR = 0·22; 95% CI = 0·06–0·83).

Splenomegaly occurred in only 4·1% ($n = 8$) in 1996 and 1·6% ($n = 3$) in 1998. No one aged <26 years had splenomegaly. Six of the 8 1996 splenomegaly cases reverted after treatment. The 2 patients with persistent splenomegaly were aged >61 years. Only 1 person (aged 55 years) developed splenomegaly after treatment.

Correlation of serum fibrosis markers with infection and morbidity

Abnormal levels of LA, HA and collagen IV were found for 27·7%, 31·9% and 25·5% of the cohort, respectively. LA and collagen IV were higher in males; LA and collagen IV, but not HA, correlated with re-infection (Table 4). Subjects with moderate or heavy intensity infections (>100 epg) had higher mean levels (320 ± 200 ng/mL) of LA than those with light intensity (211 ± 71 ng/mL) or no re-infection (182 ± 97 ng/mL) ($P < 0·01$). Five cases with heavy intensity re-infection (epg >400) had even higher collagen levels (307 ± 387 ng/mL), double the level for those not re-infected (153 ± 175 ng/mL) ($P < 0·05$). LA and collagen did not correlate with parenchymal and periportal findings ($P > 0·05$). HA correlated with parenchyma stages ($P < 0·001$) (Table 5). Older subjects (aged >50 years) had higher HA levels (157 ± 163 ng/mL) than those younger (aged <50 years; 58 ± 75 ng/mL; $P < 0·01$).

Table 4. Serum levels of three fibrosis markers in 188 subjects with or without re-infection with *S. japonicum*

Infection status	n	Laminin (ng/mL)	Collagen IV (ng/mL)	Hyaluronic acid (ng/mL)
Not re-infected	145	182 ± 97	153 ± 175	83 ± 109
Re-infected	43	243 ± 127	197 ± 226	98 ± 134
P value[a]		<0·001	<0·05	0 > 0·05

Values in the first 2 rows are mean ± SD.
[a]Kruskal–Wallis test.

Table 5. Serum levels of three fibrosis markers and endpoint ultrasound staging in 188 subjects in 1998, two years after their treatment for schistosomiasis japonica

Fibrosis markers	Parenchyma grading					Periportal grading			
	0 ($n = 21$)	I ($n = 112$)	II ($n = 47$)	III ($n = 8$)	P value[a]	0 ($n = 115$)	I ($n = 52$)	II–III ($n = 21$)	P value[a]
Laminin	185 ± 101	193 ± 94	203 ± 142	219 ± 85	0·6	190 ± 112	209 ± 106	195 ± 77	0·45
Hyaluronic acid	76 ± 117	67 ± 74	111 ± 129	242 ± 280	0·001	82 ± 112	79 ± 74	130 ± 148	0·09
Collagen IV	170 ± 222	151 ± 182	178 ± 181	217 ± 222	0·12	155 ± 175	178 ± 221	168 ± 171	0·76

Values are mean ± SD (ng/mL).
[a]Kruskal–Wallis test.

Cumulative incidence and correlations for HBV infection

Exposure to HBV affected 39% of the cohort in 1998. Positive results for HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc were found in 19%, 6·7%, 5·7%, 25·7% and 18·1%, respectively. HBV prevalence did not vary much ($P > 0.05$) by age, sex, re-infection or ultrasonography findings. The serum levels of fibrosis markers in the 6 HBeAg-positive cases were higher (LA 435 ± 300 ng/mL; HA 165 ± 89 ng/mL; collagen IV 438 ± 459 ng/mL) than those ($n = 99$) HBeAg-negative (LA 194 ± 91 ng/mL; HA 91 ± 134 ng/mL; collagen IV 153 ± 167 ng/mL). These differences were statistically significant (Kruskal–Wallis test, $P < 0.05$) for LA and HA. When this comparison was restricted to those positive for HBV, the HBeAg-negative group still had lower levels of all 3 markers than those who were HBeAg-positive. However, the differences were significant for only LA and HA (Kruskal–Wallis test, $P < 0.05$).

Discussion

Praziquantel was first manufactured in China in 1984 and has been used for community treatment in the study locality since 1988. Effectiveness of praziquantel is still unquestioned in this area and we observed an 83% cure (62/75) after a single dose. Most infected individuals in our study area now have low worm burdens (and infrequent splenomegaly) because chemotherapy has been used for more than a decade and other methods of control have been used since 1956.

We measured the impact of curative treatment on *S. japonicum* infection and subclinical morbidity. After 2 years the infection incidence was high (22%) but the prevalence and geometric mean intensity of infection fell, respectively, 21% and 65% below pre-treatment levels. Baseline subclinical hepatic morbidity was highly prevalent but fell by one-third or more over the 2 years after curative treatment. In this area a 2-year treatment cycle with coverage focused on those at risk will not control transmission but will control disease.

Parenchymal abnormalities were the most common and distinctive findings for all subclinical morbidity due to *S. japonicum* infection. This is notable given that these ultrasound features are found only with *S. japonicum* infection. Parenchymal pathology was slow to develop and was much less evident among the young, even when they were heavily infected. Despite the slow development, 30% of stage II–III cases improved quickly over the 2 years after treatment. But moderate alcohol intake, age >35 years and past recurrent infection impeded treatment-related reversal of parenchymal abnormalities substantially and significantly. In contrast, periportal fibrosis was less prevalent, slower to reverse and had no clear relationship to alcohol. Past recurrent infection was strongly related to periportal fibrosis, and prevention of heavy infection slowed its incidence substantially. Portal vein dilation fell substantially and significantly over the 2 years; its incidence was significantly related to re-infection. Several other findings, although not statistically significant, were noteworthy and consistent with our knowledge of the underlying biology. Thus left-lobe enlargement was associated with re-infection, and its reversal with cure of heavy infection. Spleen enlargement reduced substantially and persisted or developed only in 3 subjects, all aged >50 years.

With *S. japonicum*, few reports have explored the dynamic relationship over time between infection and hepatic fibrosis measured by ultrasound using the CAIRO standard. Previous studies have correlated periportal fibrosis measured by ultrasound with biopsy-proven liver pathology in individuals infected by *S. mansoni* (HOMEIDA *et al.*, 1988; DOEHRING-SCHWERDTFEGER *et al.*, 1989). In this study we could not perform liver biopsies. The area is remote and lacks hospital facilities or adequate transport. In such a setting, risks of liver biopsy outweigh personal benefit and performance of the procedure would be unethical.

Liver fibrosis is a complex process involving production and deposition of insoluble components that constitute the extracellular matrix. The major components of basement membranes are type IV collagen, LA and heparin sulphate proteoglycan. HA is a glycosaminoglycan and is mainly synthesized by hepatic stellate cells and taken up and degraded almost exclusively in hepatic sinusoidal endothelial cells. In this study we found serum concentrations of LA and collagen IV correlated well with active schistosome infection, manifest by egg excretion. This suggests that LA and collagen IV may be involved in inflammatory granulomas and pseudotubercle formation around trapped eggs. Serum concentration of HA, but not of LA and collagen IV, correlated well with ultrasound grading of fibrosis. Thus it appears that LA and collagen IV levels respond to egg-associated inflammation and HA to fibrosis. Serum markers for individuals were rather insensitive and non-specific predictors of fibrosis but mean levels of these markers in populations may indicate endemic infection and fibrosis that would fall with effective control.

Prevalence of HBV exposure was similar for patients with and without hepatic fibrosis detected by ultrasound. HBV was studied in only 54% of the cohort and our data lacked statistical power for investigating this factor as a co-determinant of fibrosis. But the stable HBV exposure rate (40% in 1992 (LI, Y. *et al.*, 1997) and 39% in 1998) suggests that improvement in hepatosplenic morbidity in the 2 years that followed praziquantel treatment in 1996 cannot be attributed to changes in HBV in this population.

Age or body height may influence the normal size of organs measured by ultrasound (YAZDANPANAH *et al.*, 1997). We did not adjust for body weight and height because our study involved self-comparison of ultrasonography before and after treatment. Also, we did not use the CAIRO integrated grading system for hepatic fibrosis as we aimed to assess the dynamics separately for both parenchyma and periportal changes. Alcohol exposure was investigated by questionnaire and we accept that consumption of alcohol based on self-report is difficult to validate. Despite the measurement difficulties, trends linking alcohol to parenchymal features of *S. japonicum* infection were easily detected, and have not been reported before.

Our 2-year study quantified the substantial morbidity benefit of lowering *S. japonicum* worm burdens by at least half for 2 years. Although re-infection 2 years after therapy remained relatively frequent, both the intensity of infection and the morbidity attributable to this parasite were markedly reduced. But chemotherapy-based control in China faces several problems, including low compliance from local populations (WIEST *et al.*, 1991; LI, Y. S. *et al.*, 1997; ROSS *et al.*, 1998b) partly caused by concurrent over-prescribing of supplementary medicines as an income-earning device for village doctors. As well, because successive stool egg counts vary and symptoms may be minimal, lightly infected persons may remain undetected and miss periodic community-based treatments.

In future, control based on chemotherapy in China could focus on those shown by questionnaire or past history to be at high risk of infection. Also, our data show that moderate–heavy alcohol intake exacerbates schistosome-induced parenchymal morbidity, and this message should be incorporated into health education and healthy lifestyle programmes of the future. In addition, ecological interventions to reduce human or bovine exposure or faecal contamination of transmission sites, or vaccines that prevent infection or lower egg production would complement the power of praziquantel.

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Announcements

Working in the tropics—how to do it
A joint meeting of the Royal Society of Tropical Medicine and Hygiene, the Wellcome Trust and the Medical Research Council

Manson House, London, UK
9 May 2000

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Ever wondered how to go about it as a basic scientist or a doctor?
This is the meeting for you!

The objective of this meeting is to encourage and assist doctors and scientists with an interest in carrying out research in the tropics. Speakers include directors from Wellcome Trust and MRC Tropical Centres (including: Prof. Kevin Marsh, KEMRI–Wellcome Trust, Kenya; Dr Steve Allen, Director of Training, MRC Laboratories, The Gambia; Prof. Eleanor Riley, London School of Hygiene and Tropical Medicine, UK). Also hear from trainees who have done it and survived. Representatives of the Wellcome Trust, MRC, Department for International Development and the International Health Exchange will talk about funding opportunities. All speakers will be available for informal discussion.

Admission free, but all participants must register beforehand. Closing date for applications, Tuesday 2 May 2000. Application forms available from the Royal Society of Tropical Medicine and Hygiene, Manson House, 26 Portland Place, London W1N 4EY, UK; phone +44 (0)20 7580 2127, fax +44 (0)20 7436 1389, e-mail mail@rstmh.org

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