The Use and Limitations of Ultrasonography in the Diagnosis of Liver Morbidity Attributable to *Schistosoma mansoni* Infection in Community-Based Surveys

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The objective of this population-based study was to estimate the liver morbidity attributable to Schistosoma mansoni *infection by ultrasonography adopting the proposed standard protocols of the Cairo Meeting on Ultrasonography, 1991. We examined 2384 individuals representing 20% of the households of the rural population of the Ismailia Governorate, East of Delta, Egypt. Prevalence of* S. mansoni *and* S. haematobium *infections were 40.3% and 1.7% respectively. Portal tract thickening (PTT) grade 1, 2 and 3 considered diagnostic of schistosomal liver morbidity was detected in 35.1%, 1.3 and 0.2 individuals respectively. Generally, ultrasonographically-detected pathological changes increased with age, but correlated with intensity of infection only in age group 20-59 years. Comparing individuals with and without* S. mansoni *infections in an endemic and a non-endemic community indicated no significant difference between the former and the latter in either case.*

In conclusion: *ultrasonography had a limited value in estimating schistosomal liver morbidity in our population-based study where early grades of liver morbidly were prevalent. The criteria of diagnosing grade I portal fibrosis need to be revised as well as the staging system proposed by the Cairo Meeting on ultrasonography in schistosomiasis.*

Key words: hepatic schistosomiasis - ultrasound in *Schistosoma mansoni* infections - community-based surveys in *Schistosoma mansoni* infections

Increasingly, abdominal ultrasonography has been established as a reliable, sensitive and specific tool for the direct measurement of liver morbidity attributable to schistosomiasis (Homaida et al.1988a, Abdel-Wahab et al. 1989, 1992a). With the advent of portable machines, opportunities for extending the use of the procedure to the field have been welcomed as a convenient, safe and reliable tool for measurement of schistosomal morbidity in community-based studies, thus promising to feed useful information for planning and monitoring control programs (Homaida et al. 1988b, Doehring-Schwerdtfeger et al. 1990, Abdel-Wahab et al. 1990). Early experiences have indicated the necessity of standardization of the procedure among investigators, as well as for setting guide-lines for quality control and minimizing inter- and intra-observer variability (Doehring-Schwerdtfeger et al. 1992, Hatz et al. 1992).

An Expert "Meeting On Ultrasonography in Schistosomiasis" (MOUS), held in Cairo, (Hatz et al. 1992) proposed standard protocols for the diagnosis, assessment and staging of schistosomal morbidity. Most of the earlier field studies referred-to above have been limited to certain population groups and none reported so far has adopted the standard protocols proposed by the Cairo Meeting on a population-basis.

The here-in-reported study describes our experience in the use of ultrasonography in a community-based study for the assessment of liver morbidity attributable to *Schistosoma mansoni* infection in the governorate of Ismailia in North-East Egypt as a part of a national multi-governorate study, adopting the standard protocols proposed by the Cairo Meeting. The overall purpose of the study was to provide estimates of infection and morbidity to guide schistosomiasis control programs. Our results provide such estimates[1] and highlight the limited usefulness of ultrasound in the diagnosis of the early grades of liver morbidity

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[1]Detailed demographic, clinical and parasitological results will be reported separately.

which prevail in the community. Also modification of the previously proposed staging is provided.

MATERIALS AND METHODS

Study area- The study was carried out at the Governorate of Ismailia which has a total population of about 500,000, nearly equally divided between rural and urban areas. The rural inhabitants constitute about 0.9% of the total rural population of Egypt. The governorate lies in the middle of Suez Canal zone, along the west bank of the canal, irrigation water is supplied by Ismailia canal, which is a main branch of the Nile. Schistosomiasis is known to be endemic in this area as the rest of rural Egypt. Over the last decade, progressive decline in *S.haematobium* infections has been observed in the Delta, including Ismailia, so that most infections are caused by *S.mansoni*. Ismailia governorate has been included since four years in a national schistosomiasis control program.

Study design and sampling plan- A survey was conducted for a representative sample of the population in three out of the four rural districts. A multistage probability sample was selected, with hamlets as primary, and households being secondary, sampling units. Hamlets were selected randomly from a listing of all hamlets in each district. Households were selected by a systematic random method with a proportion dependant on the size of the hamlet. All individuals above one year of age were surveyed. A 20% random systematic sub-sample of the selected households within each hamlet were selected for ultrasonographic examination.

For the purpose of testing the association of ultrasono-graphically measured liver morbidity and evidence of *S.mansoni* infection in the community, a sub-sample comprising the inhabitants of seven randomly selected hamlets in rural Ismailia was compared with the inhabitants of one village in North Sinai (Kattia), an area where transmission of schistosomiasis is precluded by the absence of fresh water canals.

Data collection and measurements- Standard questionnaires were developed to collect information on: (1) environmental and household characteristics, (2) demographic characteristics, water contact and history of infection and treatment from schistosomiasis. The interviews, medical history and physical examination were conducted by trained physicians at the field sites according to standardized forms.

Ultrasonographic examination was conducted at the field using a portable Toshiba EUB 200 machine. Sonographers were trained and standardized for procedures and measurements according to the standard protocols of the Cairo working group (Hatz et al. 1992).

Liver size was measured in the mid-clavicular and the mid-axillary lines. Peripheral portal tracts were measured at three sites from outer to outer diameter between the first and third branching in the liver, and portal tract thickening (PTT) was recorded as the arithmetic mean of three measurements. Portal vein dilatation was recorded when the inner to inner wall diameter at mid length was > 12 mm. The spleen was measured at its longitudinal axis and considered enlarged if > 12 cm. Collateral and ascites were recorded as either absent = 0 or present = 1. The classifications proposed by the MOUS for grading the severity of portal fibrosis and staging the evolution of liver morbidity attributable to *S.mansoni* were adopted. Accordingly, PTT was recorded as either grade 0 = < 3 mm, grade 1 = 3-5 mm, grade 2= > 5-7 mm or grade 3 = > 7 mm.

Stool and urine samples were collected in midday. Two thick smear slides were prepared from each sample at the field site, according to Katz modification of Kato method (Katz et al.1970). Two kato slides were examined independently by two trained technicians at the central laboratories. Urine samples were examined by nucleopore filtration method (Wilkin & El Sawy 1977).

Data management and analysis- EPI INFO 5 computer software program was used to compile data forms into a specially developed program. The Chi-square test and Student-t test were used to compare findings as appropriate. Results were considered significant when $p < 0.05$.

RESULTS

The total number of individuals investigated was 12,512. Demographic clinical and laboratory data will be reported separately. This report concerns 2,384 individuals (19% of the study population) who were examined by ultrasonography.

Table I summarizes the sample actually surveyed and ultrasound sub-sample. There was no appreciable difference between the ultrasound subsample and the survey sample, as regards age and gender distribution. The distribution of the latter was consistent with the age and gender distribution in 1986 census for Ismailia. Although the prevalence of *S.mansoni* was slightly higher in the ultrasound sub-sample, it was well in the range of prevalence of various hamlets (12.3%-73.9%).

The frequency of various ultrasongraphic findings is shown in Fig. 1. Portal tract thickening (PTT), the suggested "pathognomic sign" of schistosomal portal fibrosis (Hatz et al. 1992) was detected in 871 (36.1%) individuals. However the vast majority, 837 (35.1%), had grade 1 (PTT = 3-5 mm). Grade 2 and Grade 3 were present in 1.3% and 0.2% respectively. Departures from normal size

of both right and left lobes of the liver were very common, but measurements were not compared to normal dimensions of adults and children which are yet to be established for that area. Portal vein dilation (> 12 mm) suggesting portal hypertension and splenomegaly were detected in 19.8% and 17.8% respectively. Only a few had collateral veins and ascites, 1.6% and 0.3% respectively.

Irrespective of the status of *S.mansoni* infection of individuals, the frequency of portal tract thickening of all grades, portal vein dilatation and splenomegaly increased progressively with age, with a small peak in all three parameters at the 30-39 years age group (Fig. 2a,b).

TABLE I

Comparison between actual surveyed sample and ultrasound sub-sample

	Survey sample	Ultrasound sample
Districts	4	4
Hamlets	42	42
Individuals	12,512	2384
M:F Ratio	1:1.07	1:1.08
Age		
Range (Years)	1-94	3-94
Mean	21.62	21.65
S. mansoni		
Prevelance	40.3%	44.6%
GM Egg/gm	79.4	76.0
S. haematobium	1.7%	1.4%

Portal tract thickening of all grades, portal vein dilatation and splenomegaly were significantly more frequently encountered in males than females (Fig. 3). Notably, males had a higher prevalence and mean egg counts/gm stools ($p = <0.001$ and <0.05 respectively).

When the correlation between the frequency of various ultrasonographic findings and the prevalence and intensity of infection in hamlets was studied (Table II), only portal vein dilatation and

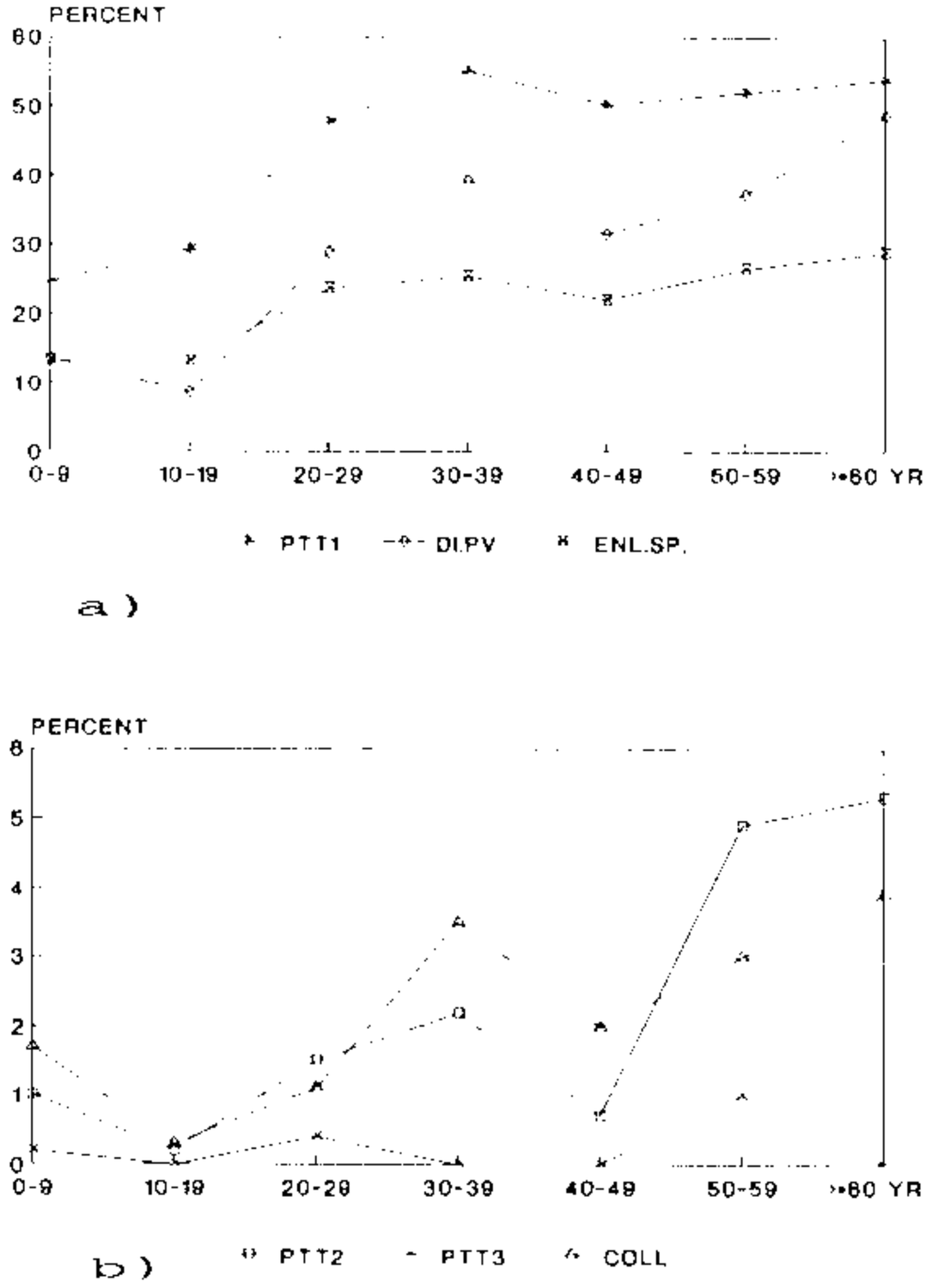

Fig. 2 a,b: frequency of ultrasonographic findings according to age distribution (%). See Fig. 1 for abbreviation.

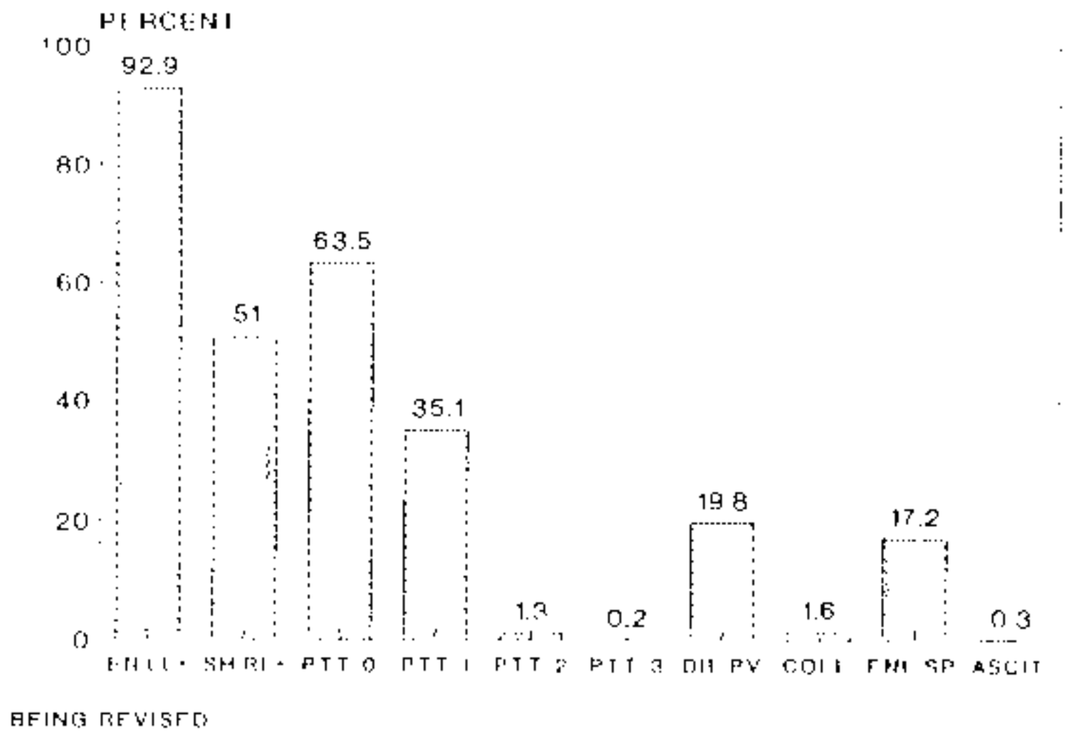

Fig. 1: the frequency of ultrasonographic findings in 2384 individuals (percent). En.LL.: enlarged left lobe of the liver; Sh.RL.: shrunken right lobe of the liver; PTT 0-3: portal tract thickening grades 0-3; Dil.PV: dilated portal vein; Coll.: collaterals; Enl.sp.: enlarged spleen; Ascit.: ascites.

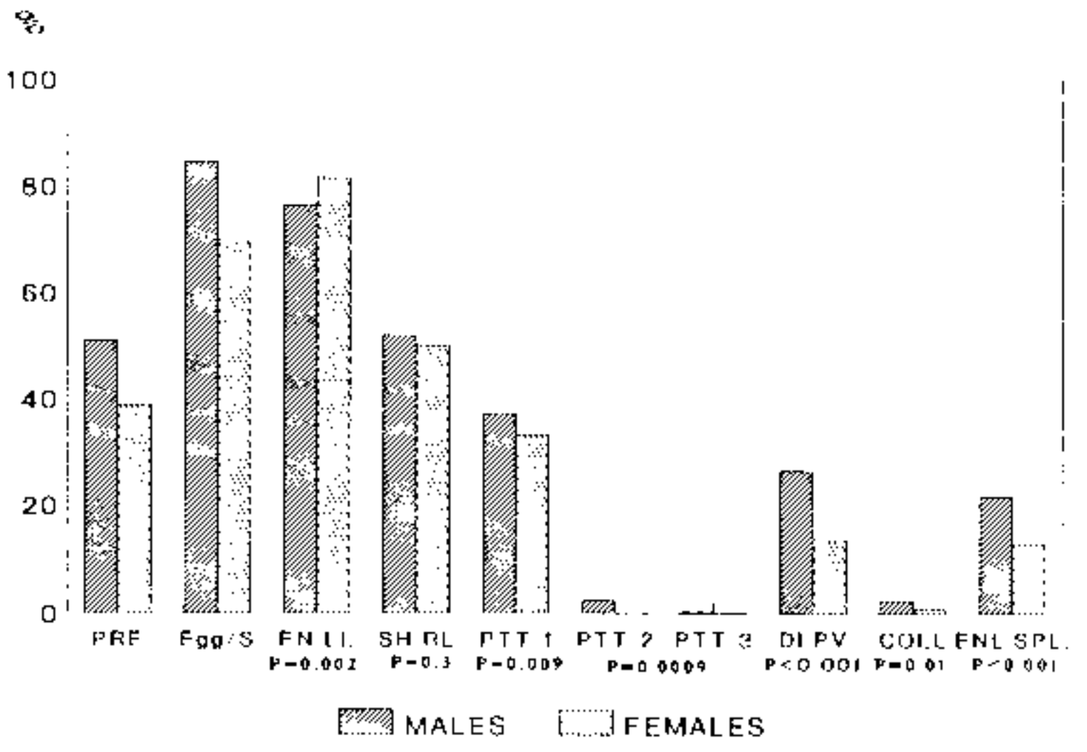

Fig. 3: sex distribution of US findings (%). PRE: prevalence of *Schistosoma mansoni* infection; Egg/S: geommetric mean of egg count/gm stool. See Fig. 1 for abbreviation.

splenomegaly had a significant correlation with prevalence ($r = 0.34$, 95% CI $0.01 < r < 0.60$ and $r = 0.63$, CI $0.36 < r < 0.80$ respectively). On the other hand, there was no correlation between the various ultrasonographic findings and intensity of infection in hamlets.

Table III shows the comparison between the frequency of PTT, portal vein dilatation and splenomegaly in *S.mansoni* infected individuals and those considered non-infected on account of absent ova in stools besides having negative history of ever having received chemotherapy. PTT and splenomegaly were significantly more prevalent in the positive than in the negative individuals in the age groups 0-9 and 20-59 years. In the latter age group, portal vein dilatation was also significantly more prevalent in the positive than in the negatives. In older individuals, ≥ 60 years, PTT and splenomegaly were more prevalent in the non-infected

TABLE II

Correlation between the frequency of ultrasonographic findings and prevalence and intensity of *Schistosoma mansoni* infection in hamlets

Findings	Pearson Correl. Coeff.	Prevalence 95% C.I.	Pearson Correl. Coeff.	Intensity 95% C.I.
1. LL+	0.10	-0.23<r<0.41	0.27	-0.05<r<0.55
2. RL-	0.32	-0.00<r<0.58	-0.03	-0.35<r<0.29
3. PTT	0.34	-1.50<r<0.48	-0.12	-0.42<r<0.22
4. PV+	0.34	0.01<r<0.60	-0.03	-0.35<r<0.29
5. COLL.+	0.16	-0.17<r<0.46	-0.12	-0.34<r<0.21
6. SPLN.+	0.63	0.36<r<0.80	0.21	-0.14<r<0.52

1: enlarged left lobe of liver; 2: shrunken right lobe of the liver; 3: portal tract thickening; 4: portal vein dilatation; 5: collaterals; 6: splenomegaly

TABLE III

Association between ultrasonographic (US) findings and status of *Schistosoma mansoni* infection in different age groups

	Age groups							
	0-9 Y		10-19 Y		20-59 Y		≥ 60 Y	
S. mansoni	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve
Total	229	644	348	223	449	280	38	38
US finding percent +ve								
PTT	33.2[c]	22.9	32.8[a]	26.0	58.6[c]	45.4	74.4[b]	71.1
PV+	15.7[a]	12.4	10.3[a]	6.3	38.8[c]	25.4	55.3[a]	42.1
Splenomeg.	20.5[c]	10.4	15.2[a]	9.9	26.7[b]	20.0	21.1[a]	36.8

[a]: not significant; [b]: significant; [c]: highly significant.

individuals. Generally speaking, therefore and except in the latter group, the three parameters were more frequent in the *S.mansoni* infected individuals, but still appreciable numbers of individuals lacking evidence of that infection exhibited those ultrasonographic parameters.

When we examined the association of each of PTT, portal vein dilatation and splenomegaly and the intensity of infection within the age groups 0-19, 20-59 and ≥ 60 years, only in the 20-59 years age group was there an increase of the GM egg count/gm stools with the increasing severity of PTT ($p = 0.004$).

The results of the comparative measurement of ultrasonographic liver morbidity between an *S. mansoni* endemic and non endemic communities are shown in Tables IV and V. Portal tract thickening of > 3 mm diameter-considered pathognomonic for *S.mansoni* morbidity was detected in 46.7% of 23% sub-sample of the rural community and 37.2% of a 15% sub-sample of the mostly bedouin community of North Sinai. The difference was not significant ($p = 0.2$). *S.mansoni* infection was 26.3% and 7.4% in the rural and bedouin communities respectively ($p = < 0.001$).

Using the criteria proposed by the Cairo working group for staging of *S.mansoni* hepatic morbidity (Table VI) yielded unsatisfactory results, with about 75% of subjects not fitting into any of the proposed stages and less than one percent without any liver morbidity (stage 0). In an attempt to improve the fitting of individuals into the stages, we first omitted the criteria for liver size and kept the other criteria unchanged. This modification improved the distribution markedly, but still there was over 20% of individuals unclassified.

By analyzing those who did not fit the staging by this modification, it became clear that most of them had either enlarged spleen or dilated portal vein separately. A second modification was attempted which allowed for two separate stages (IIa with either splenomegaly or portal vein dilatation, and IIb with both of them together) in place of stage II. Applying this new staging provided a reasonable distribution of subjects with 53% of individuals with no detected liver morbidity (other than

TABLE IV

Comparison of portal fibrosis (PTT) among an endemic and non-endemic communites for *Schistosoma mansoni* infection

Community	Kattia	Ismailia
Population	Bedouin	Rural
SM transmission	Absent	Endemic
Population	809[a] (1 village)	1854[a] (7 hamlets)
Prevalence of infection	7.0%	46.0%
	$p < 0.001$	
GM egg/gm stool	82.0	153.46
	$p < 0.001$	
US sample size	121 (14.9%)	429 (23.1%)
% infection in US sample	7.4%	26.3%
	$p < 0.001$	

[a]: matching for age ($p = 0.4$), sex ($p = 0.16$) and occupation

TABLE V

Portal fibrosis (PTT): Kattia vs Ismailia

	Kattia		Ismailia	
	No	Transmission	Endemmic	
Grade 0	74	62.7%	230	53.2%
Grade 1	43	36.4%	190	44.0%
Grade 2	1	0.8%	11	2.5%
Grade 3	0	0.0%	1	0.2%

$p = 0.2$

TABLE VI

Proposal for staging of liver morbidity in *Schistosoma mansoni* infections (Meeting of Ultrasonography in Schistosomiasis, Cairo, 1991)

Stage	0	I	II	III
Preipoertal thickening	-	+/++	+/++	++/+++
Enlarged spleen	-	-	+	+
Enlarged left lobe	-	+/-	+/-	+
Shrunken right lobe	-	+/-	+	+
Portal vein diameter increased	-	-	+	+
Collaterals (Adult)	-	-	+/-	+

- = not pathological; +/- = may or may not be pathological at this stage; +/++/+++ = pathology (grading)

possible alteration in liver size) and only about 10% still not fitting within any of the proposed stages for *S.mansoni* hepatic morbidity. Fig. 4 compares the distribution of study sample among stages using the MOUS staging criteria, the modified staging and the new proposed staging.

DISCUSSION

To our knowledge, our study is the largest population-based study to be reported of the use of ultrasonography for assessment of liver morbidity attributable to *S.mansoni* in an endemic community and the first to involve a representative sample of the population. The standard protocols for procedure, measurement and recording proposed by the Expert Meeting on the Ultrasonography in schistosomiasis (Hatz et al. 1992) have been adopted in our study. To that extent, our findings represent a feed-back to the scientific community on the validity of these proposals which were intended for testing in field conditions.

With a prevalence of *S.mansoni* infection of 40.3% and 1.7% for *S.haematobium* in the study population (Table I), it can be safely assumed that our liver morbidity findings represent largely effects of *S.mansoni* rather than *S.haematobium* infections (Nooman et al. 1974, Abdel Wahab et al. 1992b). However, *S.haematobium* could account for a fraction of recorded liver morbidity particularly in older age groups who were widely exposed to both infections before the decline of that caused by *S.haematobium* over the last decade.

Our study provides data on the prevalence of various ultrasonographic indicators of liver morbidity (Fig. 1), their age (Fig. 2a,b), and gender (Fig. 3) distribution and their relation to prevalence and intensity of *S.mansoni* infection in the studied hamlets (Table II) and in the various age groups (Table III). Most outstanding however are our findings related to the prevalence and specificity of ultrasonographically detected portal fibrosis defined as portal tact thickening ≥ 3 mm diameter (Hatz et al. 1992, Abdel-Wahab et al. 1992a) advocated as the "pathognomonic" ultrasonographic sign of *S.mansoni* induced liver morbidity. Such evidence of portal fibrosis, has been detected in 36.1% of our 2384 ultrasonographically examined population, a high prevalence which is more than double that reported by Homaida et al. (1988b) in a Sudanese population with comparable prevalence and even higher intensity of *S.mansoni* infections, who used different but comparable criteria for diagnosis of peri-portal fibrosis. About 90% of instances of PTT detected in our survey however belonged to the rather mild grade 1, only a small minority of individuals had grades 2 or 3 (Fig. 1). It is likely that the very low prevalence of the latter two grades of severity is an under-es-

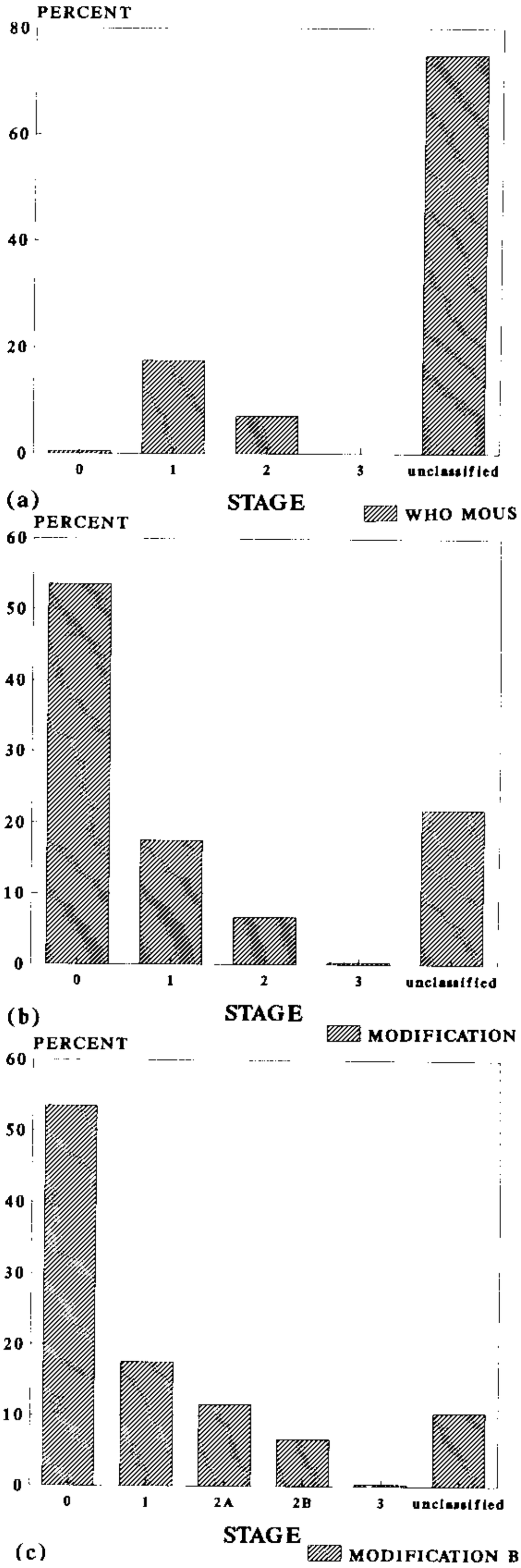

Fig. 4: staging of liver morbidity attributable to *Schistosoma mansoni* morbidity. (a) According to WHO MOUs, Cairo, 1991; (b) Modification A; (c) Modification B.

timation, because very sick people tend to drop out of community-based studies, being more likely to appear in hospital wards. That most of subjects with PTT had the mostly symptomless grade 1 of the disease, could be a favorable outcome of the population-wide praziquentel chemotherapy campaign underway since about four years providing the drug free for all infected patients. There is ample evidence for the resolution and regression of severity of portal fibrosis under the effect of praziquentel chemotherapy (Homaida et al. 1988c). Related to the latter argument is our finding of lack of correlation between all ultrasonographic parameters of liver morbidity and the intensity of infection measured as the egg count/gm stools (Table II). Assuming that the latter observation is attributed mainly to the clearance of infection by effective chemotherapy, our findings would then document the superior role of ultrasonography in the community diagnosis of schistosomal liver morbidity in situations of ongoing control programs (Jenkins & Hatz 1992). Pertinent to this argument, however, is the important question: How reliable, and really specific to schistosomal pathology would be the demonstration of grade 1 portal tract thickening by ultrasound in field conditions? The same rural population would be exposed to myriads of hepatotropic pathogens and insults including hepatitis B and C viral infections, pesticides, phytotoxins etc. that would presumably confound the attributability of milder grades of PTT to schistosomiasis alone. The latter viral marker is prevalent in around 15% of our rural population. Final resolution of the question of specificity of grade 1 PTT to schistosomal infection would be by histopathological evidence, which so far is precluded for ethical considerations as well as the appreciable likelihood of false negative results in schistosomal hepatic fibrosis (Jenkins & Hatz 1992, Abdel-Wahab et al. 1992a). It should be emphasized that histopathological evidence of the specificity of ultrasonographically demonstrated Symmers' clay pipe-stem fibrosis has been provided by two hospital-based studies in which wedge liver biopsy was obtained from patients with unequivocally advanced stages of the disease, who came to surgery. Such stages constitute a minority in most community-based studies. In absence of evidence of usefulness of ultrasonography in the detection of the more common earlier and epidemiologically important grades of liver pathology, the cost-benefit of promoting the use of the procedure in community-based studies to guide control programs may be questioned.

It seems, nevertheless, that in established forms of the disease, there is correlation between the grade of severity of the pathology and the intensity of infection under certain epidemiological conditions. Such relationship was reported by Doehring-Schwerdtfeger et al. (1990) in Sudanese school children aged 6-18 years, and was demonstrated also in our study, but only in the age group 20-59 years old (Table III). It seems that in the latter group, the dynamics of exposure, treatment and host immunity allow for expression of this relationship which has been documented by earlier pathological studies (Cheever et al. 1977).

Our study provided two sets of observations that would presumably help to answer the question of the extent of schistosomal specificity of grade 1 PTT through an epidemiological approach. Our finding of a generally higher prevalence of PTT in *S.mansoni* infected individuals (Table II) than in those lacking evidence of infection as well as history of ever receiving chemotherapy does not minimize the importance of finding PTT in an appreciable number (23-70%) of the latter group. Assuming that closed infections and/or failure to recollect instances of receiving anti-schistosomal treatment in older patients, could account for a fraction of the group lacking evidence of schistosomal infection, it is at least equally probable that this sonographic finding is difficult to attribute solely to schistosomal infection. Our findings are supported by a recently reported community-based study from Brazil (Rocha et al. 1993). Ultrasonography in the latter study of two endemic communities lacked the sensitivity to differentiate *S.mansoni* infected and non-infected individuals. Mention should be made that in the above referred-to Sudanese community-based study by Doehring-Schwerdtfeger et al. (1990), sixty negative school children examined simultaneously did not show any ultrasonographic evidence of portal fibrosis. The design of the latter study as well as the different diagnostic criteria would make comparison difficult with our study and that from Brazil.

A more convincing epidemiological evidence for the need to revise the diagnostic criteria for ultrasonographic diagnosis of schistosomal hepatic morbidity in the field has been provided by our comparative study of the endemic population of rural Ismailia with the non-endemic population of Kattia village in North Sinai (Tables V, VI). Although only around 15% of the 809 available inhabitants of the latter village were examined by ultrasonography, yet the findings are compelling, there was no significant difference in the prevalence of PTT, mostly of grade 1 between the two communities. Most of the Sinai inhabitants are nomadic bedouins, never exposed to schistosomiasis in their life time.

Our testing of the usefulness of the tentatively proposed staging of schistosomal liver morbidity and its sequelae (Table VI, Fig. 4) has indicated that the classification is quite unsatisfactory. Our

proposed modification (Table V) is a trial based on our findings in the field. It is felt however, that before such modifications would be considered for further application, revision of the criteria for the diagnosis and grading of the severity of portal fibrosis attributable to schistosomiasis is urgently needed.

In conclusion, our findings support the usefulness of ultrasonography for diagnosis of moderate and advanced grades of liver pathology attributable to schistosomiasis. The procedure however proved of doubtful usefulness in measuring the more frequently encountered earlier grades of the disease. Until more solid criteria for the diagnosis of the early grades under field conditions are generated, the cost-benefit of applying this procedure in population-based studies to guide the planning and evaluation of control programs will remain, in our opinion, in question.

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