

tension permitted easy regulation of the blood-pressure in out-patients.

Since the thalidomide disasters both doctors and mothers are understandably hesitant about the use of a new drug during pregnancy. It is therefore reassuring that we found no evidence of ill effects on the foetus in patients treated in the first trimester or with doses of methyldopa up to 4 g. daily.

The perinatal mortality rate of 9.3% does not seem excessive for this group of severely hypertensive women, particularly as one of the three foetal deaths was thought to be unrelated to the hypertensive disease, which reduces this figure to 6.2%. Townsend (1958), studying a similar population group in Melbourne, found a perinatal mortality of 16% when mothers had an initial diastolic pressure of 110 mm. Hg, and this figure rose to 50% in patients in whom this degree of hypertension was complicated by proteinuria. Twelve of our patients had proteinuria, including the two who lost their babies as a result of developing pre-eclamptic toxæmia before the thirtieth week.

As MacGillivray (1964) has pointed out, only a careful controlled trial will establish whether hypotensive drugs increase the rate of successful pregnancies in hypertensive mothers.

We are now conducting a controlled trial of methyldopa in pregnancy hypertension because we feel that it has definite practical advantages as well as the possible theoretical advantage of inhibition of decarboxylase (*Brit. med. j.*, 1964).

### Summary

Methyldopa has been used to control hypertension in pregnancy for periods up to the whole gestation time without any apparent adverse effect on the foetus.

The blood-pressure can usually be easily controlled on an out-patient basis and side-effects were minimal.

Only 3 out of 32 severely hypertensive women lost their babies, and as one foetal death was due to premature rupture of the membranes the corrected perinatal mortality rate was only 6.2%.

We are grateful to the obstetric staff of the Queen Victoria Hospital for referring their patients for treatment, and to Merck Sharp and Dohme (Australia) Limited and Dr. D. C. Mezey, Director of International Clinical Research, for supplies of Aldomet for this study. Professor R. R. H. Lovell gave helpful advice about the analysis of the blood-pressure findings, and the statistical analyses were carried out by Miss B. Laby, of the University of Melbourne, Department of Statistics.

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## Trial of Ambilhar, a Nitrothiazole Derivative, in *S. mansoni* Infections in Tanzania

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The schistosomicidal action of Ambilhar† (a nitrothiazole derivative, 1-(5-nitro-2-thiazolyl)-2-imidazolidinone) in mice infected with *Schistosoma mansoni* was reported by Lambert (1964). Preliminary observations of its use in man were recorded by Jordan (1966a), and the present communication reports parasitological findings obtained four months after treatment.

### Methods and Materials

The use of the percentage reduction in egg load was suggested by Jordan and Randall (1962) for assessing results of suppressive therapy in *Schistosoma haematobium* infections, and Bradley (1963) showed that the "cure rate" in this infection was inversely proportional to the initial egg output. Bell (1964) outlined the advantages of using the former parameter of chemotherapeutic activity of schistosomicidal drugs and devised a new method for the necessary quantitative studies in relation to *S. mansoni* infections (Bell, 1963). This method was used in the present trials. Bell (1964) stressed that a 100% reduction in egg load (by the filtration-staining technique) does not in fact imply a cure, but merely an egg output of less than 1,000 eggs a day. Within this context "cure rates" are given for results obtained by the filtration-staining technique. On the other hand, this method, combined with further stool examinations and the use of other techniques, more closely approaches what may be necessary to evaluate a true parasitological cure, and when three techniques have been used and three or four

stools examined the absence of evidence of *S. mansoni* is considered for the purpose of this communication to represent a cure.

Children and adults excreting eggs of *S. mansoni* were treated in these trials. The former were found infected in school surveys; the latter requested treatment—invariably complaining of abdominal pain—and on investigation were found to be infected. All patients were treated as in-patients with a dose of 25 mg./kg. body-weight daily (in two doses) for five days.

Prior to treatment patients were given a general clinical examination, and a 24-hour collection of stool was made for processing by the filtration-staining technique (Bell, 1963) in order to assess the 24-hour output of *S. mansoni* eggs and to give an indication of the intensity of infection.

At follow-up examination two and four months after treatment, patients were readmitted for the collection of a further 24-hour stool for quantitative determination of the egg load, and an additional stool was collected; three 1-g. aliquots were examined for *S. mansoni* eggs by the A.M.S. III technique (Hunter *et al.*, 1948), the rest of the stool being treated for hatching of eggs and examination for miracidia. Thus at the follow-up examinations three or four stools were generally examined and three different techniques were used for the detection of eggs or miracidia.

### Results

Comparative results of the quantitative filtration-staining technique two and four months after treatment were obtained

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TABLE I.—Comparative Results of Examining a 24-hour Stool from 40 Patients Two and Four Months After Treatment

	"Cured"	Reduction in Egg Load
2 months	42.5%	86.0%
4 "	35.0%	76.2%

from 40 patients (Table I). Forty-three patients were examined at four months by the three techniques outlined above. The results are as follows:

Number positive by A.M.S. III technique ...	10
Number positive by hatching technique ...	21
Number positive by filtration-staining technique ...	29
Total number positive for eggs or miracidia ...	33
Overall cure rate—10 of 43 patients ...	23.2%

The results obtained at four months from all three techniques applied to the 43 patients have been used to investigate the influence, if any, of the patient's age and the initial intensity of the infection on the cure rate (Table II).

TABLE II.—Number of Cures (as Assessed by Three Techniques)—in Relation to Age and Egg Load per 24 Hours

	Egg Load per 24 Hours		
	< 10,000	> 10,000	Total
Adults	6/12*	2/6	8/18
Children	2/6	0/19	2/25
Total	8/18	2/25	10/43

\* Numerator = number cured; denominator = number examined.

This analysis suggests that the results of treatment might be affected by the intensity of infection and the age status of the patient. In order to examine the latter in further detail, by excluding the influence of the former, children and adults excreting similar egg loads before treatment were matched and results of the two series compared (Table III). Though there were results at the four-month follow-up from 18 adults, it was possible to match only 10 with children, since the latter patients tended to have higher egg counts (mean 65,100 per 24 hours) than the former (mean 12,500 per 24 hours).

TABLE III.—Results from Children and Adults Matched for Egg Load per 24 Hours

Children				Adults			
Egg Load in Thousands	% Reduction in Egg Load	A.M.S. III	Hatch Test	Egg Load in Thousands	% Reduction in Egg Load	A.M.S. III	Hatch Test
0.8*	100	Neg.	Neg.	0.6*	100	Neg.	Neg.
1.8	100	Pos.	Pos.	2.0*	100	"	"
9.5	50	Pos.	"	6.7	92	"	"
13.0	86.4	Neg.	Neg.	8.3	100	Pos.	Pos.
13.0	92.4	"	Pos.	14.0†	87.1	"	Neg.
16.3	19.6	"	Neg.	16.0	98.1	Neg.	"
18.6	86.5	"	Pos.	17.6*	100	"	Pos.
20.0	85.0	Pos.	Neg.	22.0	95.4	"	Pos.
53.6	95.7	Neg.	Neg.	49.3*	100	"	Neg.
56.0	85.8	Neg.	Pos.	63.6	100	Pos.	Pos.

\* Indicates cases cured. † A.M.S. III test positive, hatch test negative.

While the cure rates suggest that adults were more successfully treated than children, the difference in the results from these matched pairs was not statistically significant. On the other hand, Wilcoxon's rank order test, when applied to the percentage reduction in egg load, showed the two series differed significantly ( $P < 0.02$ ).

### Discussion

Results of the three techniques of stool examination used in these trials reflect the different quantities of stool used in carrying them out. Thus few stools were found positive for *S. mansoni* eggs with the A.M.S. III technique where only a small quantity of faeces was concentrated; more positives were found when the rest of the stool was examined by the hatching test; and more still were found when the 24-hour stool collection was examined. These results are to be expected in post-therapy examinations when the egg load is low, and the more

faecal material that is examined the greater will be the number of positive cases found. In only one case was the A.M.S. III test positive and the hatching test negative on the same stool, suggesting that in this case the eggs found were non-viable.

The results at four months are a little less satisfactory than at two months (Table I). This is generally accounted for by the recovery of adult worms from the effect of the drug (though how long this takes is unknown), by full development of worms maturing at the time of treatment, or by reinfection.

In view, however, of our lack of knowledge relating to immunity and superinfection and the influence of treatment on them in humans, and our inability to distinguish between "failed cures" and reinfections, these are only theoretical possibilities to account for treatment which fails to stop egg excretion. If, however, reinfection does occur, it is not possible to distinguish such cases from those still excreting eggs after unsuccessful treatment. It is of interest, however, that, whereas the reduction in egg load was generally in the order of 85–100% (Table III), in two children of the matched series the figure was much less than this, and in one of these cases there was an increase in egg load. When the preliminary results of these trials (Jordan, 1966a) were considered, patients responding poorly to treatment at the two-month follow-up were noted, and it was suggested that such cases might in fact be examples of reinfection or maturing infections.

Quantitative investigations in bilharziasis are in their infancy, but when more experience of the techniques and the interpretation of results has been obtained, and when more is known of immunity and superinfection, particularly in relation to treatment, a more accurate interpretation of such findings might be possible.

The results in Tables II and III confirm that the age status of the patient may affect the results of treatment, as was suggested by Newsome (1962). The reason for this is unknown, but it may be that treatment is aided by the possibly more effective immunological status of the adult as compared with that of children. It would appear that this effect is operative in adults irrespective of the loads of infection found in the present series.

The finding that among children the cure rate was higher in those lightly infected is similar to the findings in children infected with *S. haematobium*, and the reasons for this have been discussed (Jordan, 1966b). Of importance in this respect is the difficulty of detecting low numbers of eggs in the faeces after treatment, with the result that false cures may be reported unless stringent tests are applied—as shown above, the "cure rate" obtained by the different tests used in these trials showed considerable variation. It might be expected, therefore, that lightly infected cases with few eggs before treatment and fewer still after, would show a higher cure rate than those more heavily infected. With this in mind Bell (1964) treated only children with an egg load of 10,000 or over per 24 hours, and in data provided by him there is no evidence of "cure" being related to egg load. In an earlier series (Bell, 1965), however, where a relatively crude quantitative smear technique had been used without selection of patients, there was evidence that the cure rate was related to intensity of infection—no doubt due to patients with small numbers of eggs being falsely classed as "cures" with the crude tests used.

The results obtained by the filtration-staining technique in children with a 24-hour egg load of over 10,000 are compared with those in Bell's (1964) series of TWSb-treated cases (Table IV). The results suggest that TWSb in the five-day course

TABLE IV

	Ambilhar	TWSb
Results at 2 months	2/19 "cured"; 82.4% reduction in egg load	12/38 "cured"; 88.7% reduction in egg load
" " 3 "	"	"
" " 4 "	0/20 "cured"; 76.6% reduction in egg load	"

given (30 mg./kg. body-weight) is more effective than is Ambilhar given at a dose of 25 mg./kg. body-weight for five days.

### Summary and Conclusions

Ambilhar, a nitrothiazole derivative, was given in a dose of 25 mg./kg. body-weight/day for five days to children and adults excreting eggs of *Schistosoma mansoni*.

Comparison of the results from adults and children matched for egg output show that adults were more readily "cured" than children, and there was evidence that cure was less likely in heavily infected children.

It is considered that the results of the present trials emphasize the necessity for quantitative studies of egg output to be made in trials of schistosomicidal drugs, and the need for caution in interpreting "cure rates" from drug trials in adults in endemic areas and from patients with light infections. In the absence of cure, the percentage reduction in egg load may provide data of antischistosomal activity.

It is suggested that the dose of Ambilhar was insufficient to produce satisfactory cure rates, but with the comparatively low incidence of side-effects (Jordan, 1966a), particularly among children, the dose can probably be increased with the expectation of better results.

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## Ulcerative Colitis and Finger-clubbing\*

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A number of investigations into the aetiology of finger-clubbing have been carried out. Some authors have suggested that the vagus nerve is implicated, since most of the diseases with which finger-clubbing is associated involve tissues innervated by this nerve and also because section of the vagus nerve supply to these tissues can be followed by the disappearance of the clubbing. Flavell (1956) observed its disappearance after hilar dissection of the vagus nerve performed to relieve the symptoms of hypertrophic pulmonary osteoarthropathy in three patients with inoperable bronchogenic carcinoma. Exploratory thoracotomy alone in two other patients with the same pathology had no effect on finger-clubbing. Similar findings were reported by Holling *et al.* (1961), who, in addition, recorded that ligation of the arterial supply to a pulmonary malignant lesion without dissection of the vagus nerve at the hilum had no effect on finger-clubbing. The large bowel is interesting in that it is innervated by the vagus nerve only as far as two-thirds of the distance across the transverse colon—that is, the part developing from the mid-gut (*Gray's Anatomy*, 1962). Thus, if the vagus is the afferent part of a neural reflex in the pathogenesis of finger-clubbing, the length of bowel affected by ulcerative colitis will have an influence on the presence or absence of finger-clubbing.

Diseases of the gut with which finger-clubbing has been associated are: ulcerative colitis (Schlicke and Bargaen, 1940; Mendlowitz, 1942; Honska *et al.*, 1957), multiple polyposis (Brulé and Lièvre, 1932; Bensaude *et al.*, 1932), chronic bacillary dysentery (Mendlowitz, 1941), amoebic dysentery (Brulé *et al.*, 1937), regional enteritis, tuberculosis, Hodgkin's disease, carcinoma, and sprue (Mendlowitz, 1942), ascariasis (van Creveld, 1931), duodenal ulcer with pyloric stenosis (Dennig, 1901), and idiopathic steatorrhoea (Bennett *et al.*, 1932). All these diseases involve tissues with a vagus nerve supply. Moulouquet and Salomon (1932) did, however, describe two cases of finger-clubbing associated with inflammatory stricture

of the rectum, but, although they excluded coexisting chest disease as a cause of the clubbing, they did not demonstrate the extent of the colonic disease.

The present study was undertaken in order to try to establish the relation between finger-clubbing and the extent of colonic involvement in patients with ulcerative colitis.

### Material and Method

All case reports of patients admitted to the Royal Victoria Infirmary, Newcastle upon Tyne, over the past 10 years with a diagnosis of ulcerative colitis were examined. The criteria for inclusion in the study were: (1) the patient must have had a barium-enema examination or a laparotomy at which the extent of colonic involvement was determined and histological confirmation of the diagnosis obtained; (2) the case report must have included a definite statement as to the presence or absence of finger-clubbing; and (3) the patient must have had a chest x-ray examination showing that no intrathoracic disease was present.

The 156 patients who fulfilled the above criteria were divided into two groups: (1) those with ulcerative colitis involving the whole colon or the part of the colon innervated by the vagus nerve, and (2) those with the disease limited to the distal colon, not innervated by the vagus nerve. The number of patients with and without finger-clubbing was recorded within each group.

### Results

Of the 77 patients in group 1, seven were affected by finger-clubbing, whereas no single case of it was found among the 79 patients in group 2. The probability of the finger-clubbing in the seven patients in group 1 and the absence of it in all patients in group 2 being a chance occurrence is 1 in 128 ( $P=0.008$ ).

Among the patients with finger-clubbing two had a fulminating course followed by death within one month and eight months respectively of the onset of symptoms of ulcerative

\* Based on a paper read at a meeting of the Association of Physicians of Area No. 1 on 17 July 1965.

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