and for carrying out an intradural repair as recommended by Cairns (1942). By this means the whole of the anterior fossa and anterior temporal regions on both sides can be inspected without difficulty.

In both the cases of cerebrospinal fluid otorrhoea (Cases 3 and 4) the operative findings showed that all the intracranial bleeding had ceased some time before operation, almost certainly soon after the injury—that is, eight days previously in Case 3 and four days previously in Case 4—yet in both, while the leakage of cerebrospinal fluid persisted, the state of consciousness remained satisfactory or improved. At that stage perhaps the only indication of the presence of a clot, short of air studies or angiography, might have been shift of the pineal body had it been calcified and visible on plain x-ray films of the skull. When the leakage of cerebrospinal fluid diminished, both patients quickly became comatose and developed severe hemiparesis with, in one case, evidence of a third-nerve lesion. Thus it seems that the intracranial blood clots, subdural and intracerebral in one case and extradural in the other, began to compress the brain only when the intracranial pressure rose as a result of the cessation of leakage of cerebrospinal fluid. Such cases, therefore, call for special observation when the leakage of cerebrospinal fluid is diminishing.

In the presence of leakage of cerebrospinal fluid, other causes of deterioration of consciousness and of the neurological state of the patient are spread of infection intracranially and epilepsy. Meningitis usually produces fever and neck stiffness before clouding of consciousness and can be diagnosed with certainty by lumbar puncture. Intracranial abscesses may produce a very similar picture to intracranial haematoma, but it is unlikely that the onset of symptoms will coincide with the cessation of leakage of cerebrospinal fluid. Epilepsy, when a fit has passed unobserved, would be suspected when the loss of consciousness had been very sudden, and, in the absence of further fits, would be followed by rapid spontaneous improvement. Treatment of the intracranial haematoma consists essentially in its evacuation. Fortunately, this is more easily performed than in the case of an acute haematoma requiring operation soon after injury, as bleeding from the vessel responsible for the formation of the clot will have ceased some time previously.

Summary

Profuse cerebrospinal fluid rhinorrhoea or otorrhoea resulting from head injury, by lowering intracranial pressure, may facilitate the formation of large intracranial haematomas.

While the leakage of cerebrospinal fluid persists there may be no deterioration of consciousness and no abnormal neurological signs to suggest the presence of a haematoma.

When the leakage of fluid diminishes there is a need for special observation, as a haematoma, if present, may begin to compress the brain and require urgent evacuation.

Four illustrative cases are described.

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MASS THERAPY WITH PIPERAZINE ADIPATE IN THE CONTROL OF THREADWORM INFESTATIONS

BY

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Shetland Isles

Many attempts have been made to evaluate the success of vermicides against threadworms (*Enterobius vermicularis*), notably that by Standen (1953). In recent years attention has been focused on piperazine, following the studies by Mouriquand *et al.* (1951) and Turpin *et al.* (1952). White and Standen (1953) regarded piperazine hydrate as the drug of choice for the treatment of threadworms in children. However, it seems that all these trials were made on selected populations—namely, children admitted to hospital for medical or surgical treatment. Furthermore, in each trial only individuals or, at most, families, were treated, and the tests ended at the cure of the patient. No follow-up was made to discover how soon reinfestation occurred. For these reasons the following account of an attempt at mass therapy, with a six-months follow-up of the results, may be of interest.

I am the sole medical practitioner on an island in the Shetland Isles with a total population of 866. Of these, 194 are children aged 1 to 14 years. I noticed that a number of children (18 in three months) were brought to me by their mothers suffering from the effects of "worms." In each case a threadworm infestation was found. It soon became apparent that treatment of the children individually did not eliminate the condition, owing to the rapid reinfestation which occurred. I therefore decided to undertake a form of mass therapy. This has previously been shown to be most effective in other helminthic infestations—for example, hookworm. Expense ruled out the treatment of every person on the island, so I decided to treat all the children aged 1 to 14 years. Piperazine adipate was used. A form requesting permission to do this was sent to their parents, who without exception gave their consent.

Incidence of Infestation and Symptoms

In order to estimate the frequency of infestation, 50 children living within easy access of the surgery were swabbed with adhesive "cellophane" tape swabs, and the specimens examined microscopically. A child was adjudged infested if two or more ova were found on the slide, and no child was regarded as free until five specimens had been examined. The main difference between this sample of children and the total child population of the island of the same age consisted in rather better than average housing conditions in the sample group and a higher proportion of children under 8 years of age—62% (31 out of the 50) compared with 41% for the whole island.

The age distribution of the sample group of children is shown in Fig. 1, and of those found to be infested with threadworms in Fig. 2. Thirty-two (64%) of the sample group were infested. There was a high infestation rate in those aged 2 to 11 years, while those under or above these ages were less often infested. In Fig. 3 the number of specimens necessary to obtain a positive result is given: 27 (84%) of the 32 positive results were obtained after examining three specimens. Fig. 4 shows how the percentage of infested children in a family rose with the number of children in the family. The apparently anomalous finding for families with three children is accounted for by the fact that three of the four families investigated go around persistently as a tight knot of little girls, hand in

hand, leading their younger siblings and forming a constant group comparable to a family association of nine children.

The clinical histories of the children in the sample were obtained from their mothers, who were asked: Has your child had anything wrong with him during the last two months? Has he suffered from itching or scratching of his bottom, bed-wetting, nightmares, or teeth-grinding? Have you yourself suffered lately from worms? The answers to these questions are summarized in the Table. The clinical histories were then correlated with the results of the swab examinations. Of the 34 children with no symptoms, 17 had positive swabs and 17 negative. Of the 16 children with symptoms, 15 had positive swabs and one was negative.

Details of Sample Group

	No.	Microscopical Examination	
		No. Positive	No. Negative
No. without symptoms ..	34	17	17
" with ..	16	15	1
Pruritus ..	6	5	1
Enuresis ..	6	6	0
Nightmares ..	1	1	0
Teeth-grinding ..	4	4	0

FIG. 1.—Age distribution of whole group (194 children) and of sample group (50 children).

FIG. 2.—Age distribution of the 32 infested children in the sample group.

When individual symptoms were considered, it was found that five of the six children with pruritus had positive swabs and one was negative; all the six children with enuresis were positive; the one child with nightmares was positive; and all the four children exhibiting teeth-grinding were positive. (One child suffered from both pruritus and enuresis.)

Method of Mass Treatment

On the day after the last swabs had been taken every child on the island aged 1 to 14 years began a course of piperazine adipate at a daily dose of 300 mg. per year of age up to a maximum of 1.8 g. a day. The piperazine, which was in tablets containing 300 mg. of the adipate, was given for seven days, stopped for seven days, and then given for a further seven days.

Through the courtesy of the headmasters of the two schools on the island it was arranged that the school-age group should receive their vermicide at school so far as was possible. They were dosed by their individual teachers on arrival at school again at midday, and for a third time just before leaving in the afternoon. Since the courses lasted seven days, each child on leaving school on Friday was given enough tablets for Saturday and Sunday. Thus it was certain that these children (151) took their tablets

for at least five out of the seven days. Since piperazine acts with maximum effect after three days' treatment (Turpin *et al.*, 1952), even five days' treatment should be effective. The piperazine for the children below school age (43) was distributed by the district nurse and myself, and the importance of its regular administration was emphasized. Mothers were instructed to pulverize the tablets if any difficulty was experienced in giving them whole. Each parent was given a form setting out basic rules of hygiene—for example, cutting the nails short, washing hands before meals, etc.—and a request to report any illness, however slight, in any child during the campaign.

Since the islanders are, in general, people of integrity, I feel sure that nearly all the children did get the treatment recommended. Only two of the sample (4%) failed to do so, and this figure is probably also representative of the island as a whole.

Results of Treatment

Fourteen days after the completion of treatment the 32 children in the sample group who had been previously found to be positive were swabbed on six successive

FIG. 3.—Number of specimens needed before positive result was obtained in the 32 cases.

FIG. 4.—Percentage of children infested related to number of children in family.

mornings. Only two of these children, a boy aged 3 years 11 months and a girl aged 2 years 3 months, both from the same large family, were found to be still positive. On inquiry the mother confessed that, in spite of every effort, she had been unable to induce these children to take the tablets. After a further course of treatment, with the tablets made into a mixture, both children became negative.

Six months later the whole sample group was swabbed again. Twenty children were infested—that is, 40% of the group compared with the 64% who were found to be infested before treatment began. The age distribution of these 20 children was much the same as those originally infested (Fig. 5). Of the 32 originally positive, 18 had

FIG. 5.—Age distribution of the 20 infested children in the sample group six months later. (See Fig. 2.)

become reinfested, and two who were originally negative had become positive. One of the latter, a boy, was originally the only one negative in a family of five children; six months after treatment all of this family were reinfested. The other, a girl, came from a family of four children, two of whom were positive originally, and two of whom had become reinfested after six months.

Originally, 12 of the 14 families in the sample were infested. Six months after treatment only six families were infested. Twenty out of the 24 children (83%) in these six families were infested on both occasions, whereas in the other eight families only 12 of the 26 children in them (46%) were infested originally and none six months later. The mothers in the six families found to be infested on both occasions were all themselves infested; five of the fathers were absent from home for at least 90% of the time, and the remaining father was not swabbed.

FIG. 6.—Number of specimens needed before positive result obtained in the 20 cases.

At the follow-up, positive swabs were obtained more readily than before treatment, 65% of the positives being found at the first swab and 90% by the third (Fig. 6). But it was my impression that the ova on each positive slide were much fewer than at the original swabbing. However, as counts were not done, this cannot be stated with certainty.

The original questionnaire about symptoms was repeated to each parent in the sample group six

months after treatment was completed, care being taken, so far as was possible, not to influence the replies. Of the 16 children who originally had symptoms, eight were now free of them, and one was free of one of his symptoms. Three children were relieved of pruritus, four of teeth-grinding, and one each of the nightmares and enuresis. The child who had had both pruritus and enuresis was cured of both for a time, but later the enuresis recommenced. Of the nine* children relieved of symptoms, three (one pruritus, one enuresis, and one teeth-grinding) had become reinfested. Of the eight children who were not relieved of their symptoms, five had enuresis and three pruritus. Six of these children had become reinfested; the two who were not reinfested suffered from enuresis. One of these was a boy of 2 years 7 months, the other a girl of 10 years whose father had been absent for seven years undergoing treatment for tuberculosis.

All the children in the sample who were still positive after six months were then given a further course of piperazine adipate. One month after the completion of this course they were all negative. At this date all symptoms had disappeared, except that the five children with enuresis were still as badly affected as ever.

Side-Effects

Few side-effects were experienced by the 194 children who were treated. On the first day of treatment, three girls (aged 7 years 3 months, 5 years 8 months, and 3 years 6 months) were reported to have vomited after their evening meal. The eldest of these was found to have enlarged and inflamed tonsils and a temperature of 101° F. (38.3° C.), and the piperazine was stopped. The other two were feeling quite well when seen, and, as no abnormality could be discovered on examination, their treatment was continued without further ill effects.

On the fourth day of treatment a boy aged 4 years 1 month vomited but was quite well when seen. He completed his course without further ill-effects. On the sixth and seventh days three boys in the same family (aged 11 years 2 months, 7 years 11 months, and 5 years 6 months) developed slight diarrhoea. Two other boys in the family were unaffected. The upset was so slight that I was not told about it until treatment had been completed. During the second course no side-effects were reported.

Conclusions

Piperazine adipate is an effective and safe vermicide. Of the 30 infested children in the sample who completed treatment, all were free of ova two weeks later; and, although seven cases of vomiting or diarrhoea among the 194 children treated were reported, one of these was undoubtedly caused by a concurrent infection and the remainder were of so slight a nature that the children concerned missed no time at school and when examined no abnormality could be found. No child missed a dose of vermicide because of side-effects. With piperazine adipate it is possible to disinfect a community of children by mass therapy, but unless the parents (especially the mothers) are treated at the same time reinfestation soon follows.

Although a large number of children were positive six months after treatment, their infection did not appear to be so heavy as originally. In addition, I have had only one complaint of infestation since the mass treatment, as opposed to 18 in three months before it was done.

There appears to be some relationship between the symptoms of pruritus, teeth-grinding, and nightmares and infestation with threadworms. Ten children with these symptoms were cured of them when freed from threadworms. Of six children with enuresis, however (12% of the sample), only one was cured when treated for threadworms, but she was infested at the second examination. Her cure would appear to be coincidental. In the other five the enuresis was unaffected by treatment.

*This figure includes the child in whom one of his two symptoms had been relieved.

Summary

The mass treatment with piperazine adipate of all the children aged 1 to 14 years on one of the Shetland Isles is described. The object was to rid them of threadworms. A total of 194 children were treated.

A sample group of 50 children were examined by anal swabs, and their mothers questioned about their symptoms, before and after treatment. Before treatment 32 were found to be infested with threadworms. Two weeks after treatment all 30 who completed the course were free of infestation. Six months later 20 had become reinfested, but one month after a second course of treatment all were again free. There was also amelioration in symptoms, generally ascribed to threadworm infestation, with the notable exception of enuresis.

Side-effects of treatment were few and unimportant.

It is concluded that mass treatment with piperazine adipate is effective in eradicating threadworm infestation in a community of children, but to prevent relapse parents, especially the mothers, must be treated at the same time.

My thanks are due to Dr. S. A. B. Black, medical officer of Health for Zetland, for his advice and encouragement; to Nurse Cowie, who helped to distribute the piperazine adipate; to the headmasters of Livister Primary School and Brough Secondary School for their willing co-operation; and to British Drug Houses Ltd., who generously supplied, free, the large amount of piperazine adipate required in the form of "entacyl" tablets. My thanks are also due to the mothers and children of the sample group who conducted, and submitted to, the numerous tedious and embarrassing swabbings which were necessary.

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WHIPWORM INFECTIONS TRIAL OF FOUR PIPERAZINE COMPOUNDS

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A simple satisfactory treatment for *Trichuris trichiura* (whipworm) infections in man has yet to be found. Some success in apparently light infections has been obtained with hexylresorcinol enemata and papain (Jung, 1954; MacCarthy, 1954). The worm is seldom said to give rise to severe symptoms, but if a safe and easily administered drug is found to be effective against some intestinal helminths it should be tried against *T. trichiura* also. It was noted that the ova of this worm appeared irregularly in the stools in light infections, so a comparison of a quantitative nature in groups of patients was thought more likely to give a reliable indication of the efficacy of a drug than qualitative comparisons in individual patients.

The piperazine compounds are very safe and effective against roundworms and threadworms. A trial of piperazine hydrate and adipate against *T. trichiura* infections in children has been reported from Australia by

Dunn (1955), who found that the hydrate, in a dosage of 75 mg. per kg. of body weight daily for three days, cleared only 4 out of 22 (18%) children of ova; but he found the adipate cleared 28 out of 31 (90%) children of ova in dosage of 300 mg. per year of age, to a maximum of 1,800 mg. daily for three days. An opportunity to study the adipate again, and also to try other piperazine compounds, occurred in the autumn of 1955, when news was received of heavy *T. trichiura* infections among patients at a hospital for mental deficiency. An account of the clinical aspects of these is under preparation by one of us (A.G.H.). The therapeutic trial of four piperazine compounds is reported here—the phosphate, citrate, sebacate, and adipate.

Details of Trial

The patients were divided into four groups, each of 20 individuals, and all members of each group were given one of the drugs. Most of the patients were boys aged 7 and upwards, but four were adults. The stools of all the patients in each group were collected just before treatment and the number of eggs per gramme was estimated by a modification (Caldwell and Caldwell, 1926) of the Stoll method using sugar solution. We are indebted to Mr. F. R. N. Pester, of the Helminthology Department, London School of Hygiene and Tropical Medicine, and Mr. K. A. Fuller, of the Wellcome Laboratories of Tropical Medicine, for undertaking the egg counts. For the phosphate, citrate, and sebacate the dosage given was equivalent to 500 mg. of piperazine hexahydrate three times daily for seven days in all cases. The dosage of the adipate was 600 mg. (equivalent to 502 mg. of hexahydrate) three times daily for seven days. No other measures, such as starvation or purgatives, were employed. No side-effects of the drugs were noted. Two weeks after the completion of the course of treatment the stools were again collected and examined by the same observer as had examined them previously. The observers were kept in ignorance of the nature of the preparation administered to each group.

In the stools of three patients there were ova after, but not before, treatment; and in the stools of one patient there were ova before, but not after, treatment. High egg counts, up to 75,000 per gramme of faeces, were found in some cases. The difference between the number of eggs per gramme of faeces before and after treatment was calculated for each patient. In some, especially those with comparatively light infections, large differences were noted, but these tended to cancel each other out when the mean difference for each group was calculated.

Details of Four Groups

Group	Compound of Piperazine	No. of Infected Patients	Mean Egg Count per g. Faeces before Treatment	Mean Difference in Egg Count after Treatment	Standard Error of Difference	t	P
I	Phosphate	17	4,400	+1,315	±686	+1.92	0.1-0.05
II	Sebacate	17	6,600	-2,176	±2,593	-0.84	0.4
III	Adipate	18	3,900	-367	±478	-0.77	0.4-0.5
IV	Citrate	18	10,400	+456	±602	+0.76	0.4-0.5

The mean difference for each group and its standard error are shown in the Table. The application of "Student's" t test to these figures shows that none of the means was significantly different from zero. None of the compounds of piperazine, tested in doses which are effective against *Ascaris lumbricoides* and *Enterobius vermicularis*, had any action on *T. trichiura*.

Summary

A trial of the therapeutic effects of four piperazine compounds—the phosphate, sebacate, adipate, and