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TREATMENT OF TRICHURIASIS WITH DITHIAZANINE

A PRELIMINARY REPORT

BY

D. H. D. PAINE, M.B., B.S., D.P.M.
Consultant Psychiatrist and Physician-Superintendent, Tatchbury Mount Hospital, Southampton, and Coldharbour Hospital, Sherborne, Dorset

E. S. LOWER, M.R.C.S., L.R.C.P., D.P.M.
Deputy Physician-Superintendent, Coldharbour Hospital, Sherborne, Dorset

AND

T. V. COOPER, M.B., B.S.
County Pathologist for Dorset; Director of Pathology, West Dorset Group of Hospitals

Human infestation with whipworm (*Trichuris trichiura*) is said to be world-wide, and both Stoll (1947) and Faust (1949) have estimated that about 355 million persons are affected. Faust stated that the worm is most prevalent in the warm moist regions of the world, where ascariasis may coexist with trichuriasis in the same host, but he gives the incidence of whipworm infestation in Europe as 34 million.

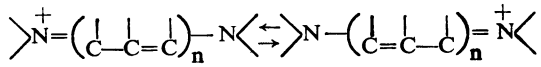
Despite the known prevalence of human infestation, there was no satisfactory treatment until Swartzwelder *et al.* (1957) described the use of dithiazanine against trichuriasis and other worm infestations. Faust refers to the use of oil of chenopodium, carbon tetrachloride, latex of the fig tree ("higueronia"), and emetine hydrochloride, but none of these preparations is considered satisfactory. Jung (1954) described the use of hexylresorcinol enemata; and Dunn (1955) claimed success in 28 out of 31 children treated with piperazine adipate. With the same compound Hoekenga (1956) reported a 50% cure rate from single-dose treatment, but other workers, including Swartzwelder *et al.* (1956), failed to confirm these findings. Hucker and Schofield (1956) observed no therapeutic effect in a trial of four piperazine compounds, used orally, on patients heavily infected with whipworm.

The following report describes the preliminary findings in six mentally defective patients, treated with dithiazanine at Coldharbour Hospital, who were found to be carriers of a moderate whipworm load as judged by faecal egg counts. A more extensive trial is being conducted as larger quantities of dithiazanine become available.

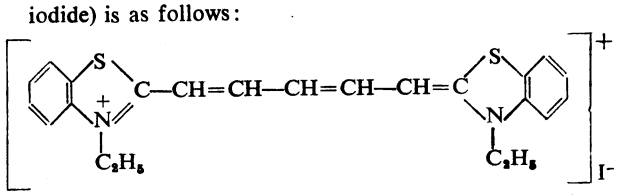
The adult whipworm is usually found in the human caecum, but may also occur in the colon and rectum and posterior part of the ileum. The female worm may measure up to 5 cm.; the male rather less. Trichuris eggs are barrel-shaped, having an outer and inner shell and transparent polar prominences. The eggs measure about 50 μ in the long axis. Infection can occur only by the ingestion of fully embryonated eggs, a process which requires three weeks in a warm moist habitat. After the egg is ingested a further three months must elapse before the worm can complete its development and begin egg-laying. Migration of the larva to other parts of the body does not occur.

The anthelmintic effects of the cyanine dyes, and of dithiazanine in particular, have been investigated by Peters *et al.* (1949) and by Swartzwelder *et al.* (1957). It seems that the action of the cyanines is due to their interference with oxygen uptake and carbohydrate metabolism, and the fact that certain parasitic worms make use of enzyme systems different from those required by mammalian tissues. Bueding and Swartzwelder (1957) have shown that the "amidinium" ion system is responsible for inhibiting oxygen uptake in the filarial worm of the cotton-rat and that cyanine dyes cause an irreversible inhibition of anaerobic carbohydrate metabolism in *Trichuris vulpis*, the whipworm of dogs. In human trichuriasis the cyanines probably affect metabolism in the worm by inhibiting oxidative processes and also anaerobic reactions. Bueding and Swartzwelder state:

> "The amidinium ion system in which a quaternary nitrogen is separated from a tertiary nitrogen by a resonating or 'conjugated' carbon chain of alternating double and single bonds" is illustrated thus:



> "If both nitrogens are incorporated in two heterocyclic rings, such compounds are known as cyanines." The formula for dithiazanine (3,3'-diethylthiadicarbocyanine iodide) is as follows:



Trichuriasis was found by one of us (T. V. C.) at Coldharbour Hospital in January, 1955, when a patient under investigation for loss of weight, anorexia, and episodal diarrhoea showed a large number of eggs in the stools. Other patients subsequently examined also showed unusually high trichuris egg counts, which were in the region of 30,000 eggs per g. of faeces. Further tests revealed that about half the 160 patients in the hospital were infected. Measures to prevent the spread of whipworm have been largely successful, but various therapeutic trials up to December, 1957, gave negative or equivocal results. Following the papers by Swartzwelder *et al.* (1956, 1957), a small quantity of dithiazanine was made available at Coldharbour Hospital, and six patients, known to be carriers of whipworm, were selected for treatment.

Method

In view of the findings of Swartzwelder *et al.* (1957) the trial consisted of a five-day course of treatment with dithiazanine, given orally as 100-mg. "telmid" tablets. These tablets contain dithiazanine covered with a coating of cellulose acetate phthalate and an outer sugar coating.

Two tablets were given three times a day in each case, regardless of age and weight, as reports in the literature had described an almost complete absence of side-effects; and 600 mg. of dithiazanine daily was considered an adequate dose in the adult. Each patient's age and weight, however, are given in Table I. Faecal specimens for egg counts were collected during the three days preceding treatment and for three days immediately afterwards. Further specimens were examined one month after treatment.

For the pre-treatment counts the Stoll technique was used: to previously weighed bottles were added 4 g. of faeces (where multiple specimens were sent, portions from each were taken approximately equal in amount). To each bottle was added 60 ml. of N/10 caustic soda; the bottles were incubated overnight and then shaken in the Kahn shaker to emulsify thoroughly. 0.15 ml. of the emulsion was transferred to 3 by 1-in. (7.5 by 2.5-cm.) slides and covered with 2 by $\frac{7}{8}$-in. (5 by 2-cm.) coverslips; which gave a relatively thick but visible picture. The *whole* coverslip was counted field by field and the result multiplied by 100 to give the figure per gramme.

Of the post-treatment counts, the pilot examination, immediately after treatment, revealed no ova by the Stoll technique. When specimens were again examined, one month after treatment, all faeces were concentrated and examined by De Rivas's (1928) technique. "Take a few grammes of faeces, emulsify in saline, coarse-filter through muslin, and centrifuge. Re-emulsify the deposit in 5% acetic acid, allow to stand a few minutes, add an equal amount of ether, shake thoroughly, and centrifuge. The top ethereal fluid containing fat, the plug of detritus between this and the acid layer, and the acid layer itself are decanted and the fine concentrated deposit examined microscopically."

Results

The figures in Table I show a complete absence of eggs at the first post-treatment examination. At the second, scanty trichuris ova were present in one case only by De Rivas's concentration technique. From Table II it will be seen that the same patient (Case 3) persistently chewed the telmid tablets and vomited on three of the five treatment days. It seems possible that this patient might also have had a negative result had he not chewed the tablets and vomited.

TABLE I.—*Results of Treating Six Known Carriers of Whipworm With a Five-day Course of Dithiazanine, as Shown by Faecal Egg Counts*

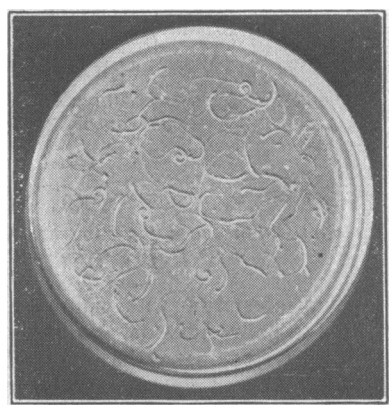
Case No.	Age	Weight in kg.	Pre-treatment Egg Counts. Average per Gramme of Faeces	Post-treatment Egg Counts Immediately after Treatment. Average per Gramme of Faeces	Results of De Rivas's Concentration Technique. One Month after Treatment
1	14	35	2,900	—	—
2	20	47	1,400	—	—
3	14	30	1,300	—	Scanty trichuris ova present
4	19	39	8,100	—	—
5	16	64	3,400	—	—
6	19	35	400	—	—

It will be seen from Table II that a number of adult worms were obtained from each patient. All the worms were non-motile, faintly stained with dye, and apparently dead. They did not appear in the stools of any patient until the third day of treatment, and in two cases (Nos. 1 and 3) not until the fifth day. Since a tendency to constipation was the rule among these patients, it is possible that the use of a laxative or enema, concurrently with dithiazanine, might bring about an earlier clearance of adult worms. Dithiazanine colours the stools blue-green and also seems to have a deodorizing effect.

TABLE II.—*Results of Treating Six Known Carriers of Whipworm With a Five-day Course of Dithiazanine, Showing the Number of Adult Worms Found in the Stools and the Side-effects of Treatment*

Case No.	No. of Adult Trichuris in Stools	Side-effects of Treatment
1	5	Slight rise of pulse rate on second and fourth days
2	72	—
3	10	Tablets chewed. Vomiting on first, second, and fourth treatment days
4	23	Slight rise of temperature and pulse rate, with vomiting on first and second treatment days. Many threadworms on third day. Pallor on fifth day
5	29	—
6	6	Slight rise of temperature and pulse rate on third and fourth days. Vomiting on first treatment day

Side-effects during treatment are shown in Table II. Vomiting in Case 3 has been mentioned. One patient (Case 6) vomited on the first day, when he was apprehensive of swallowing the tablets and chewed a number of them. Another (Case 2) vomited on the first two days of treatment for no obvious reason. Apart from transient elevation of temperature and pulse rate in Cases 2, 4, and 6, and pallor on the fifth day in Case 4, no other toxic effects were noted. The urine was not apparently coloured by the dye. It is of interest that large numbers of threadworms were obtained from Case 4 on the third day of treatment.



Adult whipworms obtained from stools of Case 2.

Swartzwelder *et al.* (1957), after treating more than 400 patients with dithiazanine, noted that associated conditions such as anaemia, malnutrition, cardiac disease, nephrosis, and pregnancy did not influence the tolerance of the drug. The only reactions to therapy which were observed were vomiting and diarrhoea. The same workers carried out extensive laboratory studies of certain adult patients who received 600 mg. of dithiazanine daily for three weeks. They found no subsequent changes in blood urea nitrogen, urine, haemograms, bilirubin, zinc-lipid-thymol turbidities, alkaline phosphatase values, and the prothrombin time. They also found no discoloration or other abnormality in the urine of children treated with dithiazanine.

Conclusions

This preliminary trial appears to provide evidence of the efficacy of dithiazanine against human trichuriasis. In view of the small number of patients treated, the absence of a control group, and the possibility that the six patients chosen might have been influenced by previous trials with other anthelmintics, it is not possible

to provide statistically valid conclusions at this stage. We are conducting a comprehensive trial with dithiazanine, and hope to publish a further report in due course.

Our thanks are due to the nursing staff at Coldharbour Hospital for their care and observation of the patients under treatment. We are indebted to Mr. H. J. Attryde, chief technician, County Laboratory, Dorchester, who personally carried out all the egg counts in the trial. We also thank Eli Lilly and Co. Ltd. for supplying the "telmid" tablets, which were specially obtained from America for this trial.

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STATUS EPILEPTICUS TREATED WITH D-TUBOCURARINE AND CONTROLLED RESPIRATION

BY

H. I. ARMSTRONG NISBET, M.B., Ch.B., D.A.
Registrar in Paediatric Anaesthesia, Alder Hey Children's Hospital, Liverpool

Status epilepticus is a condition in which a series of convulsions occur with such rapidity that in the intervals between them the patient does not regain consciousness. Many authorities agree that the prognosis is poor. Ford (1944) states that where the seizures cannot be controlled signs of exhaustion appear. The temperature rises, respiration is laboured, and tachycardia with signs of circulatory failure becomes evident. The heart may be dilated and pulmonary oedema is often the cause of death.

Small and Woolf (1957) have described severe histological damage to the brain resulting from status epilepticus with respiratory obstruction, and have stressed the dangers of anoxia in this condition, especially in children. It is desirable, therefore, that considerable attention should be directed towards the control and management of the airway in this condition, especially where it does not rapidly respond to the routine forms of treatment. Modern anaesthetic techniques involving the use of muscle relaxants and controlled respiration have proved beneficial in cases of convulsions due to tetanus. That they may also be of value in status epilepticus is shown by the following case history.

Case History

A known epileptic girl aged 11 was admitted to Alder Hey Hospital in status epilepticus. The convulsions were generalized, and began an hour before admission. Intramuscular injections of paraldehyde, 4 ml., phenobarbitone sodium, 1 gr. (65 mg.), and hyoscine, 1/150 gr. (0.43 mg.) failed to control the condition. In spite of oxygen therapy she became cyanosed, and in view of this the aid of the anaesthetic staff was requested.

On examination the child was convulsing and cyanotic, with poor air entry into all areas of the lungs. There was marked masseteric spasm, which prevented the removal of copious blood-stained secretions from the pharynx. The pulse was rapid and weak.

D-Tubocurarine, 15 mg., was injected intravenously, following which the jaw relaxed and the convulsions ceased. After pharyngeal suction, a No. 5 cuffed Magill endotracheal tube was inserted, the cuff inflated, and the tube connected to an anaesthetic machine from which a mixture of 50% nitrous oxide and oxygen was delivered at a flow of 6 litres a minute. Endotracheal toilet was performed and a considerable quantity of secretions removed from the air passages. A carbon-dioxide absorber was introduced into the circuit, and ventilation was maintained by means of a Fazakerly respirator (Esplen, 1956) for 45 minutes. On auscultation there was now good air entry into all areas of the lungs. Scattered crepitations were heard throughout. Soon after the arrest of the convulsions the pulse rate fell from 130 to 110 a minute. Similarly, the temperature fell towards normal after the institution of controlled respiration.

After an interval of 45 minutes, as the effects of the initial dose of relaxant decreased, it could be seen that the convulsions persisted in a modified form. Accordingly, a further 3 mg. of D-tubocurarine was injected intravenously. Controlled respiration was maintained for a further two hours, the patient being ventilated by hand at intervals in order to assess the degree of relaxation.

No further doses of relaxant were required. After three hours the convulsions appeared to have ceased and respiration was assisted manually as it gradually returned to normal.

When the tidal volume was seen to be adequate the supply of nitrous oxide was turned off. The child promptly awoke and coughed on the tube, which was removed after pharyngeal suction. She spoke quietly to the nurse before turning on her side and falling asleep.

The subsequent course was uneventful and she was discharged home.

Discussion

In the severe case of status epilepticus a state of respiratory insufficiency exists which must be relieved. Gaseous exchange is impaired by recurrent convulsions and by respiratory obstruction, while oxygen demand and metabolic rate are greatly increased by muscular hyperactivity. Heat production rises and the resultant pyrexia causes additional oxygen demand. If in addition there is a state of circulatory insufficiency and the heart is dilated, the use of drugs which markedly depress the myocardium would seem to be contra-indicated.

The method of treatment which was adopted in this case provides rapid relief from the state of respiratory insufficiency without the use of agents which add to the cardiac embarrassment. The convulsive irregular respiration of the epileptic state is replaced by controlled respiration. The adequacy of the airway is maintained by an endotracheal tube, and obstructing material in the respiratory passages is easily removed by suction. Trauma to the mouth, teeth, and tongue is avoided.

Both respiratory obstruction and hyperventilation may cause pulmonary oedema. It is known that positive-pressure respiration counters the tendency for an increased amount of fluid to leave the pulmonary capillaries. If, as Ford suggests, death frequently results from pulmonary oedema in this condition, the use of controlled ventilation should be beneficial.