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TREATMENT OF SCHISTOSOMIASIS WITH "NILODIN"

BY

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A mine medical officer in the Union of South Africa has undeniable advantages in assessing the effects of treatment of schistosomiasis. In the first place, the mines of the Witwatersrand and Orange Free State are situated in "clean" areas, whereas the labour force is to a large extent drawn from heavily infested areas; therefore once the disease has been successfully treated the question of reinfection is not likely to arise to cloud the issue. In the second place, a wholly adequate follow-up of cases is possible, as natives recruited from the infested areas do not sign labour contracts for periods of less than nine months, and furthermore any mine employee can be recalled for re-examination at any time. Thirdly, a very large percentage of the tropical labour force, especially the Portuguese East African contingent, is infected with both *Schistosoma haematobium* and *S. mansoni*, so that an adequate number of cases are available for treatment and assessment.

At the Brakpan Mines in the Transvaal a trial was made of the use of "nilodin" brand of lucanthone hydrochloride (1-β-diethyl-aminoethylamino-4-methylthioxanthone hydrochloride; "miracil D") in the treatment of both urinary and rectal schistosomiasis. In the former the infecting organism was *S. haematobium*, and in the latter *S. mansoni*. In reporting the results certain aspects, such as the clinical diagnosis, presenting symptoms, tribal incidence, and haematology, have been omitted for the sake of brevity.

In both forms of infection the diagnosis was based on laboratory examination of specimens of urine and faeces respectively for the presence of viable ova. Ova are considered to be viable if free-swimming miracidia are present or there are active movements of miracidia within the ova. Occasionally an ovum remains motionless after exposure to water in high dilution, but the flame cells can be observed beating in the organism and the cilia may be moving. An ovum with none of the above signs but morphologically normal is referred to throughout this paper as "inert." After treatment ova are passed which can be referred to only as "macrated." They contain an amorphous mass; no movement or "pulse" of flame cells can be observed. Some ova are shrunken, while others appear to have swollen and burst. It is

common to observe "globules" within macrated ova which are not seen in normal ova.

The nilodin used throughout the trial was in the form of tablets each of which contained 200 mg. In these circumstances it was usually impossible to adhere strictly to a particular scheme of dosage based on body weight. No patient was started on less than the specification decided upon, and when part of a tablet was indicated a whole tablet was given. Thus when the dosage was 20 mg. per kg. of body weight a day, a patient weighing 56.5 kg. would actually receive six tablets=1,200 mg. daily instead of the 1,130 mg. indicated by his weight.

URINARY SCHISTOSOMIASIS

Results of treatment in a total of 46 cases of infection with *S. haematobium* are presented. These are divided into two series in which the dosage, the course of treatment, the method of follow-up, and the method of urine collection differed.

Series 1

This series originally consisted of 37 cases, but 13 of these were excluded from the investigation for various reasons: in 9 cases the follow-up was inadequate, 3 proved to be cases of rectal schistosomiasis, and in the other case no viable ova were demonstrable before treatment. The remaining 24 cases were followed up for at least three months. Cases were re-examined once a week for the first three months and thereafter at monthly intervals.

Laboratory Examination

In most of these cases viable ova or miracidia were found in the first (casual) specimen of urine passed. In no case were more than three specimens required to make a positive diagnosis. The technique of urine examination used for both diagnostic and follow-up purposes is as follows.

The conical glasses of urine are allowed to stand for a variable period after collection, but not less than 15 minutes. The supernatant urine is then decanted; the remainder is well stirred, poured into a centrifuge tube, and spun down at 3,000 r.p.m. for three minutes. The supernatant urine is now discarded, and the centrifuge tube filled with tap water and again spun down. The supernatant water is discarded and the sediment shaken up in the few drops remaining. With a clean pipette in every instance the remaining drops are placed on a slide and examined. The search for ova can be made very satisfactorily with the low-power objective of the microscope, but to establish viability of an ovum the high-power lens (×800) is required. It is of the greatest importance that the complete sediment—that is, four drops as a rule—be examined at every re-examination. Each centrifuge tube as used contains 14 ml. of urine.

The great advantage of this technique for follow-up purposes is that the viability of ova can be established almost at once, it being common to find miracidia swimming in the drops upon examination immediately after preparation of the slide. The World Health Organization Expert Committee on Bilharziasis (1953) recommends that centrifuging be limited to 1,000 r.p.m. to obviate the risk of ova disintegrating. I have never, however, found excessive centrifuging, either for too long a time or at too high speed, to cause disintegration of ova.

Dosage

The dosage of nilodin was worked out to give 20 mg. per kg. of body weight per day divided into three equal doses. However, as explained above, the strength of the tablets made it impossible to conform exactly to this amount; consequently, and taking into account reduction of dosage because of toxic symptoms, the average daily dose received by these patients was 22 mg. per kg. No case received less than a 12-day course of treatment, and in one case the treatment extended over 13 days.

Toxicity

Of the 37 cases in which treatment was started 21 (56.7%) had toxic symptoms. These were easily controlled and in no case was it necessary to discontinue treatment, although

the initial dosage of the drug had to be reduced in 11 cases (29.7%). (In two cases the dose had to be reduced on two separate occasions.) A list of toxic manifestations with their frequency is presented in Table I.

TABLE I.—Toxic Manifestations

Symptoms	No. of Cases	Percentage of All Cases (21) with Toxic Symptoms	Percentage of All Cases (37) Treated
Nausea and vomiting	12	57.1	32.4
Abdominal pain and discomfort	5	23.8	13.5
Anorexia and nausea	3	14.3	8.1
Suprapubic pain	1	4.8	2.7
Total	21	100.0	56.7

Toxic symptoms first appeared as early as the third day and as late as the tenth day (one case each), the average time being the sixth day. Phenobarbitone, 1 gr. (65 mg.) twice daily, was used to control such symptoms; if this was not effective, the dosage of nilodin was reduced by 200 mg. a day. Although "jaundice" has been reported (Haseeb, 1952) to occur during nilodin therapy, this was not noted in the present series. In all cases there was a very deep reddish-brown pigmentation of the palms and soles, but the conjunctivae were not affected. The urine became bright yellow and so did the tongue—the latter merely from contact with the pills. Examination of the blood on the last (12th) day of treatment in 19 consecutive cases showed that not one had a total serum bilirubin level above 0.5 mg. per 100 ml. and that the highest icteric index was 7. There was no apparent effect upon the kidney glomeruli as evidenced by tests for albuminuria following treatment. Toxic symptoms developed more rapidly and were worse, however, in patients whose renal function was already impaired.

During the 12 days' treatment 22 (59.4%) of the 37 patients had a weight loss ranging from 1 to 17½ lb. (0.45 to 7.7 kg.), with an average of 7 lb. (3.175 kg.). Of these 22 patients 14 complained of toxic symptoms, so that there is a fair correlation between weight loss and toxic effects. Loss of weight was accompanied by a marked diuresis in certain cases.

Results

The clinical response was good. In most cases of frank haematuria the bleeding stopped on about the eighth day; in only two or three cases did it persist, and was then due to granulomata. Patients who continued to pass blood were examined cystoscopically to exclude the possibility of the presence of carcinoma; if there was any doubt a urologist's opinion was sought. In pyrexial cases the temperature responded by the sixth day at the latest, and this response was obtained with nilodin alone. The temperature would probably have fallen much sooner had urinary antiseptics been used to combat the secondary infection which was usually present, but, as the effect of such drugs on *S. haematobium* infection was not known, this might have nullified any claim that the assessment was accurate. Results can be assessed correctly only by an adequate follow-up, which must extend over a period of at least six months. The more examinations which can be made in this period the more accurate will the assessment be.

Of the 24 cases reported five relapsed within the three-month period. In two more cases relapse occurred after this period, in one case eight and a half months and in one six months after treatment. Only ten cases which did not relapse within the first three months could be followed up for six months. There was only one further relapse among these ten cases. Nevertheless, out of 15 cases in which either relapse occurred or the full six-month period of follow-up was completed, six relapsed. (See Table II.) It is therefore obvious that relapse does occur up to, and even after, six months following treatment. I would like to stress that the term "relapse" is here used in its strictest sense. If only one viable ovum or miracidium was observed at any time after the first week following treatment, then

TABLE II.—Results of Follow-up Examinations

Series No.	After Three Months				After Six Months			
	No. of Cases	No. of Re-examinations	No. of Cases Relapsed	% of Cures	No. of Cases	No. of Re-examinations	No. of Cases Relapsed	% of Cures
1	24	13 each	5	79	15	16 each	6	60
2	22	4 "	5	77	18	9 "	12	33

that case was considered to have relapsed. In actual fact only one "clinical" relapse occurred.

In this series, therefore, we claim to have achieved a 60% "six-month cure," although as this figure does not include the case which relapsed after eight and a half months it is somewhat optimistic. I would, however, stress that, with only one exception, every case was of extremely long standing or chronicity. The cases which relapsed all had very heavy infections, as judged by the number (usually hundreds) of miracidia and ova found at the diagnostic examination.

It is necessary to explain why the cases in which viable ova continued to be passed seven days after treatment cannot be considered as relapses. In the first place it takes an average of six days for nilodin to reach its highest concentration in the serum, as shown by the time taken for the deep pigmentation of the palms, the coloration of the urine, and the toxic symptoms to develop. Therefore the drug is still acting on the worms six days after stopping treatment. Secondly, any ova found at the first re-examination were certainly laid at least 24 hours, and probably three to four days, previously. In chronic cases with much induration, and even calcification, of the bladder wall it may take a considerably longer period for an ovum to penetrate into the lumen of the organ. This being the case, the viability of these ova is no criterion of the state of the parent worms. Once encased within its shell, it is questionable whether the miracidium is as vulnerable to the action of a drug as the adult worm. Furthermore, the eggs lie in the tissue and not in the main blood stream and are thus not exposed to the same concentration of drug. Thirdly, any ova found at the first examination after a 12-day course were not normal; they can only be described as "deformed." Within the ovum large vacuoles and globules had formed, and any movement present was extremely sluggish. When such ova hatch the miracidia are grossly abnormal in shape; the smooth outline is lost, to be replaced by a wavy, irregular periphery; movements are sluggish and the clear protoplasmic outlines are obscured by a degenerate mottling. These changes may have been due to the effect of the drug on the egg-producing organs of the female worm, or possibly on the eggs held up in the tissues.

Of the seven cases in which relapse did occur, three were noted to have viable, though abnormal, ova at the first re-examination. This may be a prognostic point in cases treated with nilodin, as only six cases were observed to have viable ova at the first examination and three of these relapsed later. The mean time of relapse was at the seventh week after treatment.

Series 2

The second series consisted of 22 cases. Every case was seen one week after completing treatment, and thereafter at monthly intervals for six months. Four of the cases did not complete the full six-month period. Four months after completion of treatment every patient was readmitted to hospital for three days, during which time a different method of collecting urine for examination was employed. At all other examinations urine was simply passed into a urine-analysis glass, whereas, in hospital, urine was collected after each patient had taken a 15-minute "ride" on a physiotherapy bicycle every morning for three consecutive mornings. One "24-hour" specimen of urine was also collected. This was voided into a Winchester bottle, and then by a repeated process of decanting and settling a volume of urine and sediment small enough to be centrifuged and examined was obtained.

Dosage

The aim in this series was to give a more concentrated course of treatment over a shorter period. Accordingly the initial dosage was scheduled to be not less than 25 mg. per kg. of body weight per day and the course covered nine days. After the dose had been reduced in two cases because of toxic symptoms the average total dose was 225 mg. per kg. of body weight, so that the average daily dose was in fact 25 mg. per kg.

No specific notes on toxicity were made in this series, as nilodin had been proved by the first series to be relatively non-toxic and without after-effects. In this connexion it will be sufficient to point out that the dosage had only twice to be reduced.

Results

The clinical response was much the same as in the first series. Of 18 cases in which a six-month period of follow-up was completed, 12 (67%) relapsed (Table II). Of these only one was a clinical relapse and 11 were technical relapses. In 7 (58%) of these 12 cases viable ova were found at the first weekly re-examination following treatment. This would seem to confirm that the presence of viable ova at the first weekly re-examination may be a useful prognostic point. In one case relapse occurred seven months after treatment, in this instance a full clinical relapse.

Thus, regarded in the very best light, a 33% "six-month cure" was obtained. Once again this figure is optimistic when it is remembered that one case relapsed after seven months.

Discussion

The results in Series 2 are far worse than those in Series 1, but it is difficult to decide whether this should be attributed to the different scheme of treatment or to the different method of follow-up. A comparison of the three-month post-treatment period in the two series reveals that in Series 1 relapse occurred in 20.8% of cases, or 71.4% of total relapses, whereas in Series 2 the corresponding figures are 22.7% and 38.4%. This difference is due to the fact that the cases in Series 1 had three times as many re-examinations during this period as those in Series 2 (see Table II). A comparison of the six-month results shows that in Series 1 only 15 cases had either relapsed or were still undergoing re-examination. The relapse rate was 40%—6 cases out of 15, including five cases which relapsed in the first three months. In other words, only one new relapse was found in the second three-month period. Of 18 cases in Series 2 which completed the six-month follow-up, 12 (67%) relapsed. This, too, includes five cases which relapsed in the first three months. In this series, however, three cases of relapse were discovered by the special examination at four months described above, without which these cases might have been missed. Excluding these cases the relapse rate was still 50%, as compared with the 40% of Series 1. Four cases were recognized as having relapsed when examined five or six months after treatment, though they had been missed at the four-month special examination. This examination did not prove as effective as it was hoped.

To my mind the follow-up in Series 1 was more adequate than that in Series 2. In the former each case had at least 16 re-examinations in the six months following treatment, whereas in the latter each case had only nine re-examinations in that period. The fact that in Series 2 the results were worse despite a less adequate follow-up would seem to indicate that the important factor in treatment is the length of the course rather than the daily amount of the drug given. Shorter courses of treatment as previously tried have proved, in my experience, even less effective.

In any event the important fact that emerges from this investigation is that even with a nine-day course of treatment only a 33% "cure" can be expected. Even this figure may be too high. In the light of claims that have been made of an 80% cure rate following a five-day course, this should serve as a warning against over-optimism. Such claims can be attributed only to an inadequate follow-up.

It appears from the above that a good method of follow-up would be a fortnightly re-examination for six months following treatment, with a special examination, as described, at the end of that period, and thereafter a monthly examination for another six months.

Mode of Action of Nilodin.—From one to two months after treatment with this drug I have often observed abnormal, non-viable ova in patients' urine which are from one-half to one-third the normal size. Although small, these ova have a perfectly formed shell, but contain only an amorphous mass. They are totally unlike "degenerate" ova which have been held back in the tissues in chronic cases. It is my belief that these may be "sterile" or unfertilized ova, and that the male worm may be more susceptible to treatment than the female. It is also possible that oviposition in the female is affected by the drug, and even temporarily stopped completely. In cases in which such ova are found relapse may occur later or, on the other hand, the urine may become perfectly clear of ova. Another factor is that nilodin may cause temporary immigration of the worms to the liver plexuses. In view of these points it would seem that the only real test of cure would be a complement-fixation test. This would have to be done a fairly long while after treatment.

RECTAL SCHISTOSOMIASIS

In view of the paucity of information about the effect of the newer drugs on rectal infection with *S. mansoni* a short account of our treatment of this condition with nilodin may be of interest. Although a goodly number of cases have been treated, the results in only four cases which have been followed up are presented.

Method of Examination

In all cases in which dysentery was the presenting symptom the diagnosis could be easily arrived at by examination of the faeces, especially of the mucus contained in the stool. Usually the first few fields were enough to demonstrate the presence of ova. The technique used was to tease apart strings of mucus in a drop of tap-water on a slide. The first examination was made with the lowest-power objective lens available. If no ova or miracidia were seen, then a cover slip was placed over the specimen and the high-power lens used in a search for parasites of pathological import. As the clinical manifestations of amoebic dysentery and rectal schistosomiasis so closely resemble each other the differential diagnosis can be made only by an adequate examination of the stools.

In cases without dysentery and in which formed stools were passed examination for *S. mansoni* ova called for a different procedure. In such cases a proctoscope was passed with the patient in the lithotomy position on an operating table. The rectal mucosa was cleaned and then scarified until bleeding occurred by means of a clean swab held in the artery forceps, the mixture of blood and debris removed being transferred to a clean, dry slide. Two slides were prepared in this way so that a fairly large amount of material could be examined. Water was dropped on to the specimen and two cover slips placed on each slide. Slides were examined under the low-power objective of the microscope. In addition all positive cases were examined for the presence of urinary infection.

Every case was re-examined by the direct proctoscopic method—weekly, when possible, for the first three months. Thereafter a monthly proctoscopic examination was conducted until the patient left the employ of the mines. In addition, in every case the urine was examined for *S. haematobium* ova weekly for the first three months and then at monthly intervals while the patient was available. In only one case in this series was there a double infection, *S. haematobium* and *S. mansoni* infesting the urinary tract and *S. mansoni* the rectal plexuses.

Dosage

The daily dosage of nilodin aimed at was 20 mg. per kg. of body weight, though as the tablets of the drug were not divided, as explained above, patients received slightly more

than this amount. Three cases were given a 12-day course of this treatment, but the remaining case had only six days' treatment. No adjuvants were employed apart from intravenous infusion of saline and glucose in two cases in which the patient was suffering from a salt-depletion syndrome on admission to hospital.

Clinical Response

Provided that the patient's general condition was treated adequately, then the response was good. On treatment with nilodin alone, without any antibiotic therapy for the secondary infection, the cases with dysentery made a complete response by the sixth day. It is noteworthy that in many cases (not included in the present series) with symptoms due to stricture of the bowel, treatment of the schistosomal infection had no effect on such symptoms, and where necessary one had to resort to surgery.

Results

Of the four cases here reported not one relapsed clinically during the follow-up period. I stress "clinically" because in one case viable ova were recovered from the rectal mucosa on two occasions after the end of treatment. In another case an inert ovum was recovered on one occasion. This ovum was morphologically normal but the flame cells were not beating. This case should be regarded as having relapsed because, in my experience, successful treatment results in the recovery of macerated ova from the mucosa. The recovery of an inert ovum at the 20th week after treatment, as in this case, should be regarded as highly suspicious.

Results in the four cases are shown in Table III. Two of these cases had previously had courses of "fantorin" (antimony pyrocatechol sodium sulphionate)—in one case

TABLE III.—Results of Follow-up Examinations

Case No.	Length of Course (Days)	Length of Follow-up (Weeks)	No. of Re-examinations	Clinical Relapse	Technical Relapse	Time of Relapse
1	6	24	14	No	No	—
2	12	23	16	"	Yes	10th and 13th weeks
3	12	22	13	"	?	20th week
4	12	18	11	"	No	—

two months, and in the other three months, earlier. Both cases had a clinical relapse with the demonstration of viable ova in the stools. They were then given nilodin treatment as described.

Discussion

Too few cases are presented for any scientific assessment of the results. However, many more cases have been treated with nilodin although not followed up, and in all the clinical response was good.

The case of mixed *S. mansoni* and *S. haematobium* infection of the bladder is particularly interesting, because during the follow-up period macerated ova of *S. mansoni* were recovered from the urine at 7 out of 15 examinations; on one occasion, too, a macerated ovum of *S. mansoni* was recovered from the rectal mucosa.

The stumbling-block to the correct appraisal of a particular method of treatment in cases of *S. mansoni* infection is the follow-up. There seems to be no really accurate technique available, and certainly none that is simple to carry out.

With the method of follow-up here described I have been pleasantly surprised at the high proportion of positive diagnostic results obtained. At re-examination, however, recovery of ova was variable. In the first of the four cases only one macerated ovum and one macerated miracidium were recovered in the course of 14 re-examinations; in the second case macerated ova were recovered twice, and viable ova twice, in 16 re-examinations; in the third case macerated ova were recovered at seven, and an "inert" ovum at one, of 13 re-examinations; and in the last case macerated *S. mansoni* ova were recovered at only one out of 11 re-examinations of the rectum, while they were present at 7 out of 15 re-examinations of the urine.

When regarded in the light of claims made for other methods of examination our technique would appear to be very poor; but this is no doubt due to the fact that it was applied after treatment—an important point. When used to establish a diagnosis it was highly effective, although no records were kept to substantiate this claim. Furthermore, our results show that if ova are present in the mucosa this technique reveals them. This is exemplified by the third case, in which ova were recovered at 8 out of 13 examinations.

I have come to the conclusion that there is little variation in the susceptibility of *S. haematobium* and *S. mansoni* to nilodin when given in adequate dosage over a long enough period. This contention is well borne out by the case of mixed infection of the urinary tract. For this reason I am of the opinion that research workers should concentrate on urinary schistosomiasis, in which assessment of the results of treatment is much easier and far more accurate.

Summary and Conclusions

Two series of cases of urinary schistosomiasis (*S. haematobium*) occurring in mine-workers in the Transvaal have been treated with nilodin (lucanthone hydrochloride). In the first series (24 cases) an average daily dose of 22 mg. per kg. of body weight was given for twelve days, and in the second (22 cases) a daily dose of 25 mg. per kg. for nine days.

Results did not come up to expectation in either series. A "six-month cure" of 60% was obtained in Series 1 and of 33% in Series 2, the poorer results in the latter being due to what is considered an inadequate course of treatment. One case in each series relapsed after the six-month period of follow-up, so that final results were less good.

Toxic symptoms, though frequent (56.7% of cases), were never severe and were easily controlled. Loss of weight and diuresis were a striking feature in some cases. Toxicity was greater in cases in which there was renal insufficiency.

Results are also given of the treatment with nilodin of four cases of rectal schistosomiasis (*S. mansoni*). Clinical response was excellent. No case of clinical relapse occurred, though in two cases there was a "technical" relapse, as shown by the recovery of viable ova from the rectum.

An interesting case of *S. mansoni* infection of the vesical plexus which was apparently cured by the treatment is described.

Nilodin was found to be easy to administer, and, considering the high percentage of cures if it is adequately used, relatively cheap. It should be stressed that the clinical response to treatment is exceptionally good and that every case benefits in some degree. Treatment should extend over a period of at least twelve days, and preferably sixteen days, and patients should be followed up for at least six months.

It is concluded that, provided an adequate course is given, nilodin is highly effective in the treatment of *Schistosoma* infections in the non-European mine labourer in South Africa; also that the mines of the Witwatersrand and Orange Free State are ideal testing grounds for anti-schistosomal drugs.

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