in regard for the rights of others, and bitter. It may well be that if complete separation from the mother is so harmful, prolonged crying in the home, with a refusal of the mother to pay heed to it, may render the child unhappy and insecure later, and lead to a variety of behaviour problems. It is certain that when babies are left to cry for prolonged periods in this way they do not quickly grow out of it. It is a matter of common observation that the crying may continue for week after week, and month after month, until eventually with increasing age they stop it. Aldrich and Aldrich (1938) wrote: "Most spoiled children are those who as babies never had essential gratifications owing to a mistaken attempt to fit them into a rigid regime. The spoiled child who has missed satisfaction as a baby adopts the efficient technique of whining and temper tantrums to get what he wants. The mechanism of spoiling is the neglect of needs rather than overindulgence. Twenty-five years' experience has taught me that responsive adults breed responsive babies, and that rigid disciplinarians of babies at this age breed spoiled, unhappy children with no confidence in themselves or their parents."

The idea held by some that crying may lead to convulsions is untrue. The so-called "crying convulsions" or "breath-holding convulsions" are due to holding the breath in expiration. They frequently follow a short cry, but they are not the result of it.

As for the second question, whether it does any harm to pick a baby up when he cries, it can be said with certainty that there is no evidence that it does harm. Some babies are a great deal more demanding than others, and experience has shown that when demanding babies are picked up as often as they reasonably can be when they ask for it they settle down and stop demanding so much attention after the first few weeks. They do not, in other words, develop a bad habit of constantly expecting to be picked up. In any case, if such a habit did develop, as a result, perhaps, of unnecessary picking up, it can be broken as soon as it is realized that the crying has become a habit. Crying out at night certainly does become a habit in the older baby, and it has to be dealt with firmly (Illingworth, 1953). The young baby should be picked up when he cries, certainly when by the nature of his cry it is obvious that if left he will continue to cry for a long time. He should not be picked up at the slightest whimper. He should not be picked up when he is crying from fatigue and about to go to sleep—unless he has been allowed to get so tired that he cannot go to sleep, when he may have to be rocked until he lapses into slumber. A baby who screams because of colic or because of pain from teething should certainly be picked up and soothed. No baby should ever be left crying for prolonged periods—except when one is breaking a habit produced by mismanagement.

A baby is spoiled by being constantly picked up when he is lying perfectly content in his pram, or by being constantly played with when he is quite happy in his play-pen or elsewhere. He is spoilt by being picked up at the slightest whimper, but there is nothing whatsoever to be said in support of those who advocate leaving a baby to cry for prolonged periods so that he will "learn good habits" or "learn that he cannot have all his own way." It should not be forgotten that babies are human beings, and all human beings want love. Why not give it to them?

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AN AMIDO-NITROTHIAZOLE FOR TRICHOMONIASIS

BY

S. R. M. BUSHBY, M.Sc., Ph.D.
Wellcome Research Laboratories, Beckenham, Kent

R. D. CATTERALL, M.R.C.S., L.R.C.P.

AND

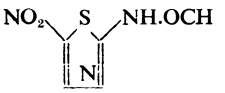
MARY WILLIAMSON, M.B., B.S.
Department of Venereal Diseases, London Hospital (Whitechapel Clinic)

Some 16 different drugs have been recommended at various times for the treatment of vaginitis due to *Trichomonas vaginalis*, but methods of treating this infection are still unsatisfactory. Although acute vaginitis is much improved by treatment with some of the drugs, relapses are common and the evidence of infection often persists as a chronic leucorrhoea. The unsatisfactory results have been attributed either to reinfection or to incomplete eradication of the trichomonads. Whether the origin of the infection be primarily venereal, or due to accidental contamination from infected lavatory seats, towels, and other fomites, it seems probable that the prevention of reinfection will always be difficult in practice. Failure to eradicate the primary infection, however, can only be due to the use of insufficiently active drugs or to inaccessibility of some of the trichomonads. If failure is due to inaccessibility then no topical drug, however active, will be fully successful. If, however, the failure is due solely to low activity of the drug, then the solution to the problem should be relatively simple, for more active drugs than those generally used are available.

Up to the present nitrothiazoles have not been used for the treatment of human infections, but Waletzky *et al.* (1949) found 2-amino-5-nitrothiazole, "enheptin T," to be effective for the treatment of turkeys experimentally infected with *Histomonas meleagridis*, a flagellate related to the trichomonads; and Carmichael and Maclay (1952), McGreggor (1952), and Swales (1952) found it effective for the natural disease. Stabler and Mellentin (1953) have reported that it cures pigeons infected with *Trichomonas gallinae*, and they suggested that it should be tried for human infections. Enheptin T is, however, bright yellow and stains skin and clothing intensely, an undesirable property for a drug that is to be used as a vaginal pessary. Bushby and Copp (1955), who made an independent study of the activity *in vitro*

of nitrothiazoles for *T. vaginalis*, found that some of them which were only slightly coloured had about ten times the activity of enheptin T and more than a hundred times that of acetarsol.

In this investigation we have compared the activity *in vitro* of the most active of these compounds, 2-formamido-5-nitrothiazole (291 C 51), with 14 of the



antitrichomonal drugs which have been recommended during the last 10 years, and which are still readily available. We have also used it in the treatment of 96 women with trichomoniasis, comparing the results with those obtained in the 49 women treated with acetarsol.

The 14 drugs which were compared with the nitrothiazoles were: phenylmercuric dinaphthylmethane disulphonate ("penotrane"), phenylmercuric acetate, 5-chloro-7-iodo-8-hydroxyquinoline ("vioform"), silver picrate, 5-nitro-2-furaldehyde semicarbazone (nitrofurazone), sodium perborate, mild silver protein ("argyrol"), chlortetracycline, 2-methoxy-6-chlor-9 (α-methyl-o-diethyl-aminobutyl)-aminoacridine dihydrochloride (mepacrine hydrochloride), 3-acetylamino-4-hydroxyphenylarsonic acid (acetarsol), 5,7-di-iodo-8-hydroxyquinoline ("diodoquin"), 4:4'-diamidino-diphenoxypropane di-(β-hydroxyethane sulphonate) (propamidine), 7-iodo-8-hydroxyquinoline-5-sulphonic acid (chiniofon), *p*-carbaminophenyl-arsonic acid (carbarsone).

Activity in vitro

Methods.—A recently isolated strain of *T. vaginalis* grown in serum-glucose-nutrient broth enriched with an extract of ox liver (*p*H 6.4) was used for comparing the trichomonastatic and trichomonacidal properties. The drugs were added to the medium usually at a concentration of 10,000 μg. per ml., serially diluted 1 in 3, and then sterilized by heating for half an hour at 56° C. For the trichomonacidal tests 1 ml. of a suspension containing 400 trichomonads per c.mm. was added to 1 ml. of the dilutions and incubated at 37° C. Each tube was examined microscopically for motile organisms, and viability tests were made on those containing no motile organisms by subculturing into fresh medium free of the drug and incubating for 48 hours.

In the trichomonastatic tests the inoculum was 1/10 of that used in the trichomonacidal tests, and the tubes were examined for increases in the number of trichomonads after 48 hours' incubation.

Results.—The activity of the various drugs is shown in Table I.

TABLE I

Drug	References to Clinical Use*	Minimum Effective Concentration (μg./ml.)			
		Trichomonacidal Activity			Trichomonastatic Activity
		1 Hr.	6 Hrs.	24 Hrs.	48 Hrs.
291 C 51 ..	—	1,000	100	10	3
Penotrane ..	1, 2	3	3	1	1
Phenylmercuric acetate ..	3	3	3	3	3
Vioform ..	4, 5, 6, 7	100	30	30	30
Silver picrate ..	8, 9, 10	300	100	100	100
Nitrofurazone..	11, 12	1,000	100	100	100
Sodium perborate	13, 14, 15	300	300	300	300
Argyrol ..	16	1,000	1,000	300	300
Chlortetracycline	17, 18	10,000	10,000	1,000	1,000
Mepacrine ..	19	10,000	10,000	1,000	100
Acetarsol ..	20, 21, 22	10,000	10,000	10,000	1,000
Diodoquin ..	23	1,000	1,000	1,000	1,000
Propamidine ..	24	10,000	10,000	3,000	100
Chiniofon ..	25	10,000	10,000	10,000	3,000
Carbarsone ..	26, 27, 28	25,000	25,000	25,000	25,000

* See page 80.

Chemical Properties and Pharmacology

291 C 51 is a weak acid; a saturated aqueous solution (0.1% at 37° C.) has a *p*H of 4.5. The solid compound and the aqueous solutions are faintly yellow, and the colour increases slightly when the solutions are made alkaline. Animal experiments show that 291 C 51 has a low toxicity: 5 mg. produced no reaction when placed on the conjunctivae of rabbits once daily on three consecutive occasions; the insertion twice daily for 15 days of one of the 100-mg. pessaries used in the clinical trial (see below) into the vagina of each of two dogs caused no irritation; and the daily instillation of 30 ml. of 0.5% aqueous solution of the sodium salt into the bladders of two dogs for three weeks also caused no ill effects.

The oral and subcutaneous $L.D._{50}$ single doses in mice are approximately 400 mg. per kg. Subcutaneous doses of 100 mg. per kg. twice daily for four days to mice and two daily oral doses of 200 mg. per kg. to rabbits were non-toxic. A daily oral dose of 100 mg. per kg. to a monkey for 44 days and a single oral dose of 600 mg. to man produced no toxic effects. After oral or parenteral administration the urine becomes a deep yellow colour and paper chromatographic analysis shows that the drug is not excreted in its original form. The urine and the serum of the rabbits, monkey, and man, collected during the toxicity experiments, one, two, and four hours after dosing, possessed no trichomonastatic activity when tested *in vitro*, showing that 291 C 51 is changed *in vivo* to an inactive form.

Clinical Trials

Material and Methods

The patients treated in this trial were attending the Whitechapel Clinic of the London Hospital. They were divided into three series: the first consisted of 10 whose treatment was restricted to seven days; the second, of 38 treated for 14 days; the third, of 98 treated for 14 days with 250-mg. pessaries of acetarsol or with 291 C 51, in alternate cases. Series I and II consisted of patients who had relapsed after treatment with acetarsol or some other antitrichomonal drug. The patients of series III had not been previously treated in this clinic. 291 C 51 was used as a foaming pessary* containing 100 mg. of the drug, and the procedure ordinarily followed in this clinic when using acetarsol was employed. The routine procedure was: two tablets were inserted high into the vagina nightly for 14 days except in the first 10 cases (series I) in which the treatment was for seven days only. After the initial insertion of the first two tablets by nursing staff, patients were instructed in the method of inserting the tablets "as high up as possible," and subsequent treatment was left to the patient.

Assessment of Results

These fell into three groups—cure, relapse, and defaulters. For the assessment of cure the following criteria had to be fulfilled: (1) After completion of the course there must be no symptoms or clinical evidence of vaginitis for at least three months. (2) Smears taken from the vagina must remain negative for trichomonads in a series of tests extending over three menstrual periods after completion of treatment. Relapses also included probable cases of reinfection because it was impossible to differentiate these. Defaulters were patients who failed to renew their appointments in spite of letters of reminder to each of them.

During treatment the signs and symptoms of vaginitis disappeared and no trichomonads could be seen in smears, but in each series the relapse rate was high. The results are given in Table II, and the ultimate effect of treatment is not significantly different with either drug. Seven days' treatment with 291 C 51 produced no cures and is presumably insufficient. The high proportion of defaulters is unfortunate, especially in the third series. The reason for patients not attending again are unknown and it is purpose-

*The trade name for these pessaries is "aroxine."

TABLE II

	Series I	Series II	Series III	
	291 C 51	291 C 51	291 C 51	Acetarsol
Duration of treatment ..	7 days	14 days	14 days	14 days
No. treated	10	38	49	49
Cures	0	3	5	6
Relapses:				
After 1 week		7	5	1
„ 1 month	2	4	7	6
„ 2 months	—	5	8	8
„ 3 „	3	3	1	2
Defaulters	5	16	23	26

less to speculate on whether they considered themselves cured or decided that the treatment was useless. A high incidence of defaulters is the rule among these patients, however treated. In series III the defaulter rate is almost identical in the groups treated with 291 C 51 and with acetarsol. Whatever the causes, they appear to have operated equally in both groups.

None of the patients treated with 291 C 51 complained of toxic side-effects, except one who suffered from a reaction due to sensitization. This produced irritation and burning of the vulva with visible oedema early in the course of treatment. The condition quickly subsided when antihistamines were given and treatment with 291 C 51 was stopped. No evidence of hypersensitivity to 291 C 51 was obtained in this patient by intradermal testing with 0.1% solution or by patch testing with a crushed pessary on a scarified area of skin of the forearm. The patient denied using any additional drug during the course of treatment.

Discussion

The examination *in vitro* confirms the high antitrichomonal activity of this nitrothiazole. Of the drugs that have been previously recommended for the treatment of trichomonal vaginitis, only penotrane and phenylmercuric acetate are somewhat more active than 291 C 51, and this applies especially to the rate at which they kill the organisms. Both of these drugs, however, have to be used in the relatively low concentration of 1:500 or less, whereas 291 C 51 is used with only slight dilution and so has the higher therapeutic index.

Compared with acetarsol, 291 C 51 has a very much higher activity *in vitro*, yet clinically it is no more effective. Both drugs are, however, very effective in suppressing the infection, and most of the patients who had relapsed after treatment with 291 C 51 had no symptoms of vaginitis, the relapse being judged solely on microscopical or physical examination.

The fact that a drug with about a hundred times the activity *in vitro* of acetarsol should prove no more effective *in vivo* suggests that the failure of local treatment to prevent relapses is not due to the lower activity of the drug. Whether systemic treatment would be more efficacious by reaching inaccessible organisms is unknown, for as yet there is no suitable drug available; 291 C 51 is too rapidly inactivated when taken orally or parenterally to be used systemically, and Bushby and Copp found it inactive when given orally or subcutaneously to mice infected intraperitoneally with *T. vaginalis*. Chlortetracycline is a highly efficient systemic drug for bacterial infections, but its antitrichomonal activity is too low for it to be effective except when applied locally. The antibiotic trichomycin has antitrichomonal properties *in vivo* when given to mice with peritoneal infections (Hosoya *et al.*, 1953), but so far there are only reports of its use locally in women (Hosoya *et al.*, 1953; Magara *et al.*, 1954), and information about its systemic effects are awaited with interest. In the meantime if the resistant character of trichomonal vaginitis, due either to failure to eradicate the infection or to unavoidable reinfection, necessitates prolonged and suppressive treatment, 291 C 51 has the advantages of being non-arsenical and non-toxic, and in our experience it is as effective as any non-arsenical drug at present available.

Summary

2-Formamido-5-nitrothiazole has an antitrichomonal activity *in vitro* some 100 times greater than that of acetarsol. It has low toxicity.

Nevertheless in a clinical trial it proved no more effective than acetarsol in preventing relapses, which suggests that relapses are not necessarily due to low activity of the drug. This new antitrichomonal drug is a non-arsenical and therefore possibly more suitable than acetarsol as a suppressant.

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Asking "What is a Virus?" Dr. K. M. SMITH, F.R.S., begins by outlining two theories (*Nature*, 1955, **175**, 12). First, they may be parasitic organisms that have developed their parasitism to the highest possible degree. Alternatively, viruses, or at least some of them, may have no external origin; they may be derived from the cell proteins of one organism and become viruses only when introduced into the cells of another organism. Some support for this second theory may be obtained from a study of certain plant viruses. The potato King Edward, Dr. Smith points out, is invariably infected with a virus, yet the infection is entirely symptomless. The virus can be detected by transferring the sap to other plants, when they show signs of virus infection. Such a wholly latent virus, which causes no symptoms at all in its normal host, Dr. Smith compares with the partially latent virus of herpes simplex, which causes symptoms only when activated by some stimulus, emotional or infective, as during an attack of the common cold. Dr. Smith also discusses the use of viruses to exterminate insect pests, a method already used with some success in Canada and the U.S.A.