

tory work are fairly small, but there is a possibility, where solvents in quart bottles or gallon jugs are standing around on laboratory desks, of their being knocked over and broken. I think that the chief caution is to use them in smaller quantities and in metal containers equipped with stoppers that will not come off if the containers are knocked over, so that the material will not spill. The real preventive measure is to prevent the dissemination of the fumes, either by local exhaust systems and good general ventilation, or by using these substances in closed systems. The latter methods are more applicable to industrial processes than to preventive measures for small quantities used in hospitals.

EVALUATION BY CONTROLLED SERIES OF VAGINAL TRICHOMONIASIS THERAPIES

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CHICAGO

Vaginal trichomoniasis is one of the very common gynecologic clinical entities; and yet, in spite of numerous American and European publications in the last one and one-half decades, controversies continue unabated, especially on the subject of therapy. There are considerable differences also in the criteria employed to diagnose cures. Today the drastic scrubbing procedures have been almost replaced by a dry technic, with the patient self-administering much of the treatment. The type of vehicle, nature of the medicaments and method of treatment are too divergent and unrelated to review at this time. Because too few controls have been established, the favorable reports of many preparations have yet to be properly confirmed. Notable exceptions are the reports of Bland and Rakoff¹ and Pattyson.² Consequently, it was deemed wise to observe the therapeutic effect of three arsenical, one silver picrate and two lactose preparations and their respective controls on obstetric and gynecologic patients. The importance of prophylactic, as well as curative, therapy is emphasized. Only the lack of clinical material has restricted the scope of this study.

A small number of the regular clinic personnel treated the patients in accordance with a prescribed routine and with the assignment of control cases. So far as was feasible, the regular (or special) preparations and the control materials were coded. Such safeguards may eliminate, perhaps, some of the otherwise unavoidable experimental errors of observation and thus aid materially in pointing out the merits of procedures and preparations.

PROCEDURE

The therapeutic agents were studied primarily for their curative effect. Cervical erosion, urethritis and other associated inflammatory lesions were treated by appropriate means only when such lesions were obvious. Examinations of the urinary and intestinal tracts were not made as a matter of routine, nor were the husbands of all the patients available for examination. However, a special study for foci of infection was undertaken when patients did not respond to the therapeutic agent in question. Special periods at the clinic were allotted,

and the patients were treated as often as possible by the same physician. This centralization favored proper supervision of patients, clinic physicians and technic of treatment. The results obtained under these conditions should indicate significantly the value of the preparations and procedures in question.

The five supposedly active medicaments were acetarsone (Merck), acetarsone (Winthrop), carbarsone (Lilly), silver picrate (Wyeth) and lactose with citric acid or kaolin. The control patients received the preparation minus the supposed active medicament; i. e., the vehicles alone were used. The patients were assigned in rotation, every other patient being used as a control, except in the lactose series. Unless a time interval was set by the proponent of a preparation, the Chicago Lying-in standard (Adair-Hesseltine³) was used for determining cures. To be diagnosed as cured by this standard the gynecologic patient must go through two consecutive menstrual periods without treatment, remain free from symptoms and present no clinical or laboratory evidence of the disease. The pregnant patient must fulfil these requirements over a period of two months during pregnancy or before and after parturition.

TABLE 1.—Results of Acetylaminohydroxyphenylarsonic Acid* and Control † Therapy in Patients with Vaginal Trichomoniasis

	Pregnant Patients	Nonpregnant Patients		Total	
		Number	Average Weeks Treated	Uncured	Treated
Regular therapy.....	None	17			17
Cured.....		13	3		
Uncured.....		4	4	4 (24%)	
Control therapy.....	None	17			17
Cured.....		13	3		
Uncured.....		4	4	4 (24%)	
				8 (24%)	34

* Acetarsone (stovarsol).

† Materials furnished by Merck & Co.

In the accompanying tables the ages were omitted because they fell well within the limit of experimental range. All the patients were adult women. The youngest was 18 and the oldest 55.

Gellhorn⁴ reported the use of 12.5 per cent acetylaminohydroxyphenylarsonic acid (acetarsone) in equal parts of kaolin and sodium bicarbonate. His standard dose is 1 teaspoonful, which contains 7½ grains (0.5 Gm.) of the drug. The treatment is administered by a special blower two or three times a week. Douches are not permitted. He stated that six treatments should cure obstinate cases. This procedure was followed exactly throughout. The control material contained the same ratio of kaolin and sodium bicarbonate, but the acetarsone was omitted. The results were judged on a basis of four weeks' treatment, as suggested by Gellhorn.

About four years ago acetarsone in special carbohydrate material (partially hydrolyzed and partially oxidized) began gaining favor in Germany. The material for this study was dispensed entirely in tablet form. From two to four tablets were ordinarily placed about the cervix by the physician, and the patient was instructed to insert two each evening into the vagina. Office visits were once a week for the first two or three

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1. Bland, P. B., and Rakoff, A. E.: The Investigation of a New Pentavalent Arsenical, Aldarsone, in the Treatment of Trichomonas Vaginitis, *Am. J. Obst. & Gynec.* **32**: 835 (Nov.) 1936.

2. Pattyson, R. A.: Trichomonas Vaginalis Vaginitis: A Laboratory and Clinical Study, *New York State J. Med.* **37**: 41 (Jan. 1) 1937.

3. Adair, F. L., and Hesseltine, H. C.: Histopathology and Treatment of Vaginitis: II. Biochemical Approach in Treatment, *Am. J. Obst. & Gynec.* **32**: 1 (July) 1936; idem, unpublished.

4. Gellhorn, George: The Treatment of Trichomonas Vaginitis with Acetarsone (Stovarsol), *J. A. M. A.* **100**: 1765 (June 3) 1933.

times and later at longer intervals. Douches were not allowed. The number of tablets was decreased as the condition improved. The special carbohydrate material minus the acetarsonone was used for the control.

Drabkin's⁵ carbarsone (*p*-carbamido-phenylarsonic acid) routine has been used only a comparatively short time. Briefly, for the first week the patient at bedtime takes a soapsuds enema, followed by a plain water enema, and then inserts into the rectum a carbarsone suppository. Immediately a soapsuds douche followed by one of plain water is taken, after which 5 grains (0.3 Gm.) of carbarsone and 5 grains of sodium bicarbonate (dissolved in 2 teaspoonfuls of water) are injected into the vagina and retained. The next morning one carbarsone suppository is inserted into the rectum and one into the vagina. This routine is repeated each night and morning for the first week. Thereafter it is decreased gradually by weekly steps. Lactic acid or vinegar douches are used as necessary and daily during menstruation. The rectal therapy is discontinued after three weeks. If the condition is not cured in one month, or if it recurs later, the routine is repeated. The control material was the same throughout but lacked the arsenical compound.

The silver picrate compound of Buxton and Shelanski⁶ required weekly visits for the insufflation of kaolin and the silver salt. The patient inserted each evening on retiring a medicated boroglyceride-gelatin suppository. The control material was free from silver picrate.

Adair and Hesseltine³ reported that 95 per cent lactose and 5 per cent citric acid tablets and powder gave a high degree of success in cases of vaginal trichomoniasis. Each tablet contained about 2 Gm. of the mixture. After their value became evident, control cases were started, plain lactose tablets or equal parts of lactose and kaolin being used. From this time on each case was assigned in turn to one of the three preparations. The plain lactose perhaps serves best as the control.

RESULTS

Let it be remembered that the interpretations or comparisons of regular and control materials are only for each unit. Comparisons with other materials would be unfair because the experimental conditions were not identical or simultaneous. The study was to evaluate the influence of so-called specific materials and the influence of the vehicles on the course of the disease and not primarily to compare one so-called specific material with another. The regular, as well as the control, materials were furnished for the most part by the respective companies.⁷ These companies, unsolicited, requested the clinical trial and willingly consented to the establishment of controls.

The results of acetylamino-hydroxyphenylarsonic acid (acetarsonone) in 12.5 per cent concentration in sodium bicarbonate and kaolin, as recommended by Gellhorn,⁴ and its control were observed in only thirty-four patients long enough to analyze. Other patients started on the treatment did not complete the course and naturally cannot be included. Table 1 shows that four of the seventeen controls and four of the regular series were unimproved. The average periods of treatment were identical, and only gynecologic patients were used. No

untoward results or complications resulted from the use of the arsenical mixture. Certainly no particular merit was evidenced.

In table 2 the results of acetylamino-hydroxyphenylarsonic acid (acetarsonone) in the ten obstetric patients are shown to be excellent, but the number of patients is entirely too small. The two gynecologic groups had the same number of failures. Although there may be definite merit in the regular preparation, it is not enough

TABLE 2.—Results of Acetylamino-hydroxyphenylarsonic Acid* and Control† Therapy in Patients with Vaginal Trichomoniasis

	Pregnant Patients		Nonpregnant Patients		Total	
	Number	Average Weeks Treated	Number	Average Weeks Treated	Uncured	Treated
Regular therapy.....	5		16			21
Cured.....	4	3	14	10		
Uncured.....	0	0	2	12	2 (10%)	
Control therapy.....	5		13			18
Cured.....	5	6	11	7		
Uncured.....	0	0	2	8	2 (11%)	
Totals.....	10		29		4 (10%)	39

* Acetarsonone.
† Materials furnished by Winthrop Chemical Co., Inc.

better for its superiority to be established positively here. Again, eighteen and twenty-one patients, respectively, are too small a series from which to draw positive conclusions unless there is a great difference in the results. Thus, acetarsonone prepared by another company did not show a pronounced specificity.

Nine cases, as summarized in table 3 (*p*-carbamido-phenylarsonic acid [carbarsone] and its control), are too few for final conclusion. These are included only because the experiment is still in progress. The procedure as outlined by Drabkin⁵ is rather detailed and time consuming, and some objection and lack of cooperation on the part of the patients were encountered. Rectal therapy is surely a prophylactic measure. It is an interesting observation that the control material has given cures in all four control patients.

TABLE 3.—Results of *p*-Carbamido-Phenylarsonic Acid* and Control† Therapy in Patients with Vaginal Trichomoniasis

	Pregnant Patients	Nonpregnant Patients		Total	
		Number	Average Weeks Treated	Uncured	Treated
Regular therapy.....	None	5			5
Cured.....		5	9		
Uncured.....		0		0	
Control therapy.....	None	4			4
Cured.....		4	9		
Uncured.....		0		0	
		9		0	9

* Carbarsone.
† Materials furnished by Eli Lilly & Co.

Table 4 shows that three of the twenty-two patients treated with the regular silver picrate material were unimproved while only two of the nineteen controls failed to be benefited. This apparent discrepancy in the results of the silver picrate is unimportant, since it falls well within the experimental range. Furthermore, no untoward results developed, and some of the patients did get very satisfactory results from the substance. A sufficiently large series might not only give a reversal of these results but even show an advantage for the regular silver picrate preparation.

5. Drabkin, Charles: *p*-Carbamino Phenyl Arsonic Acid in the Treatment of Trichomonas Vaginalis Vaginitis, *Am. J. Obst. & Gynec.* **33**: 846 (May) 1937.

6. Buxton, R. v. L., and Shelanski, H. A.: Trichomonas Vaginalis Vaginitis: Incidence, Diagnosis and Treatment with Silver Picrate, *Am. J. Obst. & Gynec.* **33**: 842 (May) 1937.

7. Acetarsonone (Stovarsol), Merck & Co.; acetarsonone, Winthrop Chemical Co., Inc.; carbarsone, Eli Lilly & Co.; silver picrate, John Wyeth & Brother, Inc.

The data of Adair and Hesselstine³ (table 5) show that lactose alone gave about a 2 per cent better result than did the citric acid or kaolin mixtures. There is no indication that citric acid or kaolin prolonged appreciably the period of treatment. Citric acid in 5 per cent concentration may be irritating, and apparently it did not contribute therapeutically. On the other hand, the

TABLE 4.—Results of Silver Picrate and Control* Therapy in Patients with Vaginal Trichomoniasis

	Pregnant Patients		Nonpregnant Patients		Total	
	Number	Average Weeks Treated	Number	Average Weeks Treated	Uncured	Treated
Regular therapy.....	2		20			22
Cured.....	2	6	17	7		
Uncured.....	0	0	3	14	3 (14%)	
Control therapy.....	2		17			19
Cured.....	2	5	15	6		
Uncured.....	0	0	2	13	2 (10.5%)	
Totals.....	4		37		5 (12%)	41

* Materials furnished by John Wyeth & Brother, Inc.

kaolin mixture was associated with less watery vaginal discharge. Again the control comparisons were within the experimental range.

Table 6 shows that by pooling the data on the arsenical preparations and their respective controls little difference is revealed between them. This likewise applies to the lactose group.

COMMENT

Thus, it becomes evident that good results may be obtained with various agents in approximately 85 to 90 per cent of the patients, while the remaining 10 to 15 per cent may not remain relieved or may even fail to be improved. Even though many husbands whose wives were in the unimproved groups refused urologic examinations, three of those examined were found to have prostatic infections. Such observations have already been reported by Drummond,⁸ Cornell and Riba,⁹ Karnaky,¹⁰ Adair and Hesselstine³ and others. Allen, Jensen

TABLE 5.—Results of Lactose with Citric Acid, Lactose Alone and Lactose with Kaolin in Patients with Vaginal Trichomoniasis (After Adair and Hesselstine³)

	Pregnant Patients		Nonpregnant Patients		Total	
	Number	Average Weeks Treated	Number	Average Weeks Treated	Uncured	Treated
Lactose and citric acid.....	11		55			66
Cured.....	11	9	49	8		
Uncured.....	0	0	6	14	6 (10%)	
Lactose and kaolin.....	0		21			21
Cured.....	0		19	6		
Uncured.....	0		2	9	2 (10%)	
Lactose (only).....	4		20			24
Cured.....	4	8	18	6		
Uncured.....	0	0	2	9	2 (8%)	
Totals.....	15		96		10 (9%)	111

and Wood¹¹ have demonstrated the likelihood of foci in the urethra and bladder of some patients. Karnaky¹⁰ and others have demonstrated trichomonads in the

8. Drummond, A. C.: Trichomonas Infestation of the Prostate Gland, *Am. J. Surg.* **31**:98 (Jan.) 1936.

9. Cornell, E. L., and Riba, L. W.: Treatment of Trichomonas Vaginalis and Trichomonas in the Male, *Surg., Gynec. & Obst.* **63**:511 (Oct.) 1936.

10. Karnaky, K. J.: Trichomonas Vaginalis and Monilia Albicans as Causes of Leukorrhoea, *South. M. J.* **28**:795 (Sept.) 1935.

11. Allen, E. D.; Jensen, L. B., and Wood, I. H.: Clinical and Bacteriologic Observations in Trichomonas Vaginitis, *Am. J. Obst. & Gynec.* **30**:565 (Oct.) 1935.

intestinal tract, but some controversy still exists as to whether any of these are the vaginal type. Therefore, it seems that to improve the results of therapy for vaginal trichomoniasis one must not only cure the disease but eliminate the source of reinfection. Reinfection may occur so frequently and rapidly that therapy is of little aid. Hence failures may represent in part persons not having proper prophylactic care or instruction against reinfection.

The fact that vaginal mycosis did develop during or immediately after completion of therapy with silver picrate and with acetarsone indicates that the vagina was not at that time an unfavorable nidus for the fungi. This clinical observation parallels the histologic evidences that the normal vaginal epithelium in pregnancy is rich in glycogen-like material.

The biologic state of the vagina appears to be highly important. The works of Cruickshank and Sharman,¹² Plass and Oberst,¹³ Adair and Hesselstine,³ Bland and Rakoff¹⁴ and others reveal that the vaginal acidity, the glycogen-like content of the epithelium and the bacterial and cellular flora are intimately related. The normal relationship is disturbed in vaginal trichomoniasis by a

TABLE 6.—Comparison of Three Arsenical Substances, One Silver Picrate and Two Lactose Combinations with Their Respective Controls

Substances in Question and Controls Studied	Patients		Group Totals	
	Treated	Failed	Treated	Failed
1. Acetarsone (Merck).....	17	4 (24%)	43	6 (14%)
Control.....	17	4 (24%)		
2. Acetarsone (Winthrop).....	21	2 (10%)	39	6 (15%)
Control.....	18	2 (11%)		
3. Carbarsone (Lilly).....	5	0	22	3 (14%)
Control.....	4	0		
4. Silver picrate (Wyeth).....	22	2 (14%)	19	2 (11%)
Control.....	19	2 (11%)		
5. Lactose and citric acid.....	66	6 (10%)	87	8 (10%)
Lactose and kaolin.....	21	2 (10%)		
Lactose.....	24	2 (8%)		
Totals.....			234	27

lessening of the vaginal acidity, a decrease in the glycogen-like material and a conversion of the vaginal flora to type 2 or 3.

A plea is made for the establishment of adequate and proper controls when one makes such a study and especially before recommending new preparations to members of the profession. Certainly any ethical pharmaceutical house would endorse this attitude and would cooperate if an honest evaluation was desired. In establishing controls it is urged that one adhere strictly to a routine and assign alternate cases to the control series and employ codes for the regular and control preparations whenever possible to eliminate further unavoidable personal prejudice in observations and interpretation of the therapeutic results. Moreover, before one can state correctly that any preparation is superior to others, one must have a series sufficiently large to exclude at least some of the experimental errors.

CONCLUSIONS

1. The majority of patients with vaginal trichomoniasis can be benefited by more than one therapeutic material and method.

12. Cruickshank, R., and Sharman, A.: The Biology of the Vagina in the Human Subject, *J. Obst. & Gynaec. Brit. Emp.* **41**:190, 369, 1934.

13. Plass, E. D., and Oberst, F. W.: The Hydrogen Ion Concentration of Human Vaginal Discharge, *Am. J. Obst. & Gynec.* **32**:22 (July) 1936.

14. Bland, P. B., and Rakoff, A. E.: Some Bacteriologic Aspects of Trichomonas Vaginalis Vaginitis, *Rev. Vida Nueva* **37**: (May 15) 1936.

2. Probably in from 8 to 15 per cent of the cases of vaginal trichomoniasis particular care should be taken to eliminate foci of infection from the patient's rectum or urethra and bladder, or from the husband's urethra and prostate, and perhaps from other sources still undetermined.

3. The physiologic restoration of the vagina is apparently of paramount importance in accomplishing cures.

4. An adequate and proper control should be employed in the evaluation of the merits of any procedure or preparation.

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ABSTRACT OF DISCUSSION

DR. A. E. RAKOFF, Philadelphia: Interesting as are the uniformly high percentage of cures obtained by the various methods, my attention was attracted by the almost equally good results in the control series, treated with relatively inert substances such as kaolin. This is not in accord with my experience, since only 10 per cent of a group treated by kaolin insufflations alone responded permanently, although almost all were temporarily relieved. It is notable that the drugs employed were all in a dry form. It is the present consensus that "dry antisepsis" affords the most successful basis for elimination of the flagellates. Two preparations were insoluble pentavalent arsenicals, acetarsone and carbarsone. Dr. Bland and I made a study of these drugs plus a related soluble derivative, sodium-methylene-sulfon-amino-hydroxy-phenyl-arsionate. The latter was more effective clinically and in vitro. Dr. Hessel-tine pointed out that a plan of treatment based on the associated pathologic conditions is frequently more important than the choice of an antiseptic. Thus the realization that organisms are harbored in surrounding structures may mean the difference between cure and recurrence. In my experience the urethra and para-urethral structures are the most common offenders, since trichomonads are frequently found here. I am persuaded that a few organisms harbored in the cervix may also be the source of recurrences. The male is probably a source of reinfestation in a small group of cases. I found the organisms in about 6 per cent of a group of men. The anterior urethra was much more commonly the seat of infestation than was the prostate gland. The intestinal tract is rarely if ever the source of vaginal infestation. Evidence indicates that the vaginal and intestinal trichomonads are morphologically and culturally distinct and that in this climate intestinal infestation is relatively uncommon. Experimental inoculations with the intestinal forms were unsuccessful, whereas I have produced the infestation with vaginal trichomonads. Administration of toxic drugs by mouth or bowel to eliminate an intestinal infestation whose existence is not first proved is hardly justifiable, yet many patients are treated in this fashion. Examination of the vaginal bacteria affords a reliable indication of progress during the course of treatment. Döderlein's bacilli tend to become reestablished with the disappearance of the trichomonads. Lactose or lactic acid douches are sometimes helpful in favoring this return after preliminary chemotherapy.

DR. H. CLOSE HESSELTINE, Chicago: I have not been able to confirm Dr. Rakoff's observations of finding trichomonads in the cervix, although others agree with this statement. Might not these flagellates be due to contamination by the vaginal discharge? Dr. Curtis has just reminded me that one should be very cautious as to what one considers cures. I agree heartily with his views. Cures can be established in part by repeated examination over a sufficient time. I used the words "uncured" and "cured" to simplify tables; perhaps that is incorrect. I have reviewed the cases becoming positive after intervals of two months following menstruation, and I believe it is very probable that some of these may represent reinfection rather than recurrence or exacerbation. May not these reinfections be comparable to colds? A patient may have a cold one month and again in a few weeks. Would this be a new cold or does it mean that the patient is more susceptible to colds? I feel that the same rules apply here. Until more is known about the sources of spread, some of our problems will remain unsettled. The problem of therapy is yet unsettled also.

INTENSIVE CASE FINDING WORK IN TUBERCULOSIS

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AND

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DETROIT

There has been a definite reduction in the death rate from tuberculosis in the United States, the rate now being less than one-third that which obtained at the turn of the century. However, the combat with this age-old foe of mankind has by no means been completed. Although displaced by heart disease, cancer and pneumonia at the summit of the causes of death (for all ages), in the very prime of life (from 20 to 35 years) tuberculosis still ranks first as a cause of death. There are not less than 500,000 sufferers from this disease in the United States at the present moment. Let us not be lulled into any false sense of security from past accomplishment; let us attack this disease with the same vigorous attitude with which we confront small-pox or diphtheria. Health departments have been prone to accept the crumbs from monies spent for social betterment. We have been too reticent in a fight in which modern tools are at our disposal. Possessing knowledge, we are derelict in our duty when we fail to use every artifice and ingenuity in winning and maintaining public confidence and support, which alone can provide the wherewithal to deal intelligently with a pestilential disease.

How can so many health officers remain complacent knowing full well that more than 80 per cent of all tuberculosis cases reported to health departments are already in an advanced stage? How successfully could we maintain our warfare against diphtheria and small-pox if four out of five cases were officially reported to the health department only shortly before death? Why not apply the same reasonable procedures in epidemiology to tuberculosis as we daily employ in our attack on other communicable diseases?

We can all agree that the local health officer should play a commanding part in the fight against tuberculosis, even though he may not have every detail as a function of his department. It is his responsibility to see that a program of prevention is carefully planned and executed. The school health service, the hospital care of patients, the health education program, and many other essentials may be carried on by voluntary agencies or other public agencies not a part of the health department. In every instance, however, the health officer must assume responsibility for the community program. He must be a planner, a coordinator, and take full authority and responsibility to see that the various units, organizations and individuals function smoothly in their respective fields. The ideal condition demands the establishment on a full time basis of an efficient local health service, the employment of a well trained public health administrator assisted by the essential technical personnel and blessed with reasonable financial support. A tuberculosis program cannot be successful without the cooperation of all agencies concerned with health education and the active participation of the medical profession, individually and collectively.

No intelligent progress can be made in combating an enemy unless we know his whereabouts, and in the case

From the Detroit Department of Health.
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