

History of the treatment of trichomoniasis

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Feminists have been heard to say that the late entry of women into the ranks of the medical profession has meant that, left to the tender mercies of mere men, the ills to which female flesh is heir have not been given the attention which they deserved. Our knowledge, for example, of the cause and prevention of mammary carcinoma seems to have made little advance since Ramazzini reported in 1713 that cancer of the breast was especially common in nuns. Similarly it could be said that, since Donné discovered *Trichomonas vaginalis* in 1836, no really successful method of treating trichomonal vaginitis had been devised in the 120 years that followed; and today our knowledge of the life cycle of that micro-organism is still virtually nil. That three-letter word probably correctly describes the incidence of trichomoniasis in nunneries, but elsewhere it is a widespread infection occurring in women mainly in their most sexually active years.

The history of the treatment of any disease is of necessity related to the history of the disease itself. For long the pathogenicity of *T. vaginalis* was questioned, and it has been in the professional lifetime of venereologists practising today that trichomoniasis has emerged as a clinical entity from that indeterminate rag-bag of conditions associated with what was descriptively called leucorrhoea and was popularly called 'whites'. In the early 1930s both gynaecologists and venereologists were concerned about the prevalence of vaginal discharges, and at a meeting of the M.S.S.V.D. Mr. Alan Brews made some striking suggestions. He advocated complete co-operation between venereologists and gynaecologists, with outpatient clinics held at the same time, in adjoining premises with communicating doors. Only so, he thought, could a substantial reduction be brought about of the high incidence of vaginitis. He regarded trichomoniasis as 'a primarily infectious disease'.

Shortly before the second world war, at a meeting of the Society at which a series of papers was read on non-gonococcal vaginal discharges, the third speaker remarked that in neither of the first two

papers had mention been made of what he thought was a not uncommon cause of vaginitis—*Trichomonas vaginalis*—which might (the italics are mine) become pathogenic in the presence of other organisms favouring its growth. Not long afterwards Mr. Ambrose King stated that the extraordinary proportion of young women with *T. vaginalis* in their discharge had been a complete revelation to him. He added that it was almost always of venereal origin, and that he was afraid that this idea would not receive general acceptance and would horrify some people. He had never seen a case in which infection could be traced to a swimming pool.

In time, of course, the concept that trichomonal vaginitis was a venereal disease became generally accepted: the habits and habitat of *T. vaginalis* were studied, and in a paper to the M.S.S.V.D. Dr. Glen Liston gave a detailed account of his findings. He stressed the importance of the pH of the vagina, which in the normal adult is around 4, a level at which the trichomonad cannot live in the vagina. This degree of acidity depends on the production of lactic acid from the glycogen in the vaginal epithelium by the action of Döderlein's bacillus. The trichomonad, by consuming the glycogen, alters the vaginal pH. It is essential, Dr. Liston insisted, that treatment should aim not only at destroying the parasite but at restoring glycogen to the epithelial cells and re-establishing Döderlein's bacillus in the vagina. The best guide to ascertain the effect of treatment was to take the pH of the vaginal contents at repeated intervals and to observe the amount of glycogen in the epithelial cells as well as the character of the bacterial flora of the vagina. A cure was established when the pH had returned to and remained at about 4. He went on to say that drugs could kill only the parasites which they reached—on the surface of the vaginal epithelium—and that relapses were due either to the failure of the chemical agent to reach the organisms in the ducts and glands about the vulva or to re-infection from a male consort.

Although it was as far back as 1894 that trichomonial infestation of the urinary tract of a male

patient was first recorded, no account of male trichomoniasis appeared in a medical journal in Great Britain until 1939. Attention was focused on the subject by a paper by Glen Liston and Robert Lees, read to the Society in the following year (Liston and Lees, 1940).

It was customary to treat vaginal discharges of whatever origin by the local application of many different substances. One of the most popular and apparently effective in trichomoniasis was an arsenical preparation, supplied as vaginal inserts and as powder for insufflation, containing a carbohydrate to replace the lost glycogen—in accordance with Liston's teaching. The manufacturers recommended that no more than six vaginal tablets should be applied in the course of a week but reports were published of satisfactory results from the use of seventy tablets a week. The fact that many cases relapsed after menstruation or during pregnancy may have prompted higher doses, but these were not without danger and, as recently as 1959, one woman died in a London hospital from overdosage. Recurrence after arsenical treatment was sufficiently frequent for other methods of treatment to be tried, including direct application to the vagina of ultra-violet radiation, and even psychotherapy. Aureomycin, mapharsen, mepacrine, trichomycin, 'negatol', and a host of other substances were tried for a time and then fell into disuse. One elaborate technique, for which close on 100 per cent. success was claimed, began with electrofulguration of Skene's ducts and cauterization of erosions and removal of polyps (not nowadays regarded as related to trichomoniasis). The vagina was then dried and insufflated with argyrol, kaolin, and lactic acid. Pessaries containing the compound powder were inserted at night after a douche of vinegar water. Treatment was continued for 3 to 4 weeks, and in the event of relapse was resumed for 6 weeks: but other workers failed to get the results reported by the originators of the method.

The dramatic success of the sulphonamides in gonorrhoea led to their trial in trichomoniasis, given locally and by mouth, and in combination with the arsenical vaginal tablet; but the results were not appreciably better than those from arsenic alone.

It could be said that patients suffered much at the hands of many physicians, and if the last state of the woman was not worse than the first it was not much better. Venereologists spoke of ringing the changes on various forms of treatment: and it was perhaps cynically but probably correctly stated that success depended more on the length of time that treatment was persevered with than on the method of treatment employed.

In such a situation the idea of a systemically active trichomonicide was attractive, and the profitable market likely to be realized for such a product induced some manufacturers without adequate clinical testing to advertise drugs with claims which deceived a too trusting medical profession and which experience showed to be obviously false. Despite the much vaunted virtues of the Committee on the Safety of Drugs, we had, until very recently, no protection against the promotion of medicines that are innocuous but ineffective. It is a reproach to parliament, the medical profession, and the chemical manufacturers that in the field of medicine black sheep could still safely graze.

Because of the disappointment with the poor results from the allegedly systemically active drugs, it seemed likely that when a really effective compound arrived it would get a chilly reception, but such was not the case. To French workers belongs the credit for metronidazole, and the first clinical reports were published by Durel, Roiron, Siboulet, and Borel (1959, 1960). They did not, however, seem to be fully aware of its value, for they modestly claimed that its oral administration was no more than a useful adjuvant to its local application. British workers demonstrated that, given by mouth without any form of local treatment, metronidazole achieved a very high rate of cure, and the results reported by Rodin, King, Nicol, and Barrow (1960) and by Nicol, Barrow, and Redmond (1960) were amply confirmed by other workers. The meeting of the M.S.S.V.D. at which many of their reports were presented was described as a landmark in the history of the disease. With proper caution the possibility was pointed out of the trichomonad developing resistance to metronidazole, and of the appearance of as yet unsuspected toxic effects; and the hope was expressed that some other and equally effective drug would be discovered. The success of metronidazole stimulated competition, and preparations appeared for which the claims made proved to be over-optimistic; but it now seems that with nitrimidazine the hope for an equivalent product may have been realized. After world-wide use of metronidazole for a dozen years no resistant strain of *T. vaginalis* has been found, and no serious side-effects have been observed. Because papers published abroad and hopeful rumours nearer home represented that metronidazole had in fact begun to fail, it was deemed desirable to compare the current rates of cure of trichomoniasis with those obtained in the early 1960s. Several such comparisons were undertaken, and the author of one stated unequivocally: 'The results of this survey leave one in no doubt. Metronidazole is still the drug of choice for tricho-

monal vaginitis. No toxic action was observed and there was no evidence that the drug has lost efficacy in the last 10 years' (Keighley, 1971).

Although venereologists in Great Britain were quick to recognize the merits of the new drug (to which the French gave the proprietary name of 'Flagyl', still in current use), gynaecologists, perhaps because they have been less dependent on chemotherapy than venereologists, did not so rapidly realize the revolutionary change that was taking place in the treatment of trichomoniasis. Eventually, however, they made up for a slow start, one gynaecologist criticizing the manufacturers for claiming only 80 to 90 per cent. of cures, which—he said—did not encourage doctors to ask themselves the question 'Why not 100 per cent.?' The answer is because some women do not take the tablets as prescribed, others are re-infected by an untreated partner, and (in a very few cases) bacteria are present in the vagina which inhibit the trichomonocidal action of the drug. From Scotland came a request for a photograph of the man who discovered 'Flagyl', because gynaecologists wished to hang it on the wall of their Society's headquarters in recognition of the greatest contribution to gynaecology of the last fifty years.

The 'welcome' given to 'Flagyl' in the U.S.A. was of a very different nature. The objections to its use put forward by the Food and Drug Administration (F.D.A.) are well-nigh incredible to anyone who believes that the medical profession and its administrators are all actuated by honourable motives. Because mention had been made in early British reports of a few women who had shown a transient reduction of leucocytes, the bogey of blood dyscrasia was raised. Because in another report giddiness was referred to in one case (and unfortunately the term 'Rombergism' had been used), the danger of (non-existent) nerve damage was stressed; and because some male rats, given metronidazole in a dosage relative to body weight many hundred times the therapeutic dose, developed necrosis of the testis, testicular biopsies in man were called for. One (mis)leading American gynaecologist went so far as to speak of teratogenic effects, and stated in print that there were few cases of trichomoniasis that required the new and potentially dangerous drug. He continued to find satisfactory (to himself) the use of powder which rendered the pH of the vagina unfavourable to the growth of *Trichomonas vaginalis* and required his (paying) patients to attend his office week after week to have the powder applied. Even today the F.D.A. has such influence that distributors of metronidazole in the United States feel obliged to publish a long list of side-effects (most

of which are got with an inert placebo), to recommend repeated white cell counts, to prohibit administration throughout pregnancy, and to confine its use to trichomoniasis—regardless of the fact that metronidazole is dramatically successful in acute ulcerative gingivitis and amoebic dysentery. One is reminded of a conversation with a gynaecologist in Johannesburg 25 years ago, in the course of which he said, 'Doctor, if you ever discover a drug that really destroys the trichomonad, I shall lose half my income'. In that sense—and in that sense alone—is 'Flagyl' a dangerous drug!

No matter how effective the treatment, the complete abolition of an infectious disease requires that every infected individual and every contact be traced and treated: but how few medical officers of health give a thought to trichomoniasis! Perhaps the next chapter in the history of that disease will record the epidemiological approach to its extinction. Meantime the clinicians have made remarkable progress, thanks to the success of metronidazole. There are of course several yardsticks by which the success of a remedy may be measured, depending on who it is that is making the assessment. These include the permissible profits of those who make the drug and the more questionable gains of those who do not make use of it. Dr. Elizabeth Keighley (1971) reminded us of others who, after all, are those most concerned. 'It is a good thing', she wrote, 'to pause and contemplate the change that oral medication for trichomonal vaginitis has made in women's lives. 'Flagyl' is now taken as a matter of course, and a whole generation has no knowledge of the suffering of women with trichomoniasis before its introduction—the indignities and discomfort of the perpetual local treatment, douches, paintings, insufflations, and insertion of pessaries. All these things women suffered for months and sometimes years on end, only to relapse when the treatment was discontinued'.

In the final analysis perhaps the discoverers, the manufacturers, and the prescribers of 'Flagyl' would agree that their greatest grounds for satisfaction lie in the knowledge of the contribution which they have made to the health and happiness of womankind.

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