NON-SPECIFIC URETHRITIS

BY

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Non-specific urethritis is one of the most perplexing conditions encountered in the venereal diseases clinic today. In Britain it was thrown into sharp relief during World War II as those affected in the military hospitals were daily examined for the gonococcus which was found wanting. Although non-specific urethritis had been recognized as an entity for many years, many venereologists still considered it to be a manifestation of gonorrhoea. Its full recognition in the United States came even later and, when it appeared in force amongst the American troops in the Pacific theatre, it was at first believed to be penicillin-resistant gonorrhoea. In 1953, in the clinics of England and Wales, 13,157 cases were treated as compared with 15,242 male cases of gonorrhoea.

The causes of non-gonococcal urethritis are legion. They fall into four main groups:

1. Secondary to external and internal irritants.
2. Secondary to intra-urethral sores and tumours.
3. Secondary to other urethral, bladder and kidney disease.
4. Primary urethritis.

The commonest is a primary urethritis of unknown aetiology.

Before considering these groups in detail it should be recorded that certain conditions may simulate urethritis. Thus in phimotic persons a subpreputial discharge, due to balanitis, primary syphilis, chancroid or condylomata acuminata may lead the patient (and sometimes the doctor) erroneously to believe that a urethritis exists. Similarly, excessive physiological secretions due to prostatorrhhea or spermatorrhoea may bring the patient to the clinic in the belief that he has a urethritis. In the latter condition, usually seen in unmarried young men, the “discharge” comes from the prostate and seminal vesicles. In prostatorrhoea there is a clear sticky glycerine-like discharge, which is most noticeable after defecation due to pressure of the faeces on the prostate.

I. URETHRITIS SECONDARY TO EXTERNAL AND INTERNAL IRRITANTS

A. EXTERNAL

(i) Traumatic, due to cystoscopy, urethroscopy, passage of a sound, catheterization, urethral syringing, foreign bodies introduced by the patient, urethral calculus, frequent masturbation or excessive coitus.

(ii) Chemical due to injudicious urethral irrigations or insertion of prophylactic material, use of chemical contraceptives, self-infliction, and occasionally following exposure to noxious vapours.
B. INTERNAL (*Urethritis ab ingestis*)

(i) *Crystalluria*, from phosphates, oxalates, sulphonamides, etc.

(ii) *From irritants excreted by the kidneys*, cantharides, turpentine, potassium iodide, potassium nitrate, phenolphthalein, etc.

*Phosphaturia* is a physiological condition, part of the mechanism of maintaining a constant pH of the blood. Phosphaturia may sometimes produce a milky deposit at the end of the act of micturition which may be mistaken for a urethral discharge. The urine is alkaline and cloudy but clears on the addition of dilute acetic acid. Phosphaturia can be temporarily alleviated by making the urine acid with ammonium chloride 0.5 g. taken three times a day by mouth.

The intake of certain foods, notably strawberries, beetroot, rhubarb, horseradish, cocoa, tea, alcohol, pepper and mustard, have all been reported as occasionally causing a urethral discharge. Most of these foods contain oxalates and a "powdered wig" deposit may be noted in the urine resting on a cloud of mucus. Asparagus will produce a urethral discharge in some persons, presumably due to hypersensitivity to methyl mercaptan (asparagine) which is excreted in the urine.

II. SECONDARY TO URETHRAL SORES AND TUMOURS

Primary syphilis.
Chancroid.
Carcinoma (rare).
Lymphogranuloma venereum, primary lesion.
Lymphogranuloma venereum, late lesions.
Condylomata acuminata.
Herpes simplex.
Balanitis xerotica obliterans.

Lesions of most of these conditions are visible at the urinary meatus, but if not can be seen at urethroscopy. The state of the inguinal glands may be very helpful, being typically enlarged in intra-urethral chancre, chancroid and lymphogranuloma venereum, but not enlarged in uncomplicated non-specific urethritis.

III. SECONDARY TO OTHER CONDITIONS OF URETHRA, BLADDER AND KIDNEYS

A. URETHRA

Post-gonococcal urethritis.
Urethral stricture.
Urethral calculus.

B. BLADDER.—Secondary to cystitis from any cause:

*B. coli* cystitis.
Enlarged prostrate.
Diverticulum of bladder.
Stone of the bladder.
C. KIDNEYS

Stone.
Tumours.
Pyelitis.
Tuberculosis.

*Post-gonococcal urethritis* may be due to slow resolution, secondary infection of the glands of Littré, Cowper or prostate with mixed organisms, to a meatal wart (condyloma acuminatum), urethral stricture, or commonly to a superimposed attack of non-specific urethritis.

Bilharzia (schistosomiasis) caused by the helminth *Schistosoma haematobium* should be borne in mind as a possible cause in all countries where bilharzia is endemic. If the other causes listed are not immediately suspect from their history, investigations to exclude them can reasonably be deferred until after the effects of treatment have been noted. In the majority of cases the additional investigations will not prove to be necessary.

IV. PRIMARY URETHRITIS

A. Bacterial.
B. Abacterial:

1. Protozoa: Trichomonads.
   Amœbæ.
3. Spirochaetes.
5. Viruses.
6. Idiopathic.

A. BACTERIAL URETHRITIS

Some workers subdivide urethritis into bacterial and abacterial forms according to whether or not visible bacteria are observed in stained smears of the discharges. A large variety of organisms have been incriminated in individual cases, including *Staphylococcus albus*, diptheroids, streptococci (especially *Strep. faecalis*), pneumococci, *H. influenzae*, *B. proteus*, and *Staphylococcus aureus*, Neisseria other than the gonococcus, e.g., *N. sicca, N. flava*, etc., diphtheria and tuberculosis bacilli, *Pasteurella, Sarcina, B. crassus, M. tetragenus*, etc.

Bacterial urethritis may follow anal or buccal coitus and is said to have a short incubation period of four to eight days. In my own experience the organisms most frequently cultured from the urethra in non-gonococcal urethritis...
are *Staph. albus*, diphtheroids, coliforms and occasionally streptococci, enterococci, *Staph. aureus*, *B. proteus* and *Monilia*. The pattern of the urethral flora does not materially change with treatment and similar findings are noted in unaffected controls. While not denying that a true bacterial urethritis can occur, it is personally believed that it is a comparatively uncommon variety of non-gonococcal urethritis.

B. **ABACTERIAL URETHRITIS**

1. **Protozoa**

   (a) *Trichomonas vaginalis*.—This flagellated protozoon, larger than a pus cell and smaller than an epithelial cell, is found in large numbers of women especially in conjunction with a vaginitis. It has four free flagella at the rounded anterior end and a fifth is reflected back to be attached along the body as an undulating membrane. It has a macronucleus and a micronucleus, and an axostyle at the posterior end with which it can attach itself to cells or debris. *T. vaginalis* can best be seen under the dark field when the motility of its flagella immediately attracts attention.

   Other trichomonads, *T. buccalis* and *T. intestinalis*, have been found in the mouth and gut respectively. These differ slightly in morphology, but whether, in suitable circumstances, they can mutate into the vaginal form is not definitely known.

   In the woman there may be an intense tender vaginitis with a profuse greenish-yellow frothy discharge. The vaginal walls bleed easily, but milder, more chronic, varieties are not uncommon. The urine can also be shown to contain trichomonads in a number of cases. Spread to the Fallopian tubes and pelvis of the kidney has been reported. It is not known for certain if *T. vaginalis* is the primary cause of the vaginitis or whether it is a secondary invader.

   There is no suitable systemic treatment, but the vaginitis can be made to subside with pessaries inserted nightly for three weeks. Acetarsol (Stovarsol, Carbarsone), chloramphenicol, aureomycin or terramycin (each pessary containing 500 mg.), Vagisol (tyrothricin), phenyl mercuric nitrate and allied compounds, Penotrate, Diodoquin, etc., are all useful. Insufflation of these medicaments in powder form is also often successful. In this condition the vagina has lost acidity and lactic acid douches may be helpful. Relapses, unfortunately, are very frequent.

   It is obvious that clinicians should try to link trichomonatous vaginitis in females with non-specific urethritis in males. Certainly the more dark-field examinations that are made on urethral discharges of males with urethritis, and the longer the time that is spent on them, the more trichomonads are discovered. Occasionally they may be isolated from the prostate and seminal vesicles. They are found with particular frequency in cases with a purulent discharge in which the gonococcus is surprisingly found wanting. However, an incidence of 10-15 per cent. is all that is usually obtained, and it is impossible, therefore, to incriminate trichomonads as the cause of the majority of cases of non-specific urethritis.
Following treatment of the urethritis with aureomycin or chloramphenicol, the trichomonads may disappear from the urethra or they may persist even after the pus content of the discharge has been largely eliminated. In these cases, and in female cases with bladder infections, it may be helpful to change the reaction of the urine by suitable drugs. Resistant male cases usually ultimately respond to daily urethral irrigations with 1/10,000 oxycyanide of mercury.

(b) *Amaebae.* Urethritis may rarely be due to *E. histolytica*, as a complication of amoebic dysentery.

2. *Metazoa (Flies, Fish, Flukes and Fungi)*

A urethritis has been recorded resulting from larvae of flies and beetles in the urethra, from the entry of certain leeches in Egypt and India, and from the activities of the South American catfish (candyru)—a small fish about 60 mm. in length and 4 mm. wide, which may penetrate the rectum, vagina or urethra of unfortunate bathers—but these are medical curiosities. Nematode worms have also on occasion been passed per urethram.

A not infrequent cause of non-specific urethritis, however, in countries in which the disease is endemic is urinary bilharzia. The adult worms of *S. haematobium* (the male lies engulfed in the gynaecophoric canal of the female) develop from cercariae in the liver which migrate to the portal and mesenteric veins to reach the submucous tissues of the bladder, prostate and urethra. Ova with terminal spines are then discharged and these give rise to hematuria and cystitis with a secondary urethritis, or directly to a urethritis. The ova develop in fresh water into miracidia which enter the intermediate host—a fresh-water snail of the *Bullinus* species, in the liver of which sporocysts form from which cercariae are ultimately liberated which penetrate the skin of man to complete the life cycle.

Fungi, too, may occasionally cause a urethritis. Spores and mycelia are then seen in Gram-stained specimens of the urethral discharge. The possibility that these might be contaminants of the staining solutions should be borne in mind. Vaginal thrush due to *Candida albicans* may sometimes be associated with a fungous urethritis in the male. The condition is more common in diabetics.

3. *Spirochaetes*

Non-specific spirochaetes may be found during dark-field examination of specimens taken from patients with balanitis, fusospirochaetosis and secondarily infected sores. Spirochaetes resembling *S. dentium* have been noted in centrifuged deposits of urine of patients with *abacterial pyuria*, and neoarsphenamine was once used in its treatment. The claim that such a spirochaete is the cause of non-specific urethritis has from time to time been pressed, but spirochaetes are not found sufficiently often to be incriminated as the cause in the majority of cases. When they are found the possibility that they are but secondary invaders is difficult to disprove.

The possibility that urethral spirochaetes are related to the practice of buccal
or anal coitus has been considered. Anal coitus, apart from by homosexuals, is utilized in some parts of the world by girls as a means of maintaining “virginity.” Anal or buccal coitus is practised in Great Britain, however, no more frequently by patients with non-specific urethritis than by patients with gonorrhoea.

4. Pleuropneumonia-like organisms

Pleomorphic intracytoplasmic inclusions, in the form of rings, commas or ovoids, may be seen in scrapings of the urethra staining purple with Giemsa’s stain. Sometimes these form morula-like bodies, but their marked pleomorphism distinguishes them from virus inclusions. Pleuropneumonia-like organisms (PPLO) grow readily on nutrient agar or in broth enriched with serum or ascitic fluid, when they form characteristic colonies with an adherent central core. Penicillin is usually incorporated in the medium as a bacterial inhibitor.

As PPLO have been noted in patients with non-specific urethritis, asymptotically in females, and less commonly in controls, they have been claimed as a possible cause of non-specific urethritis by a number of workers.

PPLO have been isolated from man and animals in a wide variety of circumstances, and many organisms apparently may produce “L” forms under certain conditions. Although the possibility that there may be certain pathogenic strains of PPLO cannot be entirely excluded, current opinion is that they are but commensals. (For possible reasons as to their more frequent presence in urethritis cases than in controls—see under Viruses.) Their attempted isolation, as a part of the routine investigations of the venereal diseases clinic, is therefore not at present justified.

5. Viruses

Inclusion-like bodies have been demonstrated, lying free or in the cytoplasm of the epithelial cells, in Giemsa-stained urethral scrapings from patients with non-specific urethritis. Similar bodies have been noted in scrapings from the conjunctiva of patients with Reiter’s disease and from the skin in keratosis blennorrhagica. These bodies have been claimed as being produced by a virus, PPLO, or by both.

Very similar bodies are seen in such known virus diseases as lymphogranuloma venereum, psittacosis, trachoma, enzootic abortion in ewes and inclusion conjunctivitis—a widely differentiated collection of diseases. The generic term Chlamydozoaceae has been applied to this group of viruses. They are found as uniform elementary bodies 2-3 microns in size, either lying free or in the cytoplasm of the epithelial cells, or occasionally as a crescent surrounding the nucleus. Larger initial bodies may also be found, sometimes indenting a nucleus, which may form colonies of elementary bodies.

Positive proof that non-specific urethritis is commonly due to a virus is lacking, and those who were at one time insistent in pressing the claims of a virus etiology for the disease now admit that a true virus urethritis is comparatively rare.

During 1951-2 the author was engaged in an attempt to find evidence for or
against a virus causation of non-specific urethritis. Direct attempts to pass the virus into the conjunctiva, joints and urethra of monkeys, the groins of guinea-pigs, the brains and lungs of mice, or into the chorioallantoic membranes of yolk sacs of chick embryos, met with failure. These findings were in accord with those of other workers, although the isolation from a case of Reiter’s disease of a filterable agent pathogenic for mice had been claimed.

From an examination of 1,463 Giemsa-stained specimens, which were reported on as to whether blue or red granules or blue or red “colonies” were noted, it soon was apparent that only the blue “colonies” could have any significance. These were found in 34.5 per cent. of 206 cases of non-specific urethritis before treatment, and four weeks after successful treatment the incidence had declined to 5.8 per cent. However, when relapse occurred and retreatment proved necessary, their incidence returned to 30.9 per cent. Moreover in a series of 80 male controls (normal persons, patients suffering from syphilis and non-venereal sores, etc.) they were found in the urethral scrapings of only 2.5 per cent. However, the positive findings were mainly in those patients whose urethrae were wet while the urethrae of the controls were dry. A further 108 cases of gonorrhoea treated with penicillin were next examined. In these the over-all incidence of blue “colonies” was 14.8 per cent., but two to seven days after the penicillin treatment of gonorrhoea their incidence was as high as 20 per cent., which compared with 27.8 per cent. in the patients with non-specific urethritis at the same time. This difference is scarcely significant. It was therefore concluded that the majority of the bodies seen in the Giemsa-stained scrapings had little to do with non-specific urethritis but rather with inflammatory changes in the urethra. Little benefit is likely to accrue, therefore, from their routine examination in the clinic.

Skin testing with various antigens of viruses of the group of Chlamydozoaceae have been largely free of cross reactions. Equivocal results have sometimes been reported with Lygranum (lymphogranuloma venereum) antigen. The occasional positive results obtained may be related to the incidence of lymphogranuloma venereum in the community. Psittacosis antigen has in my hands given entirely negative results, although a few positive results were obtained in a small series tested with cat-scratch antigen. Further work is required. On the other hand, in large numbers of my patients with non-specific urethritis, tested by complement fixation test to lymphogranuloma venereum and to enzootic abortion in ewes, entirely negative results were obtained, although there was very close agreement in the results of the two tests.

6. Idiopathic.

One must freely admit that in the general run of cases none of the causes mentioned apparently pertain. Although they must all be borne in mind and excluded as is feasible, the disease non-specific urethritis is clinically an entity with the following features:

It is a venereal disease with a variable incubation period, usually of 4-21 days, although in extreme cases it may be as long as six weeks. The discharge
R. R. Willcox

is thinner and more scanty than that of gonorrhœa and is usually muco-purulent. Sometimes it is watery and much of what was once described as "gleet" or "chronic gonorrhœa" was in fact non-specific urethritis. Occasionally the discharge is profuse and may resemble acute gonorrhœa; frequently it is watery and noted only first thing in the mornings or when the bladder has not been emptied for a long period.

A more or less hazy urine in the first glass is found in about one half of cases, but even in those with profuse discharge the haze is often less obvious than might be expected. There are usually fine threads in the first glass even when the urine is clear. Sometimes both glasses are hazy, indicating a posterior urethritis. There is frequently some mild dysuria which may precede the recognition of the discharge by the patient, while in gonorrhœa the reverse is usually the case.

In the subacute or Waelsch type of urethritis, superficial, wedge-shaped excrescences may be observed when the urethra is distended with air under the urethroscope. Later, greyish nodules from the size of a pin's head to a sago grain may give the urethra a cobble-stone appearance. "Urethroscopic stricture" may be noted. The urethroscopic appearance does not seem to be associated with a particular clinical type and there would seem to be no point in performing urethroscopy as a routine.

The disease may be associated with complications of cystitis, epididymitis, prostatitis and the blood-borne complications of arthritis, conjunctivitis and iritis.

In a study of non-specific urethritis made in British soldiers during the war the sexual habits of patients with non-specific urethritis and various skin complaints were compared. The patients in the urethritis group were more active sexually, as evidenced by their more promiscuous behaviour, their previous higher incidence of venereal disease, and in married men by the greater number of their children in a shorter period of married life. A greater degree of psychological imbalance was also noted in the urethritis group, but this may only have been due to the same factor which led to promiscuity.

The age incidence of non-specific urethritis is similar to that of gonorrhœa, the peak years of incidence being 21-35 years in each. In two civilian series compared at St. Mary's Hospital there was a higher proportion of married men in a non-specific urethritis group than in a gonorrhœa group. Generally speaking, too, there was a tendency for non-specific urethritis to be more common than gonorrhœa in "white collar workers" and gonorrhœa to be more common than non-specific urethritis in manual workers. This observation, however, was possibly only a reflection of marital status.

The somewhat higher incidence of non-gonococcal urethritis (which has sometimes been called "married man's clap") in married men prompts the suggestion that, although it is usually venereally acquired in the male, the female can perhaps become asymptotically infected outside of venery, possibly from the bowel.

Popularly, in the past, non-specific urethritis has often been blamed on
intercourse with a woman too near the period time. It is not possible, however, to reactivate the disease by the injection of blood into the urethra of a recently cured person. The explanation, however, is often a convenient one, as also is "strain" which, although unscientific, certainly reduces penetrating questioning by the patient and uncertain answers by the doctor.

Management of the Individual Case

Reducing a plethora of theory into practical procedure, it is usual to deal with a case of non-specific urethritis as follows:

(a) Ensure that the discharge complained of is of urethral and not sub-preputial origin.
(b) Ensure that there is actually a discharge. Take a smear and examine the water. The presence of fine threads even in a clear urine will indicate, in the apparent absence of discharge, that the patient's complaint is well-founded.
(c) Stain the smear with Gram's stain to exclude gonorrhoea. It is of interest to note whether other bacteria are present. The idiopathic urethritis is usually "abacterial" in type. The smear will show pus cells.
(d) It is useful to examine a specimen of the discharge under the dark-field to exclude trichomonads. The presence of spirochaetes can be noted at the same time.
(e) A blood test should be done to exclude syphilis and a gonococcal complement fixation test to exclude chronic gonorrhoea.
(f) Appropriate treatment may then be commenced.
(g) In cases which do not respond, or repeatedly relapse, other investigations such as the examination of a 24-hour specimen to exclude tuberculosis, cystoscopy, urography, etc., should be considered. Bilharzia should at all times be kept in mind in patients in or coming from areas where schistosomiasis is endemic.
(h) Treatment should be followed by tests of cure and observation to exclude the development of simultaneously acquired syphilis.
(i) Ideally the consort should always be examined to exclude gonorrhoea, trichomoniasis, thrush or other disease. As the causative organism of non-specific urethritis cannot yet be demonstrated, and many females resent being examined when the doctor cannot give strong reasons for so doing, it is sometimes politic to postpone this until the effects of treatment of the male are assessed. It should be insisted upon if relapse occurs after a return to the same sexual environment.

Treatment

Sulphonamides, penicillin and streptomycin give only indifferent or fair results, and those obtained with chloramphenicol are little better. Best results are obtained with tetracycline, oxytetracycline and chlortetracycline. The dose
should be a minimum of 250 mg. (one capsule) given four times a day for six days, although better results can be anticipated with two capsules given four times a day for five to six days.

Results of treatment of non-specific urethritis with different antibiotics without other measures have in my hands shown a 63 per cent. cumulative failure rate at three months with sulphonamides, 53 per cent. with both penicillin and streptomycin, 30 per cent. with chloramphenicol in doses of 5-6 g. over five to six days, and 19-25 per cent. with oxytetracycline and chlortetracycline both in the same dosage.

There seems to be some evidence that chlortetracycline and oxytetracycline give best results when they are the first drugs used. It may be cheaper in the long run to use the expensive preparation first with good prospects of cure, rather than try something else and run the risk of inferior results when the expensive drug is finally used.

Cases which fail to the antibiotics or sulphonamides, which may be tried in succession in failing cases, may respond to daily urethral irrigations of 1 : 8,000 potassium permanganate or 1 : 10,000 oxycyanide of mercury.

After treatment the surveillance should be as for gonorrhoea. Clinical and urine examinations should be made and the prostatic secretion examined for pus at increasing intervals of time. It is necessary also to exclude incubating syphilis and it is wise, therefore, to spread these tests over three months, at the end of which time a final blood test should be made to exclude syphilis. The possible dangers of masked syphilis obtain with all of the orally administered antibiotics.

MANAGEMENT IN SEAMEN

A urethral smear should be taken before treatment and this should be taken with him when the seaman first attends at hospital. This is the recommended practice on British ships, but it is not always observed.

In ships which carry a doctor it should be possible to have the smears examined for the gonococcus before treating. When no doctor is present the captain cannot be expected to differentiate one type of urethritis from another and the patient will therefore be treated as for gonorrhoea. This means on British ships that he will receive penicillin. The issue of penicillin consists of 300,000 units of procaine penicillin and 100,000 units of crystalline penicillin G, which is then made up in 2 ml. of distilled water. Half a dose is injected intramuscularly. It is recommended that if there is no response that sulphonamides should then be given.

In British ships the sulphonamide supplied is sulphadimidine and the initial dose is eight 0.5 g. tablets followed by four tablets morning, noon and night for four days, to a total of 52 tablets. A pint of water is given with each dose and two to three other pints are taken during the day.

At the intermediate port the smear taken at the onset should be examined. If the treatment has been successful, the first prostatic test may be performed. If time permits to obtain the results before the ship sails, serum tests for syphilis and a gonococcal complement fixation test should also be made.
If the patient still has a discharge following penicillin and sulphadimidine he should be given a course of oxytetracycline, or failing this chlortetracycline, without delay. If these drugs are not available, streptomycin should be given in single doses of 1.0 g. daily for four days.

Patients with blood-borne complications (Reiter's syndrome) are best admitted to hospital and will probably have to be left behind.

At the home port, patients showing resistance to treatment should be thoroughly examined to exclude urinary tuberculosis, bilharzia, trichomoniasis, etc., and should be hospitalized for the purpose if necessary. Those with Reiter's syndrome should likewise be admitted to hospital.

If the treatment has been successful another examination of the prostatic secretion and serum tests for syphilis should be performed. Their future surveillance, with the emphasis on the serum test for syphilis at three months, should be planned.

Cases not found to be showing underlying disease should receive oxytetracycline if they have not already done so, and if this fails they should be given urethral irrigations daily until cured.

**Prophylaxis of Non-specific Urethritis**

Short of abstinence, there is no sure prophylactic against non-specific urethritis. The use of a condom combined with prophylactic packet is probably reasonably efficient, although the ointment in the latter can on occasion give rise to a chemical urethritis. Penicillin taken orally or by injection will not prevent it, and it has been noted that the incidence of non-specific urethritis following the treatment of gonorrhoea is little different if the gonorrhoea is treated by penicillin, streptomycin or the tetracycline antibiotics.

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