The last 12 years have shown revolutionary advances in the treatment of both gonorrhoea and syphilis, and new diagnostic tools have been evolved to help in cases of suspected syphilis. As a result syphilis, at any rate, has been brought under control. No such advances, however, can be reported in the management of non-gonococcal urethritis in which condition—a disease of males—serious gaps in our knowledge remain unfilled.

Incidence

Figures of the numbers of new cases of non-gonococcal urethritis treated in the clinics of England and Wales have been published only since 1951 in which year there were 10,794 cases as compared with 11,841 male cases of gonorrhoea; in 1953 there were 13,157 cases of urethritis and 15,242 male cases of gonorrhoea (Ministry of Health, 1953). Much of what has from time to time been considered as penicillin-restraint gonorrhoea has proved to be non-gonococcal urethritis (Hughes and Carpenter, 1948; Parkhurst et al., 1947).

Aetiology

Although whole books have been written on the subject (e.g. Harkness, 1950) the aetiology of the bulk of cases of non-gonococcal urethritis remains as obscure as ever. There are many possible causes which, excluding physiological discharges as prostatorrhoea and spermatorrhoea, fall into four main groups.

1. Urethritis secondary to external and internal irritants.

In this group are considered traumatic urethritis following urethral instrumentation, introduction of foreign bodies, etc.; chemical urethritis due to injudicious urethral irrigations, insertion of prophylactic material, use of chemical contraceptives, self infliction, etc.; and those due to internal irritants (urethritis ab ingestis) resulting occasionally from crystalluria (phosphates, oxalates, sulphonamides, etc.) or from irritants excreted by the kidneys (cantharides, turpentine, potassium iodide, potassium nitrate, phenolphthalein). The majority of these can be excluded by questioning the patient.

2. Urethritis secondary to urethral sores and tumours

In this group are included urethritis due to primary syphilis, chancroid, lymphogranuloma venereum, condylomata acuminata, herpes simplex, balanitis xerotica obliterans, and urethral carcinoma. Most of these conditions are visible at the urinary meatus but if not can be seen at urethroscopy. The state of the inguinal glands is helpful in creating suspicion as they are frequently enlarged in intra-urethral chancre, chancroid, lymphogranuloma venereum and carcinoma, but not in uncomplicated non-gonococcal urethritis.

3. Urethritis secondary to other genital-urinary conditions

Other urethral causes are post-gonococcal urethritis, urethral stricture and urethral calculus. Of bladder causes, all forms of cystitis, e.g. enlarged prostate, diverticulum, stone, growths, tabes dorsalis, schistosomiasis, infection with B. coli, abacterial pyuria and genitourinary tuberculosis should all be considered—while of possible renal causes, stone, tumours, pyelitis and tuberculosis may be mentioned.

It is obviously impossible to undertake excluding examinations for all of these causes on all cases. In practice urethral stricture is an important cause and a bougie should be passed to exclude it in all cases in which there is a previous history of urethral discharge, although this may be delayed until after treatment has been given.

A possible bladder cause should be considered whenever the haziness of the urine appears to be excessive when related to the severity of the discharge. In the average case of 'idiopathic' non-gonococcal urethritis the urine is usually reasonably clear even when the discharge is comparatively profuse. An examination for schisto-
somiasis should be made in all countries in which it is endemic.

For the remainder X-ray examination by urography, examinations of and 24-hour specimens of urine to exclude tuberculosis, etc., may be reserved for chronic or frequently relapsing cases which treatment fails to clear.

4. Primary non-gonococcal urethritis

The possible causes of primary non-gonococcal urethritis are: (a) bacteria; (b) protozoa (trichomonads, amoebae); (c) metazoa (flies, fish, fluke and fungi); (d) spirochaetes; (e) pleuro-pneumonia-like organisms; (f) virus and (g) idiopathic.

(a) Bacteria. Some workers divide non-gonococcal urethritis into bacterial and abacterial urethritis according to whether or not bacteria are found in the stained smears of the discharges. A large variety of organisms have been incriminated in individual cases including: *staphylococcus albus*, diphtheroids, streptococci (especially *Strep. faecalis*), pneumococci, *H. influenzae, B. proteus, Staph. aureus*, neisseria other than the gonococcus (e.g. *N. sica, N. flava*, etc.), diphtheria and tubercle bacilli, pasteurella, sarcinae, *B. crassus, M. targasenes*, etc.

Bacterial urethritis may follow anal or buccal coitus and is said to have a short incubation period of four to eight days.

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 same pattern of urethral flora does not materially alter with treatment and similar findings are found in controls (Willcox, 1954). While not denying that a bacterial urethritis may occur it is believed to be a comparatively uncommon variety of non-gonococcal urethritis.

(b) Protozoa. Urethritis due to *E. histolytica* may occasionally complicate amoebic dysentery. The common protozoa found is *trichomonas vaginalis* which, with few extreme exceptions, is generally reported in 12 to 15 per cent. of cases of non-gonococcal urethritis (Durel et al., 1954).

It is obvious that attempts should have been made to link this common perplexing disease of non-gonococcal urethritis of males with the perhaps more common infestation of *T. vaginalis* in females. On the positive side *T. vaginalis* may sometimes be found under the prepuce of males suffering from balanitis. They have been reported in the prostatic secretion of the male consort of patients with trichomonatous vaginitis, and a urethritis can be induced in the male by the urethral inoculation of a culture of *T. vaginalis*, it being possible to recover the parasite from the transmitted discharge (Lanceley and McEntegart, 1953).

On the negative side is the fact that many of the consorts of males with non-gonococcal urethritis are apparently healthy, and it is not reasonable to consider as a main cause an organism which cannot be found in 85 to 90 per cent. of cases. May be it is there in a resting form but this is incapable of proof with existing methods.

When present in a urethral discharge trichomonads may persist even after the discharge has responded to antibiotics. In such cases the reaction of the urine should be changed by appropriate measures.

(c) Metazoa. Schistosomiasis has already been considered. The activities of certain larvae, leeches and beetles, not to mention the candyru fish which may enter the urethra of unfortunate bathers, are medical and geographical curiosities. Fungi may occasionally cause of a urethritis and vaginal thrush may be associated with a fungal urethritis in the male. This condition is more common in diabetics. Possibly fungi are responsible for more cases than at present thought (Auckland and Preston, 1954).

(d) Spirochaetes. Spirochaetes are found in the urine in the so called condition of abacterial pyuria. The possibility that such spirochaetes may enter the urethra as a result of buccal or anal coitus has been stressed (e.g. by Coutts, 1948). However, in cases of non-gonococcal urethritis seen in Great Britain spirochaetes are seldom encountered, and there is no higher incidence of the practice of buccal or anal coitus in patients with non-specific urethritis than in those with gonorrhoea.

(e) Pleuropneumonia-like organisms. Pleomorphic, intracytoplasmic inclusions in the form of rings, commas, or ovoids may be seen in urethral scrapings and may be cultured on suitable media. The fact that pleuropneumonia-like organisms have been found in patients with non-gonococcal urethritis, symptomatically in females, and less commonly in controls, resulted in their incrimination as a possible cause of non-gonococcal urethritis. Durel et al. (1954) found them in 7.4 per cent. of cases. More recently they have been recovered from a whole range of body sites and those found in the genitals seem to be related more to sexual activity than to non-gonococcal urethritis. Although it is possible they may act in symbiosis with some other agent (e.g. virus) it seems likely that they are but commensals (Nicol and Edward, 1953) albeit, being transmitted (amongst other methods) by genital contact.

(f) Virus. Inclusion-like bodies have been demonstrated in the cytoplasm of epithelial cells in Giemsa-stained urethral scrapings from patients with non-gonococcal urethritis. These are found
either as elementary bodies 2 to 3 microns in size, lying free, or in the cytoplasm of cells, or occasionally as a crescent surrounding the nucleus. Larger initial bodies are also seen.

Very similar bodies are seen in the virus diseases lymphogranuloma venereum, psittacosis, trachoma, enzootic abortion in ewes and inclusion conjunctivitis (see Harrison and Worms, 1939). The generic term *chlamydozoceae* has been applied to this group of viruses.

Positive proof that non-gonococcal urethritis is commonly due to a virus is lacking. Those who were at one time insistent in pressing the claims of a virus now admit that a true virus urethritis is comparatively rare. Durel et al. (1954) found *chamydozooson oculogenitale* in only 4.05 per cent. of cases.

It has been shown that the bodies seen, while present in cases of non-gonococcal urethritis before treatment, and not after treatment or in controls, may also be found in the damp urethrae of gonorrhoea patients within a few days of treatment with penicillin (Willcox et al., 1954). It is likely, therefore, that many are but products of inflammation. Certainly no one has succeeded in transmitting the virus successfully to mouse-brain, mouse-lung, guinea-pigs, or hens' eggs (Willcox et al., 1954a). Neither have skin or complement fixation tests shown any convincing cross reactions between non-gonococcal urethritis and other virus disorders in the group.

(g) Idiopathic. The bulk of cases of non-gonococcal urethritis seen in the clinic fall under this heading. The responsible 'virus' remains to be discovered. The disease has an incubation period of four to 21 days but may be as long as six weeks. The discharge is thinner and more scanty than gonorrhoea and is usually mucopurulent. Sometimes it is watery and, not infrequently, it is noted only first thing in the mornings or when the bladder has not been emptied for long periods.

A more or less slightly hazy urine in the first glass is found in most cases, but even when the discharge is profuse the haze is often less obvious than expected. Fine threads in the first glass are nearly a constant feature. There is also usually a mild dysuria.

In the subacute or Waelsch type of urethritis superficial wedge-shaped excrescences may be observed under air urethroscopy. Later greyish nodules varying from the size of a pin's head to a sago grain may give the urethra a cobblestone appearance. 'Urethrocopic stricture' may be noted when the urethra is distended with air. In many cases the urethra looks normal apart from some congestion. Urethrocopic abnormalities do not seem to be associated with a particular clinical type or to be related to the response to treatment. There would seem, therefore, to be no point in performing urethroscopy as a routine.

**Complications**

These include cystitis, epididymitis, and prostatitis. Some cases of urethritis are complicated by arthritis, conjunctivitis or iritis, keratosis blennorrhagica of the soles or penis, and occasionally elsewhere, and by balanitis sicca (Reiter's syndrome). Whether all cases of idiopathic non-gonococcal urethritis are potential sufferers from Reiter's syndrome, or whether this complaint is a separate entity, is not known. Patients suffering from Reiter's syndrome often require cortisone or fever therapy in addition to the treatment of the urethritis.

**Treatment**

No drug gives entirely satisfactory results. Even with the best treatments nearly one case in five will fail. Personal results in previously untreated cases are shown in the table.

It is thus noted that the tetracycline antibiotics offer the best prospects of cure with spiramycin.

### Previously Untreated Cases of Non-Gonococcal Urethritis Treated with Different Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>How given</th>
<th>Treated</th>
<th>Followed</th>
<th>Failures</th>
<th>Percentage failing of those followed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytetracycline</td>
<td>5-6 g.</td>
<td>Orally</td>
<td>85</td>
<td>82</td>
<td>13</td>
<td>15.9</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>6 g.</td>
<td>Orally</td>
<td>83</td>
<td>74</td>
<td>13</td>
<td>17.6</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>5-6 g.</td>
<td>Orally</td>
<td>115</td>
<td>108</td>
<td>20</td>
<td>18.5</td>
</tr>
<tr>
<td>Spiramycin</td>
<td>20 g.</td>
<td>Orally</td>
<td>28</td>
<td>20</td>
<td>4</td>
<td>20.0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>6 g.</td>
<td>Orally</td>
<td>101</td>
<td>85</td>
<td>23</td>
<td>27.1</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>2-4 g.</td>
<td>Inejected</td>
<td>62</td>
<td>58</td>
<td>22</td>
<td>37.9</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>20-28 g.</td>
<td>Orally</td>
<td>55</td>
<td>53</td>
<td>21</td>
<td>39.6</td>
</tr>
<tr>
<td>Penicillin</td>
<td>1.2-3.6 mega</td>
<td>Inejected</td>
<td>70</td>
<td>65</td>
<td>26</td>
<td>40.0</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>5-6 g.</td>
<td>Orally</td>
<td>39</td>
<td>37</td>
<td>15</td>
<td>40.5</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>Orally</td>
<td>29</td>
<td>22</td>
<td>15</td>
<td>68.2</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td></td>
<td></td>
<td>667</td>
<td>604</td>
<td>172</td>
<td>28.5</td>
</tr>
</tbody>
</table>
and erythromycin before streptomycin, sulphonamides, penicillin, chloramphenicol or a placebo. Doses of 6 g. (250 mg. q.d.s.) are required and best results are obtained when these drugs are the first ones given. It has to be remembered that all of the drugs listed, except sulphonamides and placebo (streptomycin least), are also active against syphilis and should not be used if the possibility of concomitant syphilis is higher than average.

Side-effects with the tetracycline antibiotics, apart from occasional allergic phenomena, include gastro-intestinal irritation, vitamin B deficiency, and those resulting from the bacterial vacuum created. Although staphylococcal enteritis (sometimes fatal) has been reported from many countries following the orally administered antibiotics (e.g., by Fowler, 1955), it has not so far been recorded in cases of non-gonococcal urethritis receiving this regime. Obstinate rectal soreness and pruritus, however, is not uncommon. Yoghourt may benefit this. Blood dyscrasias are not a complication of treatment with the tetracycline antibiotics, but may occur with chloramphenicol.

Follow-up
Treated cases of non-gonococcal urethritis should be followed up in the same way as gonorrhoea cases. Clinical examinations should take place at one week, two weeks and one month from treatment. Prostatic smears, and serum tests to exclude concomitant syphilis, may then be taken once a month for three months.

Contacts
It is desirable to examine the consort if possible, treating trichomoniiasis or other abnormality if necessary. For social reasons this precaution is sometimes omitted, but should be insisted upon in the case of recurrence. Many persons treat the female (even if clinically normal) with a course of one of the tetracycline antibiotics. It certainly seems logical to do so in relapsing cases.

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R. R. Willcox

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