

## NON-GONOCOCCAL URETHRITIS

By Wong Mook Ow, M.B.B.S. (M); V.D.O. (L'pool); F.R.F.P.S. (Glas.)  
(Middle Road Hospital, Singapore)

It is difficult to say when gonorrhoea and non-gonococcal urethritis first began to plague man. Dr. H. St. Vertue (1953) made a masterly review of classical literature and he found no mention of the disease from the times of Hippocrates to Galen. The first appearance of gonorrhoea was probably in the early mediaeval times. By the late 16th century it was commonly mentioned and was alluded to as "clap". Syphilis also made its appearance shortly after and the two were confused as one to be complication of the other and so through Hunter's day and until Benjamin Bell (1793) at last separated the two diseases. However, it remained for Ricord (1838) to make it widely known.

The recognition of various types of urethritis preceded the discovery of the gonococcus (Neisser 1879) by a long period (Schwediauer, 1784; Hernandez, 1812; Stevenson, 1823; Parker, 1839). The existence of non-specific urethritis has been known for over 70 years (Bockhart, 1886). Waelsch (1901) described a follicular non-specific urethritis which is subacute or chronic. Hecht (1927) gave a good account of acute NGU.

The introduction of penicillin in the treatment of syphilis and gonorrhoea in recent years brought the clinical problem of NGU to the fore.

In Singapore there is a rapid decline in the incidence of congenital and early syphilis no fall in cases of gonorrhoea. There is, however, a steady increase in NGU and in gonorrhoea with NGU.

| Year | G.C. | G.C. Opth. | G.C. Compl. | G.C. & N.G.U. | N.S.U. |
|------|------|------------|-------------|---------------|--------|
| 1950 | 3209 | 86         | 192         | ?             | 30     |
| 1951 | 2816 | 49         | 90          | 183           | 192    |
| 1952 | 2690 | 60         | 55          | 220           | 217    |
| 1953 | 2843 | 82         | 62          | 221           | 341    |
| 1958 | 2808 | 37         | 6           | 253           | 804    |
| 1959 | 3027 | 67         | 13          | 268           | 914    |

The ratio of NGU to G.C. is 1 to 3.

In Great Britain, the United States and other countries, syphilis appears to be under control while gonorrhoea showed a significant increase and

NGU is also definitely on the increase. In England and Wales the figures are:

| Year | Gonococcal Infection (New Cases) | Non-gonococcal Urethritis (New Cases) |
|------|----------------------------------|---------------------------------------|
| 1951 | 14,975                           | 10,794                                |
| 1952 | 15,510                           | 11,552                                |
| 1953 | 15,258                           | 13,157                                |
| 1958 | 27,887                           | 12,149                                |
| 1959 | 31,344                           | 12,752                                |

In a study of urethritis in the U.S. Army and Air Force and Korean evacuees between January 1st 1951 and June 30th 1953 (Gartman and Leibovitz, 1955), it was observed that out of 2,486 cases seen, 1,943 were NGU and 543 were gonorrhoea, a ratio of 3.6 to 1.

The increase in incidence of this disease has attracted the attention of venereologists in England, Europe as well as the United States. The International Union against the Venereal Diseases and Treponematoses held a Symposium on Non-gonococcal Urethritis at Monte Carlo, Monaco on September 1954. They recommended that every case of non-gonococcal urethritis to be termed as "Non-gonococcal Urethritis" and had asked the W.H.O. to take this terminology for consideration with a view to a possible revision of the international medical terminology. An expert committee had been established to make a more thorough study on the etiology of the disease.

### ETIOLOGY

The etiology of this disease is unknown. Many possible causes have been mentioned but the attention of research workers is directed mainly on two possible causes:—

1. Virus
2. Pleuropneumonia-like organisms (PPLO).

**Virus:** Microscopic examination of urethral discharge of some cases of NGU showed the presence of cytoplasmic inclusion bodies within the epithelial cells. Urethritis had been known to occur with certain viral infection such as measles (Kidd, 1917), herpes simplex (Nicolas, Gate, Papacoras, 1923), herpes zoster (Dubois, 1926), lymphogranuloma venereum (Hellerstorm, 1929), mumps (Spence, 1931), inclusion blemorrh-

hoea (Harrison and Worms, 1939) and dengue fever (Weyrauch and Gass, 1946).

Lindner (1909, 1911, 1913) demonstrated epithelial inclusions in the genital tracts of the mothers whose infants suffered from inclusion conjunctivitis. He produced inclusion conjunctivitis in monkeys by inoculating them with the vaginal secretions of these women. He believed that the infective agent to be identical with the trachoma virus.

Thygeson (1934) showed that the virus of inclusion conjunctivitis now called *Chlamydozoon Oculogenitale*, belonged to the psittacosis-ornithosis-lymphogranuloma group and was distinct from the trachoma virus. In animal experiment he was able to show that the virus was capable of surviving in water for several hours. He managed to produce "inclusion cervicitis" in baboons by inoculation but failed to provoke inclusion urethritis in either male or female baboons. The virus had not yet been cultivated and the only means of identification was by the stained inclusion bodies in epithelial scrapings. He found it to be a self limiting, minimal urethritis, usually without complications, its minimum duration being 5 months and maximum 11 months (Thygeson, 1954).

Willcox (1954) found inclusion bodies in 27.6% of 250 patients suffering from NGU. However, 21.7% of 108 patients with gonorrhoea were found to have similar inclusion bodies.

Siboulet in a recent statistical survey of 2,756 cases of NGU examined at the Urological Clinic of the Faculty of Medicine in Paris (Hopital Cochin) found inclusion bodies in 84 cases — an average of 3%. In patients suffering from the urethro-conjunctivo-synovial syndrome he found inclusion bodies in the scraping from the urethra and skin lesions, as previously reported by Harkness (1945).

Willcox, Howard and Findlay (1954) attempted passage of the virus through baboons in the conjunctiva and knee joint, guinea pig in the right groin, mice in the lungs and brain, and eggs using the 8 day old yolk sac and chorio-allantoic inoculations with no positive results.

**Pleuropneumonia-like Organisms (PPLO):** These organisms are often found in non-gonococcal discharges and also occasionally in association with gonorrhoea. They have been recovered in the anus of a homosexual who transmitted an abacterial urethritis containing these organisms to another (Harkness and Henderson-Begg, 1948). They occupy an intermediate position between the bacteria and the viruses. They are

filterable and can be cultivated on non-living media on which they form small colonies with a framework of fine filaments, in the meshes of which are clusters of vesicles varying in size from 2 to 10 microns in diameter. These vesicles have a lipoid envelope and contain tiny granules which may be stained with Giemsa stains. The small, bluish staining pleomorphic ovoid spheroid or rickettsia-like bodies, sometimes ring forms seen in the cytoplasm of the epithelial cells may be due to a virus or to "L" organisms.

These infectious agents were cultivated by Nocard and Roux in 1898 from contagious bovine pleuropneumonia. In 1937 Dienes and Edsall found these organisms in an otherwise "sterile" Bartholin abscess. At first the organisms were reported to occur only in the presence of some infection notably in NGU (Beveridge, Campbell, and Lind, 1946; Harkness and Henderson-Begg, 1948). Recent work showed that the PPLO occur in apparent normal male urethra and even more frequently in normal female urogenital tract (Salaman and others, 1946; Harkness, 1950; Randall, Stein, and Ayres, 1950; Melen and Linrose, 1952). The organism had been found more often in the infected than in the uninfected.

Nicol and Edwards (1953) isolated the PPLO in 26% of 140 patients with NGU. They found 11% of 90 men with no genital abnormality with similar organisms, 3 positive cultures coming from men who denied sexual intercourse. Cultures from the cervix and vagina of 154 women give positive results in 77% of cases with even higher percentage from those who suffered from G.C. and trichomonal vaginitis. The organisms were also isolated from the anal canal of men and women with or without signs of local infection. Study of the serological and biological characteristics of the organisms showed no difference in strains from healthy and infected patients. They concluded that there is no evidence that the organisms they found play a significant role in genital infections and they appear to be commensals.

Dienes and Berg (1954) found the PPLO to be the sole organism in some cases of cystitis and pyelitis. Klieneberger-Nobel (1954) describes animal experiments with originally non-pathogenic strains PPLO which became virulent if some other organisms were introduced. In 1952 Ruitter and Wentholt instilled PPLO into two volunteers intra-urethrally without any subsequent clinical or bacteriological evidence of infection.

Willcox (1954) reported therapeutic success with erythromycin in NGU and as the PPLO

is highly resistant to this antibiotic its aetiological significance is questioned (Lancet, 1954).

Csonka and Furness (1960) in a study of the aetiology of NGU found no support for a viral aetiology; neither could they attribute it to the PPLO as they found the organism only in three patients out of twenty they studied.

**Other causes:** Apart from these two main possible causes several others have been mentioned.

(a) *Trichomona vaginales*. This was first noted in the male urethral discharge by Kunstler in 1883. Since then the percentage of positive findings had varied greatly. With the introduction of cultural methods there have been higher results. Sorel (1954) observed 11.2% in 527 patients, one being acute and the rest chronic. He found the parasites in apparently healthy urethras of men whose wives suffered from trichomonal vaginitis. Lanceley and McEntegart (1953) inoculated cultures of trichomonads intra-urethrally into five male volunteers and all developed urethritis and recovered trichomona from only three of them.

Infestations with *trichomona vaginales* seems to give rise to a special clinical picture. Ocular or articular complications are not seen in such cases. On the present evidence it is not likely to be a major cause of NGU.

(b) *Haemophilus* and *Coccobacillus*. Recently these two organisms have been described as possible causes but received little support from research workers and clinicians alike.

(c) Fungi and protozoa other than *Trichomona vaginalis*. At the present moment they are not considered to be a cause of NGU.

(d) Allergy. There is no evidence to show that allergy can produce NGU.

## DIAGNOSIS

A diagnosis of NGU can only be made after exclusion of all known causes of urethritis.

A good history will help to exclude urethritis due to irritants e.g. chemicals, traumatic, metabolic and allergic phenomenon, and also those secondary to a cystitis or other systemic diseases.

A thorough physical examination will help to exclude urethritis due to intra-urethral sores and tumours foreign bodies and calculi.

The character of the discharge often helps in the diagnosis. In acute gonorrhoea the discharge at the onset is thin and watery and at the end of 24 hours it takes on the characteristic thick, creamy, greenish-yellow purulent appearance. Irrita-

tants often produce a thin watery discharge. Foreign bodies, frequent masturbation or excessive coitus may produce a thin discharge. Prostatorrhoea is characterised by a clear, slightly sticky, mucoid discharge occurring after defaecation or unsatisfied sexual stimulation. Intra-urethral sores and tumours produce a thin discharge. The trichomonatous urethral discharge is usually thick, homogenous, creamy or milky, occasionally watery. The discharge of NGU is muco-purulent, the greater amount of mucus, less homogenous discharge helps to distinguish from G.C. discharge; though it is not unknown to have acute NGU discharge indistinguishable from that of gonococcal discharge.

The International Union Against Venereal Diseases and Treponematoses in 1954 recommended routine examinations for subjects suffering from NGU:

- (1) The gonococcus should be eliminated by smear and/or culture.
- (2) Other bacteria should be sought for by cultural methods.
- (3) A search for *trichomonas vaginalis* first by simple direct examination, but if this is negative use staining after fixation, and cultural methods.
- (4) Serological examination should be carried out for the detection of syphilis, if present.
- (5) Routine urological investigations, such as massage of the prostate etc. should be carried out. A "sago grain" appearance will often be noted by urethroscopy with the presence of semi-transparent, often lozenge shaped excrescences especially of the roof and lateral walls of the urethra. Later the lesions flatten out and give a cobblestone appearance.

## TREATMENT

As the cause of the disease is still not known treatment is empirical. One of the characteristics of the disease is the tendency to relapse after apparent successful treatment. Many methods of treatment have been recommended and reports of results obtained with the newer antibiotics have been promising but for the high cost involved. Harkness (1953) claimed a cure rate of 86% with oral terramycin, 0.5g 6-hourly for 4 days (total 8g). Lyall (1953) claimed a cure rate of 85.4% with a single dose of Injection Streptomycin 1g together with 30g sulphathiazole in divided doses over 5 days. This form of treatment has the advantage of being relatively inexpensive and does not mask syphilis acquired at the same time.

Willcox (1956) studied the effect of antibiotics and produced the following results :

| Drug              | Dosage     | Cases   |          | Failures % |
|-------------------|------------|---------|----------|------------|
|                   |            | Treated | Followed |            |
| Oxytetracycline   | 5-6g       | 85      | 82       | 15.9       |
| Tetracycline      | 6g         | 149     | 127      | 16.5       |
| Chlortetracycline | 5-6g       | 115     | 108      | 18.6       |
| Spiramycin        | 10-20g     | 41      | 36       | 22.2       |
| Erythromycin      | 6g         | 101     | 85       | 27.1       |
| Streptomycin      | 2-4g       | 62      | 58       | 37.9       |
| Sulphonamides     | 20-28g     | 55      | 53       | 39.6       |
| Penicillin        | 1-3.5 mega | 70      | 65       | 40.0       |
| Chloramphenicol   | 5-6g       | 39      | 37       | 40.5       |
| Placebo           | —          | 29      | 22       | 27.3       |

Prebble (1957) using irrigation with oxycyanide of mercury in a strength of 1/8000 once daily from 3 to 7 days obtained a cure rate of 85%. Willcox (1959) using tri-acetyl-oleandomycin 250 mg 4x daily for 6 days to a total of 6g obtained a cure rate of 72.9%. Leach (1959) trying Sigmamycin obtained 71% success with 500 mg 6-hourly for 5 days. 52% control cases recovered in 8 weeks spontaneously without treatment. Gartman and Leibovitz observed that 58.5% of 106 cases of NGU subsided spontaneously in 8 weeks. They observed that the local treatment was not merely of no benefit, but probably detrimental. Inadequate antibiotic and sulphonamide therapy seemed to prolong the natural course of the disease. Willcox (1954) had presented confirmatory evidence of this observation.

In the State of Singapore NGU is treated with Injection Streptomycin 1g together with sulphatriad 20g spread over 5 days. When this fails a course of tetracycline, 250 mg 4x daily for 5 days are given. When no response is obtained a course of other broad-spectrum antibiotics is tried e.g. Spiramycin "Uropol", Sigmamycin. Irrigation daily for 3-7 days is instituted when antibiotics fail. A random sample of 222 cases of NGU was followed up in 1957 and the results were :

| Treatment   | Total | Cured | Failed | % Cured |
|---|-------|-------|--------|---------|
| Streptomycin and Sulpha   | 197   | 147   | 50     | 73.5    |
| Streptomycin and Sulpha (failed) then given Tetracycline.                   | 8     | 5     | 3      | 62.6    |
| Streptomycin and Sulpha (failed) then Irrigation.                           | 12    | 8     | 4      | 66.6    |
| Streptomycin and Sulpha (failed) Tetramycin (failed) then Irrigation given. | 5     | 3     | 2      | 60.0    |

From November 1960, Demethylchlortetracycline HC1 (Ledermycin) was given to patients suffering from NGU after they have failed to get relief from the usual therapy of Injection Streptomycin, sulphatriad, tetracycline and irrigations. The dosage given was 150 mg 6-hourly for 5 days. Of the 33 patients treated 27 were cured and 6 cases failed to respond, giving a "salvage" cure rate of 82.7%. Symptomatic relief was noted on the 2nd to 3rd day of therapy and the urine becomes clear or only shows mucus on the 5th day. No side effects were noted by the patients. A patient had nausea on taking 300 mg in the morning. The high cure rate after the usual therapy had failed showed that Ledermycin is a useful adjunct to the treatment of NGU.

Cases of infection have been observed between partners and sometimes there is a chain of infection spreading from individual to individual. Consequently the consort should also be examined and treated if necessary.

Where trichomona vaginalis are found treatment with Flagyl (Metronidazole) 200 mg three times daily for seven days orally has replaced the tedious old treatments that were mainly local and not entirely satisfactory. The results were dramatic, side effects few and eliminates local therapy.

#### COMPLICATIONS OF NGU

1. Local. This includes Littritis, periurethral abscess, prostatitis, vesiculitis, cystitis and epididymitis, all of which are similar to that caused by the gonococcus and are now rarely seen when prompt treatment has been given.

2. Reiter's syndrome or "Urethral-conjunctival-synovial (U.C.S.) syndrome". Whether this disease may be regarded as a complication of NGU or as a single entity has yet to be settled. Reiter's disease is characterised by a clinical syndrome consisting of a primary abacterial urethritis of venereal origin, bilateral conjunctivitis, polyarthrititis, frequently balanitis, and sometimes keratoderma blennorrhagica. This syndrome was first described by Brodie (1818). An identical syndrome associated with dysentery was described by Caelius Aurelianus in the 5th century A.D. The cause of the disease is still unknown, though a virus is most generally accepted and inclusion bodies have been found in conjunctival and urethral material. PPLO has also been incriminated. The natural history of the disease is characterised by self limiting attacks lasting one to twelve months, with a tendency to recurrence.

Permanent damage to the joint is not the rule and rheumatoid arthritis is not a sequel, but there are cases with residual deformities of the feet and occasional cases of ankylosing spondylitis. Ford (1953) found no satisfactory treatment for the condition and ACTH and Cortisone can only provide a temporary suppression of the clinical symptoms. Harkness (1953) obtained good results with terramycin in early cases and in established cases he had good results with terramycin together with fever therapy. King and his collaborators (1946) and Harkness (1945) have obtained good results with fever therapy. Fowler Knight (1956) reviewed the literature and assessed the effects of treatment in 70 cases. They concluded that no treatment at present in use has any influence on the course of the disease. Cameron (1956) reported that treatment with aureomycin appeared to be beneficial in keratoderma blennorrhagica.

### CONCLUSION

The aetiology of NGU is still unknown and no effective treatment has been found. Active research work being carried out by the members of the International Union against the Venereal Diseases and Treponematoses may in the future shed more light on this increasingly prevalent disease. To the individual it is a source of prolonged ill health and unhappiness. To society it involves considerable expense to keep it under control. In Singapore it is considered as a minor disease, and no epidemiological work is done on it as it is not recognised as a venereal disease. It is hoped that it will not become a major V.D. problem here as it has done in other parts of the world.

### ACKNOWLEDGEMENT

I am greatly indebted to Dr. L.M. Ram, for his encouragement, Dr. K. Y. Koh, the S.M.O., Social Hygiene and the Director of Medical Service, Singapore, for permission to publish this paper. I wish to thank Lederle Laboratories for the supply of Ledermycin.

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