NON-GONOCOCCAL URETHRITIS*

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Following the lecture given by Dr. A. H. Harkness and certain articles published in this *Journal* in September, 1953, we should like to report on our experience of non-gonococcal urethritis in the urological department of two Paris hospitals: Hôpital St. Lazare† and Hôpital Cochin‡.

(1) Incidence

Patients suffering from urethritis are becoming more and more numerous. The diagnostic categories in two series, each containing 1,000 patients with urethritis, examined recently at our two hospitals are set out in Table I.

TABLE I
DIAGNOSIS IN 2,000 PATIENTS WITH URETHRITIS

Diagnosis	St. Lazare	Cochin	Total
Gonorrhoea acute	553	252	805
Non-gonococcal urethritis (acute Hecht type)	3	4	7
Non-gonococcal urethritis (sub-acute Waelsch type)	22	76	98
Morning discharge frankly purulent but non-gonococcal	50	97	147
Minimal discharge and gonophobia	298	334	632
Urethritis with joint complications	16	78	94
Urethritis with ocular disturbances	4	22	26
Conjunctivo-urethro-synovitis (Reiter's syndrome)	2	18	20
Other types of non-specific urethritis	52	59	111
Total non-specific urethritis	447	748	1,195
Grand Total	1,000	1,000	2,000

For the past 3 years, and for technical reasons, the search for inclusion bodies has been carried out mainly at the Hôpital Cochin, whereas that for *Trichomonas vaginalis* or for pleuropneumonia-like organisms (PPLO) has been done at the Hôpital St. Lazare, patients being sent from one clinic to the other when necessary. This policy explains the

different incidence of diagnosis between the two hospital groups.

(2) Examination Technique

At present the method of examination is as follows:

After the presence of the gonococcus has been excluded by means of a smear or culture, tests are made in the following order on material from patients with a non-gonococcal urethritis or purulent discharge:

(i) A specimen of the discharge is collected with a platinum wire and examined for *Trichomonas vaginalis* (*T. vag.*). As the discharge in the male is usually minimal and the motility of any parasite found is almost nil, the diagnosis is rarely established by means of a direct smear (dark- or "light"-field) alone. We prefer staining by the May-Grünwald-Giemsa method, increasing the concentration of the Giemsa component to 1/10 and the duration of staining (Sorel, 1952, 1954).

(ii) Cultures for PPLO are made by introducing a cotton swab on a fine reed catheter into the urethra; this is immediately withdrawn and placed in a test-tube containing 0.5 ml. peptonized broth, and as soon as possible (in less than 2 hrs) the swab is removed and a culture made on a Dienes medium (Dienes, 1939). Two plates are inoculated, one with 100 units/ml. penicillin, the other without.

(iii) This swabbing out of the urethra has cleaned it. It is now possible to scrape off some urethral tissue and to search for inclusion bodies. The scraping is done with a nickel-tungsten wire with a spatula tip, and care is taken not to provoke bleeding. To prepare the slide the scraping is placed upon it and fixed in methyl alcohol (no acetone) and stained quickly with Giemsa (Kuhlmann) (concentration 1/20—for 15 mins). If all has been successful, no decolorization with acetone will be necessary; this is always preferable as decolorization blurs the staining.

(iv) If micturition has recently taken place, thereby making the search for *T. vag.* unprofitable, the patient is given two slides and instructed to take his own smears before urinating. In any case, he is advised to return for re-examination without having micturated beforehand; another smear is then taken for *T. vag.* and a culture for *T. vag.* is made on 4 ml. minced meat to which has been added 250 u/ml. penicillin pH 6.3/6.8. After 3 days' incubation at 37° C. a suspension is made, and a drop of

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this is then examined between slide and coverslip for motile *T. vag.* The diagnosis is thus established with greater accuracy than by direct smear*.

(3) Results

(a) *Trichomonas vaginalis* (Hôpital St. Lazare).—Positive cases may be grouped as in Table II.

TABLE II
POSITIVE CASES OF *TRICHOMONAS VAGINALIS*

Diagnosis	Number Positive	Number Examined
Urethritis (Hecht type) ..	2	3
Urethritis (Walsch type) ..	6	11
Purulent discharge ..	15	170
Minimal discharge ..	12	104
Total	35 (12.15 per cent.)	288

Association with the Gonococcus.—We did not look for *T. vag.* in acute cases of gonorrhoea, and we cannot say whether the two organisms are as frequently associated in males as in females. Amongst the 288 cases investigated, more than half had had gonorrhoea, but generally several months or years previously, and we cannot say whether gonorrhoea favours *T. vag.* infection of the urethra.

Clinical Characteristics.—In nine cases, the discharge was frothy, rather similar to that seen in the female; in the other cases, nothing special was noted.

Contacts.—When it was possible to examine the contacts, we frequently found them to be carriers of *T. vag.* (the contrary is luckily not always true).

Duration of Signs and Symptoms.—It is difficult to determine precisely the age of any urethritis; most of our patients had had several attacks of "non-gonococcal" urethritis, but they had not been examined for *T. vag.* each time. We believe the duration to be long, punctuated by remission and recurrences; our most spectacular case was that of a West Indian who had had for 18 years a marked urethritis of the Walsch type, with only a few remissions. His wife had a trichomonas vaginitis, and it is more than likely that the disease was maintained by the continuous passage of *T. vag.* from one to the other. This patient proved to be a good therapeutic case for his urethritis cleared up in 10 days. Occasionally, however, the disease appears to heal of its own accord.

* In the female subject, where it is easy to test for *T. vag.* infection, we have been able to draw up the following comparison of the various means of investigation:

In 110 women *T. vag.* was identified 34 times from a fresh smear, and 58 times by the staining method described above; in another series of 66 women, *T. vag.* was found 33 times by staining, and 41 times by culture on the medium used above. Therefore the culture method is superior to the staining method by 19.5 per cent., which is itself 41.3 per cent. more effective than the examination of a direct smear.

In three cases *T. vag.* parasites were found in smears which had been taken 2 to 3 months previously for other cytological studies. These patients were recalled for examination: they had undergone no treatment, but there was no urethral discharge; in two of them *T. vag.* was not found, though in the third it had persisted in the absence of any discharge.

Treatment.—We do not share the optimism shown by certain other writers.

Local treatment is applied first, Conessine hydrochloride jelly† 2.4 per cent. being introduced into the urethra after each micturition.

If a rapid result is not obtained, we either combine the above local treatment with *grands lavages* with a solution containing a mixture of potassium permanganate and mercury oxycyanide 0.25 per cent., or we alternate the Conessine jelly with aureomycin ointment 1 per cent. during the day. At the present time, we are studying the effect of various arsenical compounds. This line of treatment stops the discharge in approximately half the patients, but recurrences are frequent and the treatment has to be repeated.

Where the above therapy has failed, we give Acetarsol (1g. per day, four times a week for 4 weeks), either alone or alternating with aureomycin, which is useful because of its effect against associated pathological invaders. In six cases, a "cure" was obtained by fulgarization of the prostatic recesses, but we cannot be certain that these were the sites of resistance for the parasites.

(b) *Inclusion Gonorrhoea* (Hôpital Cochin).—The positive cases are classified in Table III.

TABLE III
POSITIVE CASES OF INCLUSION GONORRHOEA

Diagnosis	Number Positive	Number Examined
Urethritis (Walsch type) ..	7	63
Purulent discharge ..	2	274
Sterile pyuria ..	1	53
With associated articular disturbances ..	7	176
With associated ocular disturbances ..	4	92
So-called Reiter's syndrome ..	7	33
Total	28 (4.05 per cent.)	691

Clinical Features.—Positive cases occur especially in subacute non-gonococcal urethritis and in the so-called Reiter's syndrome. However, we have found inclusion bodies in the urethral tissue of three patients who were carriers of *Ectodermosis pluriorificialis* (Siboulet, 1953).

† Registered name "Roquessine", Paris. This is an alkaloid of *Holarhena Africana* and is used in amoebiasis.

Histological and Viral Characteristics.—We are disturbed by the fact that, even in proven cases, only one or two cells have inclusion bodies, whereas in other illnesses of the psittacosis group inclusion bodies are very numerous. Several of our slides have been stained by the Feulgen or Rice method, confirming their oxyribonucleic property, but this does not permit us to assume their viral origin.

Serology.—The Pasteur Institute has obtained a positive group complement-fixation test in two of our patients (one with Reiter's syndrome, the other with Waelsch type urethritis in whom we had failed to find inclusion bodies).

Treatment.—In our experience aureomycin and terramycin are satisfactory antibiotics, but relapses do occur in spite of their use. Although it is less effective, we have given dihydrostreptomycin instead because of the risk of complications.

(c) "L" Types (Hôpital St. Lazare).—In 4 years we have collected the cases set out in Table IV.

TABLE IV
POSITIVE CULTURES OF "L" ORGANISMS

Diagnosis	Number Positive	Number Examined
Urethritis (Waelsch type) ..	7	47
Purulent discharge, frank or minimal	78	584
Total	85 (7.4 per cent.)	631

Clinical Features.—In our experience no special clinical sign has been found consistently with a positive culture; and, in particular, Reiter's syndrome is not confined to these cases.

Pathological Significance of Positive Findings.—In some cases, after aureomycin, the disappearance of the discharge was accompanied by a change from positive to negative cultures, and the contacts of some cases yielded positive cultures. This may at first appear significant, but our findings in 357 apparently healthy individuals indicate the need for caution in the interpretation of results (Table V).

TABLE V
POSITIVE FINDINGS IN 357 HEALTHY INDIVIDUALS

Class of Subject	Number Positive	Number Examined
Males with no previous history and no urethral findings	5	28
Females with no urogenital signs or symptoms ..	7	31
Prostitutes	184	298
Total	196	357

It has still to be determined whether positive "L" cultures really indicate the presence of true *pleuropneumonia* (pathogens or saprophytes) in the "L" phase. The *fermentation of sugars* may provide a means of differentiation: true bovine *pleuropneumonia* ferments several sugars (the two bovine strains sent to us by Mornet over 2 years ago ferment glucose and maltose); *but none of the cultures obtained from our patients or from healthy individuals ferment any of the usual sugars*. We are thus obliged to use the somewhat vague term "pleuropneumonia-like organisms". This tallies in general with the conclusions of other writers; and in spite of worldwide efforts the full pathological significance of a positive "L" culture still escapes us. Perhaps, as so aptly suggested by Dienes, we are at the same stage in our research as when we were uncertain of the exact significance of *Treponema pallidum* because of our inability to distinguish it from saprophytic spirochaetes. Let us hope that it will soon be possible to differentiate between the various forms of "L" types, and, in the meantime, let us continue our efforts until definite conclusions are possible.

Inclusion Bodies.—We also believe that a more satisfactory technique should be developed for the correct interpretation of the presence of the inclusion bodies occasionally seen in the urethral tissue of the patients mentioned with a positive culture for PPLO.

Treatment.—A positive "L" culture is apparently an indication for the use of a wide-spectrum antibiotic, *i.e.*, aureomycin, terramycin, or tetracyclin. We usually begin with aureomycin 1 per cent. directly into the urethra. If this fails, parenteral antibiotics are given as for inclusion gonorrhoea. Relapses are not infrequent, and "L" cultures can either be positive or negative.

(d) **Urethritis of Unknown Aetiology.**—The figures previously recorded reveal our inability to determine the exact aetiology of all non-gonococcal urethritis. Ambrose (1953) often found small coccobacillary forms which may be of interest. However, we must treat these patients, who are often desperate because of a persistent urethral discharge, and we have adopted the following method:

(i) When there is a frank discharge, present only in the morning, we prescribe alternately after micturition: aureomycin ointment 1 per cent. and Conessine jelly 2.4 per cent., or, in exceptional cases, instillations of 0.5 per cent. AgNO₃ or "grands lavages".

(ii) When the discharge is present throughout the day the same treatment as above is advised together with dihydrostreptomycin, 1 g. per day for 4 days, followed by

acetarsol 1 g. orally and 0.5 g. terramycin or tetracyclin daily for 4 days.

(iii) When the above treatment fails, urethroscopy combined with fulgarization of the prostatic recesses is carried out.

(iv) In anxious and phobic patients, we resort to psychotherapy and the use of a new drug, chlorpromazine hydrochloride,* which has marked "neuroplegic" properties and is particularly useful in psychoneurosis. The initial dose is 50 m.g. increasing to 160 mg. daily, given in four divided doses.

(4) Conclusion

The social importance of gonorrhoea has greatly diminished since the advent of antibiotics. Unfortunately, this is not the case with non-gonococcal urethritis and its complications.

(a) *For the patient*, the presence of such urethritis is a great cause of concern: the discharge lasts a long time; the actual aetiology takes time to determine; and for the patients, apart from the anxiety, the illness means a loss of working hours and additional expense. After a while, they become obsessed with their illness, and we have had most interesting examples of this state of mind.

(b) *For the couple*, the danger of infection is minimal, less than for gonorrhoea. The female partner is generally asymptomatic (Reiter's syndrome is eighteen times more frequent in the male than in the female). Venereal disease is practically negligible.

(c) *For society*, non-gonococcal urethritis is a source of heavy expenditure. An acute attack of

gonorrhoea, with follow-up, necessitates only 1 g. streptomycin and four consultations. A non-gonococcal urethritis, on the other hand, demands several prescriptions for antibiotics, local treatment, and about ten laboratory tests and consultations, without taking relapses into account. In extreme cases, Reiter's syndrome entails long drawn out investigation and a long and expensive course of treatment.

The International Union against Venereal Disease is thus fully justified in showing its concern for the social problem posed by these cases of non-gonococcal urethritis.

Summary

A 4 years' study of over 1,600 cases of non-gonococcal urethritis showed the presence of *Trichomonas vaginalis* in 12-15 per cent., so-called *Chlamydozoon oculo-genitale* in 4.05 per cent., and "L" forms (much discussed) in 7.4 per cent. of the cases investigated.

Certain methods of treatment have been tried with varying success. The social importance of non-gonococcal urethritis, both for the individual and for the public in general, is emphasized; it is far greater than that of gonococcal urethritis which is so sensitive to antibiotics.

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* Trade name, "Largactil", May & Baker.