

MEDICAL INTELLIGENCE



CURRENT CONCEPTS

Nonspecific Urethritis

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URETHRITIS is an inflammation of the urethra that can be classified as gonococcal or nongonococcal. Although a small proportion of nongonococcal urethritis is associated with trichomoniasis or candidiasis, in approximately 90 per cent of cases a pathogen is not identified by routine screening and culture methods. It is this group that we refer to as nonspecific urethritis.

Nonspecific urethritis is exceedingly common. In England, it is the most frequently recorded sexually transmitted disease. In the United States, since it is not a reportable disease, few incidence data are available. In the two venereal-disease clinics with which the Center for Disease Control is associated, nonspecific urethritis represents 30 per cent of urethritis among black men and up to 70 per cent among white men.¹ (J. Armstrong, personal communication); in Seattle, 60 per cent of urethritis in men is considered nonspecific. Among women, incidence of so-called nonspecific genital infection is even more elusive, since it is uncertain whether they have a syndrome distinctive enough to be clinically recognizable.

ETIOLOGY

The cause of nonspecific urethritis is unknown. At present, major research emphasis deals with definition of the etiologic agent or agents of the disease. The two agents under major consideration are chlamydia and mycoplasma. Though markedly different organisms, they have been subject to much taxonomic uncertainty, and both require special culture technics for isolation.

Chlamydia—obligate intracellular bacteria that are cultured like viruses—are known to be responsible for trachoma, inclusion conjunctivitis, and lymphogranuloma venereum. Recently, improved culture methods have isolated chlamydia in over 40 per cent of men with nonspecific urethritis.² Approximately 30 per cent of women seen in a venereal-disease clinic harbored chlamydia.³ Moreover, colonization with this agent was observed in 66 per cent of women who were regular sexual partners of men with chlamydia-associated urethritis. From comparison groups of men and women, isolation rates of less than

5 per cent are obtained, suggesting that chlamydia are not commensals.

Mycoplasmas (also referred to as pleuropneumonia-like organisms) are a separate class of organism with morphologic and metabolic resemblance to both bacteria and bacterial L-forms. *Mycoplasma hominis* and “T-strains” (T for tiny colonies) were the two strains initially isolated in cases of nonspecific urethritis. Although the former has been deemed an unlikely etiologic candidate, the role of T-mycoplasmas remains unresolved. There are reports of a 71 per cent T-strain isolation rate among male patients with nonspecific urethritis as compared to one of 9.1 per cent among controls, and an equal number of studies with no difference between controls and patients.⁴ Similarly, reports of female infection rates have ranged between 8 and 83 per cent.

Curiously absent from the studies on pathogens of nonspecific urethritis have been well controlled investigations of patients in which screening and culture for multiple organisms are done simultaneously. A major reason for this lack has been the rather specialized nature of isolation methods for the agents currently implicated. Recently, however, Handsfield et al. presented aspects of just such a study,⁵ showing chlamydia to be the most highly associated agent. This report and others in which multiple agents are sought simultaneously may afford an important step toward definition of the causal agents of the disease.

DIAGNOSIS AND TREATMENT

The possibility of nonspecific urethritis should be considered in every man whose presenting complaint is dysuria, urethral discharge or urinary frequency. Urinary frequency is rarely the only symptom. Although nonspecific urethritis in men usually begins insidiously with a scanty, watery discharge, some patients have no discharge at the time of examination. In others, a copious purulent discharge indistinguishable from that found in gonococcal urethritis is present. In female sexual partners of these men, a history of acute or recurrent cystitis may be obtained.

Given this dearth of clinical history and the limitations of accurate diagnosis on clinical grounds alone, the key to diagnosis is exclusion by laboratory means. In men, a Gram stain of urethral exudate is imperative primarily to detect the presence of *Neisseria gonorrhoeae*, although candida may be observed when diligently sought. The physician should carefully inquire about the possibility of inadvertent or surreptitious use of antibiotics, which could cause a negative smear to be obtained in a patient who initially had gonococcal urethritis. In this circumstance and all others when the smear is free of the gram-negative intracellular diplococci pathognomonic for gonococcal urethritis, a culture of the exudate on medium selective for the gonococcus should be performed. When no exudate is present, a specimen obtained with a small calcium alginate swab of the anterior urethra should be cultured. In approximately 2 per cent of cases, the gram-stained smear of urethral exudate in men will be negative in the face of a positive culture of the same specimen. In this case,

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of course, appropriate therapy for gonococcal urethritis should be instituted. On the other hand, a Gram stain showing the presence of polymorphonuclear leukocytes without intracellular diplococci is highly suggestive of nonspecific urethritis and is presumptive evidence for the diagnosis.

Tetracycline is clearly the treatment of choice. Virtually all the antimicrobials have had clinical trials,⁶ although the major drawback in nearly all trials has been the inability to distinguish between relapse and reinfection. The sole study adequately controlling for re-exposure is that by Holmes et al., conducted aboard an aircraft carrier at sea.⁷ A crossover trial of 2 g of tetracycline daily in divided doses, for four and seven days respectively, convincingly demonstrated the increased efficacy of both regimens over placebo, and of the seven-day schedule over the four-day schedule. On the basis of this and similar studies, the recommended treatment for nonspecific urethritis is 1500 mg of oral tetracycline initially, followed by 500 mg every six hours for seven days. An initial cure rate of at least 80 per cent can be expected. For a first relapse, a repeat course of tetracycline is advisable; in some cases, treatment for 14 to 21 days may prove more successful.

Failure to respond to treatment necessitates more thorough examination. A freshly obtained urethral specimen mixed with a drop of saline should be carefully examined microscopically for trichomonads. At the same time, a separate portion of the exudate mixed with a warmed drop of 10 per cent potassium hydroxide solution should be examined for the spores and mycelia of candida. If the preceding tests are unrevealing, urinalysis and urine culture are advisable to rule out urinary-tract infection. Urologic referral should be considered in very resistant cases to rule out structural abnormalities. In all cases of treatment failure or recurrence, sexual partners should be similarly examined, since they provide the key to diagnosis, and their simultaneous treatment may prevent recurrent infection in both partners. Inquiry should be made into the possibility of traumatic urethritis secondary to excessive concern about a discharge and continued "milking" efforts, which may induce a syndrome mimicking pathogen-related nonspecific urethritis.

Along with thorough examination, careful interviews to elicit a past history of gonorrhea and previous administration of antimicrobial therapy suboptimal for gonococcal urethritis should be repeated. A past history of gonorrhea is important because what initially appears to be nonspecific urethritis may be a treatment failure of gonococcal urethritis or may represent postgonococcal urethritis. Although the two types of urethritis have been considered similar or identical disorders, data on the matter are few. There is some evidence that postgonococcal urethritis may reflect simultaneous infection with gonococci and the nonspecific-urethritis agent in which the latter has been inadequately treated. Richmond et al.⁸ reported a 32 per cent isolation rate of chlamydia among a group of men with gonococcal urethritis. Follow-up studies showed this group appreciably more prone to development of postgonococcal urethritis than those with gonorrhea who were chlamydia free. Similarly, patients with gonorrhea

treated with antimicrobials effective against agents associated with nonspecific urethritis have consistently had less postgonococcal urethritis after treatment. Here again, as etiologic agents are better delineated, understanding of postgonococcal urethritis will be much enhanced. At present, this disorder should be treated in a fashion identical to that used for nonspecific urethritis. The procedures to be performed at the first episode and recurrence are summarized in Table 1.

Table 1. Diagnostic Procedures for Nonspecific Urethritis.

ORGANISM	SCREENING PROCEDURE	CULTURE METHOD	
		MATERIAL	MEDIUM
Gonococcus	Gram stain	Urethral exudate	Thayer—Martin
Trichomonas	Wet mount; saline.	Urethral exudate	Feinberg—Whittington or Bushby Sabouraud's
Candida	Gram stain; potassium hydroxide preparation.	Urethral exudate or urine	
Urinary-tract bacteria	Triple strength methylene blue stain; Gram stain; urinalysis.	Midstream urine	Phenol ethyl alcohol/MacConkey

COMPLICATIONS

It is thought that most cases of untreated nonspecific urethritis will clear spontaneously after six to eight weeks. Relapse, however, is believed to be exceedingly common, perhaps in as high as 70 per cent of cases, although the lack of clear distinction between relapse and reinfection makes such estimates highly imprecise. Prostatitis may accompany nonspecific urethritis in 20 per cent of cases; usually asymptomatic and painless, it occasionally becomes chronic. Epididymitis associated with the disease is most frequently unilateral, occurring in under 3 per cent of patients. Estimates of urethral strictures related to nonspecific urethritis range from 0.5 per cent to 5 per cent. The reliability of such figures is suspect because of poor controls for a past history of gonorrhea or other factors related to stricture formation. Similarly, it is virtually impossible in retrospective studies to determine whether nonspecific urethritis predisposed to stricture or vice versa. As noted earlier, in cases that resist all diagnostic and treatment efforts, urethroscopy is advisable in search for stricture. Reiter's syndrome, now considered a clinical tetrad of nonspecific urethritis, polyarticular nonsuppurative arthritis, mucocutaneous lesions (palatal patches and keratoderma blenorrhagica) and conjunctivitis, is said to occur in association with approximately 2 per cent of nonspecific urethritis cases. Since it is unknown whether the urethritis of Reiter's syndrome is of the same origin as that seen in patients with uncomplicated nonspecific urethritis, these estimates may be quite inaccurate. Data suggest that Reiter's syndrome cannot be considered simply a complication of nonspecific urethritis, but that genetic and immunologic factors will have to be examined to define the inter-relation of these two syndromes.

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BY THE LONDON POST

Science and the Challenge of the Time — Nurses,
the National Health Service and Inflation —
Kidney-Transplant Dilemma

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WHEN the British Association for the Advancement of Science held its annual meeting at Stirling University in September, Sir John Kendrew delivered his presidential address on "Science and the Challenge of the Time." As a molecular biologist and deputy chairman of the Medical Research Council's Laboratory of Molecular Biology, Sir John voiced his concern about the potential hazards of genetic engineering and supported the proposals made by the United States National Academy of Sciences for a moratorium on certain kinds of experiments in molecular genetics.

He referred, in particular, to the dangers of gene transfer resulting from the isolation of segments of DNA of one organism and their subsequent incorporation in the DNA molecules of another, the second organism then displaying some of the characteristics of the first. Apart from the possibility of creating dangerously virulent or oncogenic organisms, Sir John speculated on the chances of separating from the chromosomes of animal cells the genes responsible for synthesizing hormones. In theory, medically important substances could be synthesized, or missing genes could be supplied to people suffering from genetic deficiency diseases; on the other hand, undesirable consequences could easily result from uncontrolled experiment.

Sir John thought that in certain respects the situation is analogous to that in nuclear physics at the beginning of World War II, when it became common knowledge in many countries that the discovery of nuclear fission might make it possible to develop a new source of power and also to construct an atomic bomb. He believed, however, that

the possible consequences of developments in nuclear physics were easier to predict in 1939 than the possible consequences of gene transfer in 1974. Furthermore, this research in nuclear physics was carried out within a military framework, whereas the research in genetic engineering can be carried out by competent scientists in any laboratory, and apart from its medical implications, such research might have commercial and even military applications.

Although the British government has set up a Committee under the Chairmanship of Lord Ashby, FRS,¹ to inquire into the extent of current research in genetic experimentation in Britain, Sir John does not consider this precaution enough. In his address he called for a permanent international monitoring body of molecular biologists that would make a continuing assessment of the possible dangers and benefits of genetic engineering and would make authoritative recommendations on the type of experiments that should be carried out and under what conditions of security. He also thought that there should be a fact-finding program of research on gene transfers, carried out in special laboratories under high security. The results of such a program should then be published in full in open scientific literature, so that others would not be tempted to conduct such experiments under less scientifically open and less physically secure conditions.

In more general terms, Sir John spoke of the declining public and governmental support for science. Fewer students want to read natural science, and some young people have become hostile to science as the handmaiden of economic growth in which they no longer believe, as the creator of environmental pollution, as a support for the military and as the creator of other dangers. These circumstances had undermined the self-confidence of science and scientists, but Sir John did not think that if the contribution of science to human advance were fairly assessed, there would be any justification for pessimism or feelings of guilt. He emphasized one of the great challenges ahead as a reduction in the gap between the advanced nations and the poor, and this issue presented problems for which there are no obvious solutions. There was then a danger that, unless there was some form of satisfactory population control, it might be the old scourges of war, disease and starvation that would limit world population to what the earth could support. Sir John was hopeful, however, that science and scientists would respond to these challenges for the benefit of mankind.

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As anticipated, the Halsbury Committee of Inquiry into nurses' pay and conditions of work has now recommended a large increase in the salaries of all nurses working in the National Health Service, and, in accordance with the promise made by Mrs. Barbara Castle, Secretary of State at the Department of Health and Social Security, this rise will be effective from the day last May when she set up the committee at a time of great unrest in the nursing profession.

There has been general approval for the recommendations that nurses primarily engaged in clinical duties