

Meeting October 28 1965

President's Address

'Cystitis' in the Female

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'Cystitis' is without doubt a problem whether one considers it from the point of view of numbers of patients or of pathology or of treatment – or even of an accurate definition of what we are talking about. It is a kind of Cinderella of urology, neglected because of its big ugly sisters – pyelonephritis and renal failure – and it is one of those subjects, not infrequent in medicine, which overlap two or more specialties. Females now make up one-quarter of our adult urological patients and nearly a half of the children; probably the majority of them have had or are having attacks of 'cystitis'. Twenty years ago a urological clinic saw predominantly males – our out-patient clinic was once described by a nurse as 'male gynaecology'. This change of proportions is chiefly due to the larger numbers of females who are referred by their general practitioners for investigation of attacks of urinary infection with or without hæmaturia. It is important at once to realize, therefore, that the patients we see in hospital are a selected group. If 'cystitis' is fairly common in a hospital clinic, it is also common in general practice. According to the Morbidity Statistics from General Practice for 1962 (Cookson 1962) the average general practitioner sees 33 new cases of urinary tract infection per annum, of which 27 are females: this compares with about 3 new cases of prostatic hypertrophy per year. Loudon & Greenhalgh (1962) found that the incidence of urinary infections in their practice was 14.6/1,000 patients per year compared with 6.4/1,000 for prolapse, for example. Again, these must be self-selected to a certain extent because some women put up with minor attacks of 'cystitis'; a small but nevertheless surprising number consider it a minor malady associated with the reproductive side of life which has to be accepted as one of the inevitable nuisances.

Definition

If one attempts to define 'cystitis' it is immediately obvious that it means different things to different doctors. To the general practitioner it means a more or less severe infective condition of the lower urinary tract, much commoner in adults than in

children and in women than in men, which responds quickly to treatment without residual disability in the majority of cases.

To the pædiatrician it is also a common infective condition, not so obviously limited to the lower urinary tract, which is often difficult to treat effectively and has sinister undertones of congenital abnormality and possible late renal sequelæ such as chronic pyelonephritis and early renal failure.

To the gynaecologist and obstetrician it is a fairly common nuisance which is easily treatable and seldom worthy of investigation unless all possible gynaecological abnormalities have first been dealt with.

To the urologist, who seldom sees it in the acute phase, it has an element of dullness for so often it is but a history, with no physical signs on ordinary clinical examination, which must be investigated from A to Z. The interest comes later when he knows the results of radiology and does endoscopy.

Why does the general practitioner not take it very seriously and why does the pædiatrician read sinister things into it? Why does the urologist perhaps not take it seriously enough? Let us examine the natural history of 'cystitis' as far as it is possible to do so.

Natural History

In infants the condition is seldom recognized, probably is not often recognizable. A urinary infection is, more often than not, a serious generalized illness. It is interesting, in passing, that baby girls with a napkin rash do not have 'cystitis'.

Between 2 and 5 years it is unusual; the practitioner and the pædiatrician are busy sorting out the problems of late toilet-training at this age and find urinary infections because this is one of the things they must exclude. It is remarkable how difficult it is, in girls under 5, to distinguish a lower urinary tract infection from one involving also the upper tract and possibly extending further afield to a coliform bacteraemia or septicæmia with high pyrexia, rigors, enteritis and even meningitis. It is well recognized that

'cystitis' produces pyrexia in children but does not do so often in adults. The explanation of this may be that organisms readily gain access from the child's urethra to the blood stream; other organs including the kidneys are infected from the blood stream so that what is originally a local infection becomes a generalized illness.

During school-age, between 5 and 15 years, attacks of true cystitis are uncommon; urinary tract abnormalities usually present as disturbances of micturition – frequency, urgency or enuresis – or as a febrile illness with pyelonephritis: for example, in Persky's (1965) series of 150 children admitted for investigation of urinary infections only 34 (23%) had symptoms suggestive of lower tract involvement. There is, however, a peak in 5–6-year-old girls. It is impossible not to connect this with the start of school and the formation of a common bacterial pool of skin and genital organisms, similar to that which we know occurs in the upper respiratory tract.

In the reproductive age, attacks of 'cystitis' are certainly commoner than at other times and a pattern can be recognized. The age starts with so-called 'honeymoon cystitis', which must be extraordinarily common. This is emphatically a lower urinary tract infection and in the great majority of cases is an acute inflammatory condition of the urethra. It is notable that there is no associated vaginitis or cervicitis. The organism is a coliform bacillus and it is tempting to explain the condition as the proliferation of pre-existing organisms in bruised urethral epithelium. It responds readily to sulphonamide, frequently without further attacks. A small proportion of cases continue to have recurrent attacks and the occasional unlucky patient goes on to a renal infection with secondary calculi and pyelonephritis. Is honeymoon cystitis the forerunner of chronic pyelonephritis? Many have attempted to connect the two conditions, for at first sight it must seem reasonable, but there is, as yet, no proof of relationship. Recurrent cystitis seems always to lead to what once used to be called the 'surgical kidney', i.e. an acute bacterial infection of the renal parenchyma, not chronic pyelonephritis.

During pregnancy, cystitis becomes less usual: we must be careful to exclude the normal frequency common in the first and last trimesters. Perhaps here we see the truth inherent in the old wives' advice to all brides who are plagued by cystitis to hurry up and have a baby.

There is little relationship between attacks of cystitis and pyelitis of pregnancy. The relationship that Kass (1960) demonstrated was bacteriuria in early pregnancy with pyelitis later and it is presumed that the bacteriuria comes from the kidneys, not the urethra. Little (1965) has shown, in fact, that these women with bacteriuria do not

have symptoms connected with micturition, nor do they have a past history of lower urinary tract infections.

In the 30–50 group the picture is one of recurrent attacks of cystitis, not so acute as the earlier ones and often of shorter duration.

Certain precipitating factors are recognizable:

Sexual intercourse is the first and most definite: the various different contraceptive methods are not significant and the menstrual cycle is not directly related.

Alcohol is often specifically related to 'cystitis' by some women. We do not know whether the vascular congestion produced by the alcohol encourages bacterial growth or the reverse; if the vascular congestion encourages it, why is cystitis rare during menstruation? Also, the cystitis associated with alcohol comes on almost immediately – this does not sound like bacterial proliferation.

Gynaecological factors bring us to one of the most controversial aspects of this subject. The more acute conditions such as trichomonas infection and, of course, gonococcal infection, include a urethritis – and both can sometimes become chronic and recurrent so that it is necessary to treat the cervicitis before the 'cystitis' can improve. But in the great majority of cases, urologists do not lay the blame for recurrent cystitis upon the reproductive organs; they believe that they can find sufficient intrinsic urinary tract pathology to explain the attacks, but this may be due to selection of their patients for them by the general practitioner who sends the others direct to the gynaecologist. The exact part played by monilia infections, both vaginal and urethral, is hard to assess: it is said to be more common in tropical countries than in Britain. Prolapse produces a mechanical distortion of the urethra with well-defined symptoms, the chief of which is stress incontinence – it does not characteristically produce attacks of cystitis. If prolapse happens to be associated with attacks of cystitis, the surgical treatment of the prolapse does not stop the attacks of cystitis.

Allergy: It is well to be suspicious of a diagnosis of allergy; it is easy to make and very difficult to prove. Nevertheless, I can, I think, demonstrate that allergic manifestations can affect the female urethra.

A woman of 34, who had just won an equestrian competition on the Continent, had supper at a sea-food restaurant before catching the night plane to London. In London she found she could not pass urine. She drove home in this state and was eventually

referred to hospital in the early morning. Her bladder was very distended and she was in considerable pain, not only in the bladder region but also in the anus. There was no previous history of micturition abnormality. Cysto-urethroscopy showed that the urethra and bladder neck epithelium were bright red and oedematous, as also was the anal canal. The urine was sterile. She recovered in about three days with antihistamines and a spell with an indwelling catheter and has not had trouble since.

All this shows is that the urethra can be affected, like the anus, by an acute allergic reaction: this appears in keeping with allergic reactions elsewhere. What is much more difficult to substantiate is that any form of allergic response is the basis of the minor transient attacks of 'cystitis' of which so many women complain, in which the urine is never found to be infected, which they describe as 'here today and gone tomorrow' and about which others say, for example, 'It only occurs in the evenings and is gone the next day'.

Pathology

There seems little doubt that 'cystitis' is an inflammatory condition of the urethral epithelial lining associated with the multiplication of one or more strains of bacteria. These organisms can be introduced from without but predominantly are normal inhabitants of the urethra – the same organisms which can be found in and around the anus and on the skin of the perineum and the same organisms which can be found in the normal urethra. They spread, presumably by continuity, to the epithelium of the bladder neck and bladder base but do not extend much beyond this, judging by visual evidence from the cysto-urethroscope in the occasional case examined in the acute stage. The organisms can be recovered from a swab taken from the urethral epithelium and also from the urine, whether this urine is obtained by catching it as it comes from the urethra or by a catheter from the bladder or by puncture of the bladder with a needle. Is the condition an infection of the urine primarily or is it secondarily evident in the urine and primarily an infection of the urethral epithelium? The latter would seem to be the case because, first, the urethra and bladder neck can be seen to be more severely affected than the vault of the bladder and, secondly, not all patients in the acute phase complain of great frequency of micturition (some can, for example, sleep for several hours) but rather of scalding micturition and pain resulting from urethral distension and contraction.

The urine specimen contains many red cells and, as time goes on, increasing numbers of white blood corpuscles and desquamated transitional epithelial cells. Protein, derived from the inflam-

matory exudate, can be found in moderation. Bacteria are to be seen in quantity in the later specimens but may be comparatively sparse earlier. If the condition is a urethritis then surely the urine passed at the beginning of micturition should contain larger quantities of cells and organisms than that passed at the end of micturition. This is found to be so and was described by Moore *et al.* (1965).

Assuming, therefore, that this description of the pathology of the acute attack is correct, can we find any explanation of what determines the outcome – whether the attack clears up completely or recurs after a while in the form of repeated attacks or remains as a chronic infection, with possible spread higher in the urinary tract? There is no doubt that some of these patients have a urinary tract which is what we call normal by all the usual urological investigations – intravenous urography, micturating cysto-urethrogram and cysto-urethroscopy – and this makes it certain, therefore, that cystitis can occur and recur in a normal bladder and urethra in both girls and adult women. However, it is much commoner for recurrent cases to show on investigation certain definable changes which are found in the urethra and not in the bladder. By far the commonest finding is narrowing of the urethra which occurs in two distinct forms or as a combination of the two. The female urethra is normally easily distensible; in this it corresponds to the male posterior urethra with which it is morphologically closely related.

This distensibility can be illustrated by an old French method of treating a calculus impacted at the lower end of a ureter in the female by dilating the urethra sufficiently to allow the insertion of the operator's index finger into the bladder. The stone was then milked downwards into the bladder with the aid of the index finger of the other hand in the vagina. This means that the urethra must have been made large enough to admit at least size 30 French.

Therefore narrowing of the urethra can be said to exist if it will not admit an instrument somewhat smaller than this, say 26 French. Surprisingly often, in recurrent cases, the urethra will not even take the cystoscope which is about 22 French – considerably smaller, approximately the size of an ordinary pencil.

The narrow portions are always near the external meatus or at the bladder neck at the upper end or a combination of the two.

At or near the external meatus: This is a true stricture, which occurs in the distal urethra at or just distal to the place where the transitional epithelial lining is changing to squamous and is the result of fibrosis in the submucosal and

muscular layers. It often involves the whole of the distal two-thirds of the urethra which can be felt, when examined with a finger against a rigid intra-urethral instrument, to be thicker and more indurated than normal. It is noteworthy that not all these patients have the trabeculated, thick-walled bladder usually associated with obstruction.

At the internal meatus: 'Bladder neck obstruction' undoubtedly occurs in the female as well as in the male; in the adult male it has long been recognized as Marion's disease: it is now accepted as a condition which can produce obstructive phenomena at any age. It takes the form of hypertrophy of the internal urethral sphincter associated with a thickening of the inner detrusor coat of the bladder; to the urologist it is an easily recognizable condition which can be seen at any age and with any degree of severity.

Examination of the female urethra and bladder has shown that what must be essentially the same condition can frequently be found: a narrow ring at the neck with some dilatation of the urethra immediately below and, in the bladder, thickening of the detrusor muscle bundles. The ring at the neck can sometimes be felt against a urethral instrument with a finger in the vagina. The pathology of this condition is elusive: some take the view that it is due to hypertrophy of the circular muscle coat of the bladder, fibres of which encircle the bladder neck at this point, while others – notably Moore (1960) – have called it the 'female prostate' and suggested that some glandular secreting tissue homologous to the male prostate can be found in the submucosa. It is perfectly true that mucus-secreting tubular glands exist but it is also easy to show that they are least numerous, in fact almost absent, in the upper third of the urethra: furthermore, histology of the obstructing neck reveals a predominance of smooth muscle, a little striated muscle, some fibro-elastic tissue and overlying epithelium with squamous metaplasia – and no glandular tissue (Mitchell & Andrews 1953).

The term 'female prostate' conveys very readily a picture of increasing bladder outlet obstruction in women over the age of 50; there is no proof, however, that these glands are really the homologue of the prostate and, also, the age incidence is predominantly earlier than the prostatic age. This condition corresponds much more accurately to Marion's disease in the male and it is for this reason that we prefer the term 'bladder neck obstruction', which covers all variations of degree and all age groups and is more descriptive of what we see.

The significance of the polyps, which can frequently be seen at the internal meatus and which were considered important by Winsbury-White

(1957) and others, is doubtful. It is noticeable that they can appear and disappear in the same patient in the course of a few weeks without any local treatment and that they are not constant findings in any particular pathological circumstances. It is suggested that they may be related to what is called pseudomembranous trigonitis, which appears to be a physiological phenomenon varying somewhat with the menstrual cycle.

It is a pleasure to pay tribute to Winsbury-White, a predecessor of mine in this Section, who wrote and taught much about the female urethra. He was almost unique in his time because he examined the urethra, male and female, as he introduced the cystoscope into the bladder. Many of the ideas which have been described above are not original: Winsbury-White (1956) described female stricture and bladder neck obstruction as a result of what he saw.

The combination of urethral stricture distally and bladder neck stenosis proximally is common in my experience and it is easy (exactly as in the male) to forget that most of the pathological effects may be due to the obstruction at the upper end of the urethra and not to the more obvious stricture.

Clinical Findings

Some patients come to the urologist with a preliminary diagnosis of 'cystitis' and are found after investigation to have an entirely different condition which causes similar symptoms. This may have been suspected, as for example when a woman has hæmaturia as a prominent symptom of attacks of cystitis and is found to have a bladder tumour.

While in most females investigated by the urologist, perhaps 9 out of 10, the findings are limited to the urethra and bladder base and have already been described, there are several inflammatory and neoplastic conditions which must be mentioned:

Tuberculous cystitis is one of them; adequate examination of urine specimens and the typical cystoscopic appearances should make the diagnosis, but there are a few where the bacilli are very elusive indeed and it is very difficult to obtain the necessary proof of diagnosis before starting treatment.

Hunner's ulcer is another trap for the unwary urologist. It is fairly rare and difficult to diagnose if the bladder has already reached the stage of secondary infection: in early cases, of course, the urine is sterile and the deposit, showing a few red and white cells, gives a clue, as also does the marked nocturnal frequency.

Neoplasms: It is the neoplastic field that provides the majority of pitfalls. The thought that some form of tumour underlies recurrent attacks of cystitis drives many an older woman to hospital – quite rightly indeed, for it is one of the common ways in which bladder tumours present in the female; the symptoms are due to a combination of epithelial tumour and superimposed secondary infection. There is also a type of undifferentiated carcinoma of transitional epithelium which lurks, in the form of carcinoma *in situ*, in the sub-epithelial region of the bladder and urethra, while the overlying epithelium shows only hyperplasia and the patient is conscious only of an irritable, uncomfortable bladder liable to recurrent attacks of ‘cystitis’ which are not much influenced by chemotherapy, with either sterile urine or insignificant infection. Nobody, I think, who had not previously seen this type of so-called ‘cystitis’, would believe at first sight that it was basically a highly malignant tumour; it is quite unlike our normal conception of one. Biopsy is essential if doubt exists.

Treatment

It is usual for most general practitioners to treat first attacks of ‘cystitis’, at any age, at once, basing the diagnosis on the history and examination of the urine; urine examination need only be superficial, for the finding of protein in a hazy urine containing pus cells is sufficient. This brings us to the difficult question of whether or not laboratory examination of the urine is necessary and, if so, when it should be done. The specimen brought by the child’s mother in a medicine bottle may be several hours old and the bottle, of course, is not sterile. It is reasonable to test it for protein and sugar and to examine the cell deposit for red and white cells, but obviously that is as far as one can go. A midstream specimen of urine obtained in the surgery or at home requires suitable accommodation and a nurse trained in the method, to say nothing of a co-operative child who is old enough to understand what is required. It then has to be sent or taken (usually taken) to the laboratory, from which a report arrives by post on the third day; by this time the patient has received treatment and is usually better. There is, therefore, some argument for sending specimens after treatment, as a test of cure, rather than before.

Laboratory reports should be interpreted with caution because midstream urine specimens are never completely sterile. Normal urine is, of course, sterile in the bladder but picks up organisms as it passes down the urethra, which multiply because urine is a good culture medium at room temperature. The normal and abnormal

female urethra both contain the same variety of organisms. In a fresh normal specimen the number of organisms is always less than 10,000 per ml while in any infection it is always more than 100,000 per ml, ten times greater. The normal centrifuged deposit will contain varieties of desquamated epithelial cells, but no pus cells – while the infected urine always contains more than 10 per high power field and usually more than 100 per high power field. If a urine specimen is allowed to stand at room temperature there is rapid proliferation. Some strains will proliferate exceedingly rapidly under these conditions: the bacterial count multiplies itself about ten times every two to three hours. It is possible that this is the real cause of many so-called urinary infections which are needlessly treated with antibiotics. So, first, if there are no pus cells or less than 8–10 per high power field there is not an infection; secondly, if the laboratory knows the time when the specimen was taken and has done a rough bacterial count, the pathologist can recognize and advise whether the infection is significant or not. Many laboratories report a significant growth as ‘profuse’ while they reserve the terms ‘moderate or scanty’ for growths which are probably more associated with the method of collection or the lapse of time. At refrigerator temperature, of course, bacterial multiplication is very slow so that a specimen can be kept overnight and examined in the morning quite satisfactorily.

Women are usually allowed to have more than one or two attacks of cystitis before being sent for investigation. General practitioners, in my experience, become remarkably shrewd at spotting the change of symptoms which indicates the beginning of some more serious lesion or the presence of some factor preventing satisfactory treatment. It is obvious that it is not feasible to investigate every case at onset and that a line must be drawn somewhere – the question is, where?

Where children are concerned, it is probably easier to know what to do, for in infants under 1 year any urinary infection needs investigation: in girls up to 15 years a second attack indicates investigation (compared with a first attack in any boy).

Sulphonamide forms the basis of treatment for the majority, though a few favour nitrofurantoin. Either is satisfactory because coliform organisms respond well and drug resistance is not encountered among this group of bacteria outside hospital. Once a patient has had instrumentation in hospital it is possible that a streptomycin- and sulphonamide-resistant coliform and a resistant proteus infection may be added, which demand more care in the choice of antibiotic and chemotherapy.

Local hygiene undoubtedly plays a significant part in the prevention of 'cystitis' in girls and young women; it is surprising how frequently such simple advice is necessary and how effective it is. Possibly the male partner needs this advice as well. Prophylactic chlorhexidine cream is useful in the prevention of 'cystitis' following intercourse. It is doubtful if long-term chemotherapy has any place before a complete urological investigation has been done: if it is used without this it may suppress an infection which is not the primary lesion but is really the signpost pointing to a structural or functional abnormality of the urinary tract: provided the urinary tract has been passed as normal or nearly normal, it can be most valuable. In girls aged 6 to 10, long-acting sulphonamides of the sulphamethoxydiazine variety in a dosage of 0.25 g daily can ward off recurrent attacks of cystitis for many months. Nitrofurantoin has a similar place, though it must not be given like this if there is any suggestion of renal failure, because of the risk of peripheral neuritis. In the adult woman, sulphonamide is probably the most valuable single drug: it is remarkable how short a course of these tablets will suffice to relieve symptoms, indeed a number of patients acquire a stock of them and find that they can stop or ward off an attack by taking as little as 1.0 g in two divided doses. They even use them as prophylaxis if they know their own individual precipitating cause.

Concerning antibiotics, one can say with some truth that if bigger guns in the shape of antibiotics such as tetracycline, ampicillin and chloramphenicol are to be used, this should either be done in hospital or, if done at home, should be strictly controlled by urine specimens before and after treatment.

Mention should be made of the type of 'cystitis' in post-menopausal women which is associated with senile changes in the genital epithelium: local oestrogen ointment seems to be specific here, though it may need to be accompanied by urethral dilatation.

Surgical Treatment

Just as chemotherapy is the standby of the practitioner, so urethral dilatation is the standby of the surgeon. In the last fifty years numerous people have rediscovered this empirical treatment

for themselves; indeed it is one of the most satisfactory discoveries that every urologist makes, for it is seldom to be found in any surgical textbook. It is effective without doubt in a certain number of cases, though the beneficial effect is seldom permanent. In my experience, size 30 French is adequate, though Rees (1960) advocates a larger size, 12 Hegar.

What does it do? Those who favour fibrosis say that it stretches fibrous tissue and allows a better stream with less residual urine; those who favour infected mucus glands say that it opens the ducts and forces out the obstructed infected contents. Those who believe in bladder neck obstruction think that it opens the neck somewhat. Probably it does all these things, which accounts for its success in a variety of patients because in many of these women the cause of the recurrence of 'cystitis' is not one thing but a mixture of factors.

A proportion of the women referred to us are found to have definite bladder neck obstruction and, if their symptoms are bad enough or if there are signs of obstructive uropathy including residual urine, then we firmly believe that transurethral resection of the bladder neck is of benefit. There is nothing magic in the transurethral route; Winsbury-White believed in this operation but thought that it was best done transvesically. We have no hesitation in agreeing with Bennett-Jones (1962) that it is an easier operation by the transurethral route, both for the patient and the surgeon. Whether or not the condition is a 'female prostate' or a 'bladder neck obstruction' there is no doubt that resection of the neck is the answer to many of these more difficult cases.

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