THE MODERN TREATMENT OF GENITO-URINARY TUBERCULOSIS

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The majority of the views expressed today about the natural history of genito-urinary tuberculosis, and about its being a local manifestation of a generalized disease, were all recorded in the literature over 50 years ago. The natural history of the disease has not altered.

However, tuberculous cervical adenitis and intestinal involvement is becoming rare, and most renal lesions are now secondary to pulmonary involvement with human type bacilli, but the kidney is still involved in the same way during a phase of blood stream dissemination, and the lesion is, therefore, always potentially bilateral.

Most urologists now accept the view (Band, 1943) that in the majority of cases the kidney is the first organ to be affected in the genito-urinary system, certainly in the male, and that the ureter and bladder and the urethra, prostate, vesicles and epididymes are subsequently infected by tubercle bacilli in the urine coming from the kidney.

The reason why the renal lesion may not become clinically manifest for 10 to 15 years after the initial primary lesion remains unexplained, but it will probably mean that, in spite of the present marked reduction in pulmonary tuberculosis, the incidence of renal tuberculosis may be expected to remain at its present level for several more years. From now on, however, we can reasonably hope that, provided the pulmonary or other primary lesions of today are adequately treated by drugs, they will not be followed in future years by active renal disease.

The answer to this pious hope will be known within the next 10 years.

In the meantime the clinical progress of an established lesion treated adequately with anti-biotic drugs has altered so fundamentally that the urologist is already confronted with a completely new situation. It is now possible to render the urine tubercle free in any lesion which has free drainage and an adequate blood supply. Instead of extending slowly but inexorably into the surrounding healthy tissues, the lesion can be halted, in most cases, at the stage when it is first detected, so that, today, nephrectomy is the last operation to be considered and is an admission of failure.

However, if nephrectomy is no longer the treatment for renal tuberculosis, other forms of corrective surgery, based upon the fundamental uro-logical principles of free drainage, have become even more important and necessary. The conservative treatment of the disease has, in fact, made the surgical supervision of a patient more, not less, complicated. The natural healing response to any tuberculous lesion is fibrosis, and it is apparent that, in most cases, long before the tubercle bacilli are all actually killed by the drugs, they are reduced in numbers and virulence, a fact which encourages the tissues to exert this healing defence mechanism with increasing efficiency. It is, unfortunately, this natural fibrosis which can be the urologist's (or the chest surgeon's) greatest enemy, because it can obstruct the drainage from and therefore destroy, a renal or lung segment during the same time that the antibiotic drugs are effectively overcoming the tubercle bacilli.

It is quite obvious, therefore, that the conservative management of genito-urinary tuberculosis does not consist of prolonged courses of antibiotic drugs without repeated clinical and radiological observation. A 'cured' silent, sterile pyonephrosis can result from such folly.

Diagnosis of Genito-Urinary Tuberculosis

The amount of functioning tissue which remains after successful antibiotic therapy is largely dependent upon the amount of tissue involved before treatment begins, so that early diagnosis is vitally important.

It should not be necessary to state that all patients suffering from a tuberculous pulmonary lesion should have the urine examined for albumin, pus cells and tubercle bacilli at regular intervals. However, in patients with no history of pulmonary involvement detection may be much more difficult. By the time the diagnosis is finally established, there is frequently a history of several attacks of 'cystitis' during the previous six months or so.
In most cases these attacks have been investigated carefully, but the tubercle bacilli has not revealed itself. Nevertheless, persistent vague loin pain, transient and perhaps doubtful haematuria (remember the patient is sometimes right!) and, above all, nocturnal frequency in a young adult, should always be considered tuberculous until proved otherwise.

Proof of Diagnosis

The antibiotic treatment of tuberculosis should not be commenced until the diagnosis is proved, and this can only be done by guinea-pig inoculation, or by culturing the tubercle bacillus on special media. A Ziehl-Nielsen stained smear gives useful, early, supporting evidence, but must not be accepted as proof of a tuberculous lesion. In experienced hands, modern culture methods are now as reliable as guinea-pig inoculations, and are being used extensively in most centres, the guinea-pig being reserved for confirmation of doubtful positives, or as a final court of appeal.

Early Morning Urine

A factor which is frequently forgotten by clinicians, when sending specimens to the laboratory for the detection of tubercle bacilli, is that urine should be sterile for ordinary pathogens if possible. If the urine is infected it will kill the guinea-pig or result in a contaminated culture. For this reason a '24-hour urine' should be a thing of the past. Six to eight ounces of early morning urine, in a sterile bottle, should be delivered to the laboratory within three hours of voiding. In hospital, catheter specimens can be obtained from female patients, but out-patient females can be taught to obtain a clean, mid-stream specimen. If this specimen is contaminated, the problem can often be solved by prescribing gantrisin for three days before collection of the specimen. In hospital we routinely culture three consecutive early morning urines every month. This greatly increases the chance of obtaining a positive culture if organisms are present (St. Hill, 1955; Gow, 1955).

Semen Culture

Many cases of tuberculous epididymitis do not have a positive urine culture, but the semen generally contains tubercle bacilli, so that a semen culture may save months of waiting for a diagnosis by other means (Hanley, 1954).

General Management

It cannot be repeated too often that antibiotic treatment should not be commenced until the diagnosis has been confirmed, by growing the tubercle bacillus or by guinea-pig inoculation, because once treatment has commenced there may never be a further positive urine culture. If the diagnosis is not properly confirmed in the first instance, an early lesion may improve so rapidly with treatment that doubt often assails one. It is then equally embarrassing either to stop treatment or to continue for several years in doubt, because experience teaches us that drug treatment is necessary for at least two years—and probably more. Relapse is almost certain if the treatment is not intensive and prolonged, while relapses, when they do occur, often produce resistant strains of organisms.

Sanatorium or Ambulatory Treatment

When the diagnosis has been established it must be explained to the patient that the lesion is as serious as a pulmonary infection, and that treatment is measured in years, not months.

So far, where it has been possible to compare groups of cases treated in a sanatorium with those treated as out-patients using the same drug regime (Ross, 1953; Hanley and Parkes, 1957), those in the sanatorium appear to have responded more satisfactorily. The urine is converted more quickly, the patient's general health is markedly improved, while the bladder symptoms are relieved more rapidly. Admittedly, this could be due to the fact that in hospital one can be reasonably sure that the drugs prescribed are indeed being administered, but this in itself is important. Streptomycin, INAH, and, particularly, PAS, may be so unpleasant to take that much vigilance and encouragement are required from the medical and nursing staff. In my experience, while difficulties with the various drugs do sometimes occur in hospital, they are almost universal in out-patients except when the patient has already been conditioned to them in hospital.

However, the choice between sanatorium (or hospitalization) and ambulatory treatment will depend upon various domestic and financial factors, quite apart from the availability of a long stay bed, but there is little doubt, at the moment, that a sterile urine can be achieved more quickly as an in-patient than an out-patient. Once the urine is sterile and the lesion is under 'control,' out-patient therapy may eventually prove to be just as effective—if conscientiously adhered to (Ross, Gow and Hill, 1955).

General Principles of Treatment

Each patient differs in his response to the disease and to the drugs, and it is rarely possible to predict the future detailed plan of management until treatment has been in progress for three or even six months. It is most unwise at the outset to let the patient think he will only be in hospital for a 'few' months, or that surgery will, or will not be
necessary. In theory we try to avoid any type of surgery until the urine has become sterile, and in theory we attempt to retain our cases in the sanatorium until the urine has remained sterile for six months. Following this, prolonged out-patient treatment is necessary, but the patient is encouraged to return to work. Exceptions to this rule would include the case of a unilateral lesion with practically no function. This kidney would be removed following a period of drug treatment, after which the patient would be allowed to go home in about two months time (i.e. after a confirmatory negative culture had been obtained).

**Drug Treatment**

Probably the most powerful anti-tuberculous drug is nicotine hydrazide (INH), with streptomycin a close second. Neither of these drugs must ever be given alone, but should be combined, either together, or with some form of para-amino salicylic acid (PAS), otherwise the emergence of resistant strains of tubercle bacilli is a real danger. The optimum drug combinations and dosages have still to be worked out, but in general, INH (400 mg. daily) or streptomycin (1 g. daily) is combined with PAS (17 g. daily), and must be administered continuously for long periods.

In the initial stages, urines should be cultured every month, and all positive cultures must be tested for sensitivity to all three drugs. An ineffective drug must be discontinued immediately. We have not been seriously troubled by resistant strains of organisms in any of our cases which have been treated vigorously and continuously from the very start. The chief difficulties have occurred in those treated several years ago by 'streptomycin for 90 days' or by separate courses interspersed with rest periods.

**Toxic Reactions**

In ambulatory out-patients, gastric, cutaneous, and eighth nerve reactions are all very real problems, but with a little care and encouragement they can be largely minimized in hospital. It has frequently been possible to overcome the nausea of PAS, or to desensitise patients who have previously had quite severe skin reactions to streptomycin, but I think it is rarely justified to continue with streptomycin in the presence of eighth nerve involvement.

**Response to Drug Treatment**

It has been possible to render the urine tubercle free in 60 per cent. of our sanatorium patients within four months, and 80 per cent. within six months of starting treatment (Hanley and Parkes, 1957). The only cases failing to respond were (a) in the older age groups, having very long-standing disease, with numerous semi-closed foci, or (b) cases with obstruction to the drainage or vascular supply.

**Ambulatory Treatment**

A patient who has had the only known tuberculous focus surgically excised, may be able to dispense with drug treatment following two negative urine cultures (three months) but should be kept under observation for many years, during which time the urine should be cultured regularly. If the lesion is still *in situ*, no matter how small,
it will not be 'controlled' by less than two years drug treatment, and may well require much longer.

The actual drug combinations and doses are again a matter for debate but, in general, two drugs are always given together, while rest periods should be avoided.

Streptomycin is frequently reduced to 1 g. two or three times a week, combined with PAS, 17 to 20 g. daily, or, alternatively, the PAS is combined with 400 mg. INH daily.

**Indications for Surgical Treatment**

Surgery is directed towards the removal of avascular caseous material, and the maintenance of urinary drainage. Anti-tuberculous drugs, being blood borne, are ineffective in avascular areas. They also appear to be less effective when urinary drainage is interfered with, and we have shown a markedly reduced or absent concentration of drugs in closed pyocalyces, as compared with the urine in the other calyces.

The only indication for early nephrectomy is the closed non-functioning tuberculous pyonephrosis and, even here, we prefer to treat the patient...
with drugs for six to eight weeks before operation. In all other cases conservative drug treatment is started, and it may be very difficult to predict in the early stages which ones will or will not eventually require surgery. The radiological appearances when first seen (Hanley, 1957b) can be most misleading and it is only by comparing a series of films over several months, that a true picture of progress can be built up. In principle, provided the urine from a freely-draining lesion remains sterile, there is no need for surgery.

A pyocalyx which becomes radiologically 'cut off' for several months (and which we used to resect) may suddenly open up and drain into the pelvis, perhaps causing a temporary bacilluria before it 'heals' and grows a new epithelium. Radiologically, this will always be a grossly distorted calyx, but provided the urine remains tubercle free it does not matter, and need not be resected (Fig. 1).

It is obvious, therefore, that while one single X-ray film can only give us inadequate and perhaps erroneous information, a series of films taken over several months is absolutely essential in the conservative management of a case. It should be equally obvious that, at any time, serious 'healing fibrosis' may occur, and will call for rapid intervention.

**Danger Sites for Healing Fibrosis**

The three danger sites are (a) the neck of a calyx, (b) the pelvi-ureteric junction, and (c) the uretero-vesical junction (Hanley, 1957a).

(a) **The Neck of a Calyx**

A few years ago we were immediately resecting any calyx which became 'closed off' from the main collecting system, but we found evidence of such good healing and epithelialization in many of them that they are now being kept under observation for longer and longer periods. As stated previously, many of these calyces, especially those in the upper and middle zones, will eventually open up and drain out their caseous debris over a period of months.

(b) **The Pelvi-Ureteric Junction**

Progressive fibrosis at this site has been our chief indication for nephrectomy during the past five years. Many of the kidneys removed have shown extensive areas of healing, and would appear to have been destroyed by mechanical back-pressure—not tuberculosis. This problem is the chief challenge to the urologist today.

(c) **The Uretero-Vesical Orifice**

Obstruction at this level is shown radiologically by a dilatation of the lower spindle of one or both ureters, and may be a very early sign of renal tuberculosis with mild bladder involvement.

Such radiological dilatation can be caused by three factors: (a) a mild cystitis or irritable bladder (not necessarily tuberculous) which causes a transitory hold up of urine; (b) a more advanced stage of bladder involvement (generally tuberculous) which allows reflux up the ureter; and (c) a true stricture, either due to actual tuberculous ulceration of the ureter, or advanced contracture and fibrosis of the bladder around the orifice.

Again, the true state of affairs will not be diagnosed by one set of excretion pyelogram films. The picture will also alter when the bladder ulceration heals during drug treatment. Back-pressure at this site can be almost as serious as at the pelvi-ureteric junction, but it is, fortunately, amenable to surgical treatment if diagnosed in time.

**Ureteric Stricture**

Although much radiological deformity of the ureter may occur in tuberculosis, the commonest site for true mechanical obstruction is close to the ureteric orifice, but this is not necessarily associated with a deformed or 'golf hole' orifice. If excision of the stricture and re-implantation of the ureter is to be performed, it must be done early, before the kidney is damaged (Fig. 2). However, it is vitally important to be sure that back-pressure is due to a stricture and not to reflux from the bladder. Re-implantation of the ureter in the latter case would make the back-pressure worse—not better. Inability to pass a ureteric catheter on any one or two occasions does not necessarily indicate a stricture but a micturating cystogram may often be a useful diagnostic procedure.

**Ureteric Reflux**

A micturating cystogram may show reflux up many ureters which one would think were stricture. Reflux may even occur up a normal uninfected ureter as well as up the diseased side. If this phenomenon persists after the actual bladder inflammation has subsided, some form of bladder enlarging operation may have to be considered if the 'normal' kidney is to be spared.

**The Systolic Bladder**

It is hoped that this distressing condition will become less common, owing to the fact that, today, ulceration in the bladder responds rapidly to modern drug therapy, particularly when treatment starts early before the underlying muscle is exposed.

However, these cases are still being encountered, not only in older patients with long-standing chronic disease but in young adolescents as well. Quite apart from the misery of frequency and in-
continence, this is a dangerous condition which can eventually lead to death by purely mechanical means, since obstruction or reflux can destroy an otherwise "healed" kidney. In the past, uretero-cutaneous or uretero-colic diversions have been used as a last resort, but there is no doubt that surgery should be employed early, not late, if renal function is to be preserved.

A cutaneous ureterostomy, in spite of pedicled nipples and other ingenious procedures, is still prone to retraction and stricture formation, while a really satisfactory collecting apparatus has yet to be devised.

Uretero-colic anastomosis will almost certainly be followed by renal infection, owing to the large bore of the ureter, and it has become unpopular in tuberculosis during recent years.

Ileo-cystoplasty or the enlarging of the bladder by the use of an ileal loop has proved very effective in many cases of tuberculosis and there are an increasing number of patients who have now been followed up for five years or more, and who continue to be clinically satisfactory (Cibert, 1953; Annis et al., 1954; Pyrah, 1956; Jacobs, 1955; Hanley, 1956).

The Prostate, Vesicles and Epididymes

Until it can be proved otherwise, one should always assume that a tuberculous epididymitis is associated with an active prostato-vesiculitis, if not a renal lesion as well.

The fact that an epididymitis can develop 10 to 15 years after the removal of a kidney lesion, and the fact that tubercle bacilli can be found in the ejaculate 10 or more years after an epididymectomy (Hanley, 1954) confirms the belief that a tuberculous prostato-vesiculitis can remain latent for years without inconveniencing the patient in any way. Modern drug therapy is particularly effective in sterilizing the seminal fluid, and it is hoped that the long-term results will be satisfactory. Early epididymal lesions will respond to drug treatment and do not call for surgery, but, once an abscess has formed and become adherent to the skin, it is unwise to be dogmatic about this. Some sinuses heal rapidly at the beginning of treatment, but those which break down during treatment generally require surgical removal for the sake of the patient's comfort and convenience.
Male Subfertility
Azoospermia, due to a bilateral tuberculous epididymitis, is easily understandable, but it is not generally appreciated that sterility due to vesicular involvement is probably more common. When the vesicles are involved there is a steady reduction in ejaculate volume, until finally there is insufficient fluid to carry the sperms to the exterior. If the ampulla is not involved, there may be no obstruction to the passage of sperms, and this type of subfertility may improve with antibiotic therapy.

Female Subfertility
Tuberculous endometritis was at one time considered to be an absolute bar to conception, but several pregnancies following modern drug treatment have been recorded by Snaith (1955) and others in recent years.

Tuberculous salpingitis is frequently associated with disease in other organs and may subside with routine drug therapy. 'Healing' will almost certainly result in fibrosis and blockage, while a large palpable caseous mass may still have to be excised.

In conclusion it must be emphasized that, although the modern treatment of genito-urinary tuberculosis has undergone a radical change in the past few years, the tubercle bacillus is still a worthy foe, and over optimism should be avoided. We cannot tell what will become of the 'healed' lesions in years to come, but at least if the patient still has his kidney—one can think again.

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