

## THE PROBLEM OF GONORRHOEA, WITH INCIDENTAL REFERENCES TO AN INDUSTRY

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During the 1939-1945 war, mass movement of troops was a frequent occurrence. The inevitable promiscuity resulted in a sharp rise in the incidence of venereal diseases. Working as an intern in a venereal disease ward attached to a large transshipment camp in one of our ports, the treatment of gonorrhoea left vivid memories. These were the days of urethral irrigations with potassium permanganate solutions, urethral instillations and the use of sulphathiazole. Cases of chronic gonorrhoea were frequent and epididymitis, prostatitis, and urethral stricture were common complications, requiring prolonged hospitalization.

Later, while serving in Europe, the first treatment centres using penicillin were established. The return of men to their units in 24-48 hours became commonplace and the contrast with earlier experience was very striking. It seemed that the gonococcus would soon be entirely eliminated. It is common knowledge that those optimistic hopes were not to be realized.

Gonorrhoea is seen as frequently as ever, and seems very common in non-White males employed by the South African Rubber Manufacturing Company (SARMCOL) at their plant in Howick, Natal. From 1 May 1962 to 18 May 1964, 134 men have been attended for 166 episodes of clinical gonorrhoea. SARMCOL is the biggest employer of labour in the rubber industry in this country and manufactures a very wide range of articles.<sup>1</sup> The Company has grown from 100 employees in 1919 to 1,455 African, 53 Coloured, and 328 Asiatic employees in January 1963.<sup>2</sup> The present figures are appreciably higher.

### *Bacteriology of Gonorrhoea*

In 1879 Neisser discovered the causal organism of gonorrhoea—the gonococcus.<sup>3</sup> In 1885, Bumm finally proved its aetiological role by growing pure cultures on coagulated blood serum and producing gonorrhoea by inoculating the human urethra with such cultures.<sup>3</sup>

The organism is a kidney-shaped diplococcus with the hila of the kidneys opposed; it is Gram-negative. In early acute gonorrhoea most of the organisms are outside the pus cells, lying in clumps either free or applied to epithelial cells. When the discharge becomes purulent, the gonococci are found apparently within the pus cells. This intracellular position of the organisms is characteristic of gonorrhoeal pus. It is usual that a few leukocytes per field contain large numbers of gonococci, while the majority contain none.<sup>3</sup> My experience at SARMCOL confirms this statement.

The gonococci are always found in single pairs, or in clumps, but never in chain formation. Two adjacent cocci may be of different sizes and deviations from the normal standard are common. In the early stage of infections the organisms are apparently intracellular, and in infections of older standing they may be extracellular.<sup>3,4</sup>

Burke's views on the gonococcus are controversial but of great interest.<sup>3</sup> Neisser was apparently not convinced that the organisms were truly intracellular and thought they might be adhering to the leukocytes.<sup>3</sup> If the gonococci

are truly intracellular—if they have actually been phagocytosed by the leukocytes—why is it that, unlike other organisms, they are not digested and destroyed by the leukocytes? Again, if they are intracellular, why is it that no apparent damage occurs either to the gonococci, or to the leukocytes in whose substance they appear to be? (Burke).<sup>3</sup>

A further argument raised by Burke, is that if phagocytosis has any function at all, it must be the destruction of ingested organisms. In gonorrhoea, however, the apparent phagocytosis and undoubted leukocytosis coincide with the stage when the gonococci are most virulent, the disease most infectious, and when a specimen exhibiting apparently intracellular gonococci can most easily produce a pure culture.<sup>3</sup> Burke believes that as gonococci cling to the surface of the epithelial cells in the early pre-purulent stage of the disease by a process of positive chemotaxis, so do they cling to the leukocytes in the purulent stage.<sup>3</sup> When this positive chemotaxis ceases to act, the gonococci separate from the leukocytes, and degenerate. At this stage the patient becomes less infective and may cease to be capable of conveying the disease to others. When phagocytosis ceases, the gonococci are often found in the extracellular position.<sup>3</sup> If these views bear consideration (Burke admits that they may be heretical<sup>3</sup>) it follows that older methods of treatment by instilling strong antiseptics into the urethra actually increased the leukocytosis, and therefore the number and virulence of the gonococci.<sup>3</sup>

Warden, working with 22 different strains of gonococci, showed that by varying the culture media, all types of the coccus family could be produced. Processes of reversion and variation resulted in staphylococcus-like clumping of single forms, short chain formations as with streptococci, lanceolate forms indistinguishable from pneumococci, and diplococci resembling the micrococcus catarrhalis. All these were pure cultures of gonococci which returned to the classical Neisserian type when implanted on appropriate media.<sup>3</sup> Willcox mentions the possibility that the gonococcus may transmute into pleuro-pneumonia-like organisms and thereby become resistant.<sup>5</sup> L-forms have been noted in cultures and such resistant forms have been observed in patients, during therapy. Changes in growth on cultural media and ability to ferment glucose have been reported.<sup>5</sup>

The curative effect of the sulphonamides on gonorrhoea, pneumonia and puerperal infection, may be due to the fact that the organisms giving rise to these maladies are essentially similar in origin.<sup>3</sup>

There is evidence for the view that the gonococcus in the genital passages can become a harmless, but potentially harmful, symbiote.<sup>3</sup> Such a view leads to the idea that under certain stimuli this harmless symbiote of the genital passage may change and develop into the typical gonococcus. In a study of prostitutes in Paris, considerably more Neisseria found in smears and cultures were saphrophytic than gonococci.<sup>5</sup> Parallels may be found with respect

to other diseases. The pneumococcus for example is a symbiote which may exist for life in the respiratory passages without causing the disease complex known as 'pneumonia'. Certain stimuli, e.g. exposure or injury, may render the symbiotic pneumococci virulent and the result is disease—not necessarily a transference of infection from one person to another.<sup>3</sup>

If there is truth in the theory that the gonococcus may at times become a harmless symbiote of the genital passages, and that in its virulent or Neisserian form, this organism is a Gram-negative diplococcus, then in its symbiotic condition it may assume other shapes and exhibit a Gram-positive staining. Carried to its logical conclusion, this view infers that gonorrhoea may arise *de novo*—without infection being conveyed by a second person. This may explain cases of gonococcal vulvovaginitis which have occurred in epidemic form in children's hospitals where it is often difficult to prove that infection has been conveyed from without.<sup>3</sup>

22 years ago Burke made the observation that the appearance of the sulphonamides would complicate the picture of the treatment of gonorrhoea. He referred to an increase of the relapse rate, the defaulter rate, and thus an increased incidence of both gonorrhoea and syphilis.<sup>3</sup> The position today, despite the advent of penicillin and the broad-spectrum antibiotics as far as gonorrhoea is concerned, remains essentially unchanged.<sup>6</sup>

#### *Epidemiology of Gonorrhoea*

Complete failure to control gonorrhoea throughout the world in spite of the very widespread use of penicillin and other antibiotics was admitted by an Expert Committee on Gonococcal Infections recently called together by the World Health Organization (WHO).<sup>6</sup> There has been evidence for several years that the number of gonorrhoea cases has been increasing, especially among teenagers.<sup>6-8</sup> In Britain, the rise in the number of cases is attributed largely to the influx of immigrants.<sup>7, 8</sup> Promiscuity in teenagers, and the emergence of relatively insensitive strains of the gonococcus contribute to the problem.<sup>6-9</sup> A rise in the number of cases has been reported from Scandinavia, France, Italy and the West Indies, in addition to confirmatory reports from America and Great Britain.<sup>9</sup> It has been estimated that 60,000,000 cases occur every year, throughout the world.<sup>6</sup>

The short incubation period of gonorrhoea (2-5 days) before the disease develops in another person infected by sexual contact, makes control extremely difficult. One case leads to others with such rapidity that gonorrhoea is always well ahead of those trying to stop its spread. The fact that gonorrhoea is much more infective than syphilis aggravates the problem. New infections easily result from sexual contact with infected persons, while in the case of syphilis there is an even chance of escape.<sup>6</sup> Syphilis often confers immunity against a second infection while a patient cured of gonorrhoea is just as vulnerable as before, and can be re-infected many times. This fact is apparent in my experience at SARMCOL. 26 of the 134 men have had 2 or more episodes of gonorrhoea.

The basic problem in attempting to control gonorrhoea is the difference in its manifestations in the sexes. Gonorrhoea is essentially a clinically latent infection in the adult

woman so that a reservoir of undiagnosed disease persists in women. Most infected men have symptoms and attend promptly; most infected women do not.<sup>3, 4, 7, 10</sup>

Ricord, in 1852, stated that women frequently convey to men a gonorrhoeal infection without having it themselves,<sup>3</sup> and Franck reported a group of female patients who were what he termed 'gonococcus carriers without gonococci'—women who infected their partners without showing gonococci themselves. These women showed many Gram-positive diplococci, and also a few small Gram-negative diplococci, but no typical Neisserian organisms.<sup>3</sup> It is known that gonorrhoea may be difficult to diagnose, particularly in women.<sup>4, 6, 7</sup>

In the female, cultures of urethral and cervical discharges, or mucus, are usually required, but false negatives are common.<sup>4, 7</sup> In one series of women patients, 50-60% of stained smears were negative.<sup>13</sup> Under the most favourable circumstances, standard culture methods were able to detect the gonococcus in only 16-47% of female contacts of males with gonorrhoea.<sup>11</sup> For this reason Rosenblum favours the fluorescent antibody tests (FA) the result of Deacon's work, in the Venereal Disease Research Laboratory, Public Health Service, USA. Both delayed and direct methods are described and both give a greater yield of positive results, in less time than conventional culture methods.<sup>11</sup> The most reliable test for cure in women, is absence of re-infection in male sexual partners.<sup>12</sup>

It is apparent that diagnostic methods requiring laboratory investigation, pose an insuperable problem in many parts of the world where such facilities are entirely lacking. Experience at SARMCOL depends upon a clinical diagnosis, supported by a smear stained with Gram's stain, and examined by the author. Only males are seen, however, and contact tracing is far from adequate.

Males outnumber female patients in a ratio of about 4:1, but the untreated reservoir of infection in women must be considered.<sup>6</sup> In the USSR, 90% of women found to have chronic gonorrhoea were symptomless.<sup>6</sup> In another survey, questioning elicited the fact that 70% of women patients have symptoms which, although mild, included vaginal discharge, dysuria, increased frequency, abdominal pain (sometimes due to salpingitis), vulval soreness, Bartholinitis, rectal soreness and pruritis, and menstrual abnormalities.<sup>10</sup>

Asymptomatic cases may only be intermittently infectious, particularly after alcohol, orgasm, or immediately after a menstrual period.<sup>7</sup> The male can transmit gonorrhoea during the incubation stage before the appearance of a urethral discharge,<sup>7</sup> but penicillin-treated asymptomatic male carriers rarely occur.<sup>12</sup> Cases of chronic gonorrhoea in males do occur, however, and this is supported by experience at SARMCOL.

Much of the gonorrhoea in the world is found in special groups; migrants, seafarers, seasonal workers, military personnel and homosexuals. Prostitutes, particularly the younger ones, form a great reservoir of infection and as many as 50% may be infected.<sup>6</sup> The non-White workers at SARMCOL are not true migrant workers, but many live in slum-like, overcrowded, makeshift dwellings and are separated during the week from their families who are resident in neighbouring Bantu reserves. These conditions tend to encourage local liaisons in and about Howick,

and contribute materially to the problem of gonorrhoea, as seen in males, at SARMCOL.

#### THE EMERGENCE OF RELATIVELY RESISTANT STRAINS OF THE GONOCOCCUS

The statement that 'the days when gonorrhoea could be assumed to respond to a routine course of treatment with penicillin are now past'<sup>14</sup> is probably controversial. Levy maintains that resistant cases will clear, provided the concentration of penicillin in the blood can be increased and maintained for 48 hours. He achieves this by giving 500,000 units of the aqueous solution of the sodium salt of benzyl penicillin (crystalline penicillin) every 6 hours for 48 hours.<sup>15</sup> Svihus and his co-workers quote Cohn *et al.*, who support the fact that all gonococcal infections studied responded to penicillin treatment.<sup>21</sup> As no strain of the gonococcus completely resistant to penicillin has yet been encountered, cure can be effected by multiple injections of a preparation of penicillin giving a high serum level.<sup>13</sup> This may require hospitalization and is impracticable in many clinics, and at SARMCOL. Before the emergence of relatively insensitive strains of gonococci a minimum serum level of 0.03 unit/ml. of penicillin for 24 hours would effect cure in uncomplicated gonorrhoea. This was achieved by a single injection of 300,000 - 600,000 units of a repository penicillin such as procaine penicillin with 2% aluminium monostearate (PAM).

The least sensitive gonococci isolated from patients in 1960 required 20 times the concentration of penicillin required by the least sensitive organisms isolated in 1944.<sup>18</sup> It is possible that sub-lethal concentrations may have been a cause of the decrease in sensitivity of the gonococcus to penicillin.<sup>18</sup>

In treating gonorrhoea in women, Rees recorded a failure rate of 13.9%. The concentration of penicillin needed to inhibit the strains in her series varied between 0.0008, and 0.25 unit/ml.<sup>13</sup> It is generally agreed that there are increasingly frequent reports of more resistant strains of the gonococcus being encountered.<sup>5, 7-9, 12, 16-19, 22</sup> The incidence of relatively resistant strains has been found to vary widely between different areas, and at different times in the same area.<sup>9</sup> Some strains will grow *in vitro* in 0.1 - 1.0 unit/ml. of penicillin, whereas previously all were inhibited by 0.06 unit/ml. or less.<sup>22</sup> An increase in penicillin dosage will often reverse the failure rate, and once therapeutic control is inaugurated, the percentage of relatively insensitive strains is reported to be rapidly reduced.<sup>8</sup>

Early reports with penicillin therapy indicated a low failure rate; in Norway 2.9%,<sup>17</sup> and 7.3% in Birmingham.<sup>17</sup> Lately, even with doses of 1.2 mega units of aqueous procaine penicillin failure rates of 15.3% were recorded by Mead in San Francisco and 27.4% in London.<sup>20</sup> In American troops in Korea a failure rate of 20% was recorded in 148 cases; 5 daily injections of 0.6 mega units of procaine penicillin G were given.<sup>17</sup>

#### Reasons for Failure in Treatment

Before assuming that penicillin therapy has failed in the treatment of gonorrhoea, various other possibilities must be considered:

(i) *The question of re-infection.* In most cases it is

impossible to answer this with certainty. Gonorrhoea occurs characteristically in promiscuous persons whose histories are notoriously unreliable. At SARMCOL, the patients give histories which are in many cases so vague and evasive that no attempt to answer the question is possible. Re-infection cannot of course explain treatment failures in patients who show *N. gonorrhoea* in the discharge while receiving adequate doses of penicillin.<sup>17</sup>

(ii) *Low blood concentrations of penicillin* may be inadequate to eliminate the infection.<sup>9</sup> The marked variation in penicillin blood levels in different patients (and even in the same patient after successive injections of identical amounts of penicillin) may cause sub-curative concentrations in many patients.<sup>18</sup> The prolonged low level 'tail' which follows the injection of long-acting penicillin preparations may bring the gonococcus into contact with sub-curative concentrations. This applies equally to infections with *T. pallidum*.<sup>18</sup>

The theoretical possibility that the presence of large numbers of persons in the community, treated for a variety of infections with repository penicillins but having persistent low levels of penicillin in their serum, might tend to foster the development of resistance of organisms to antibiotics, must be considered. This resistance might be effected by microbiological selection as well as possible mutagenic effects.<sup>5</sup>

(iii) *Decreased sensitivity to penicillin* of certain strains of the gonococcus has been mentioned.<sup>5, 7-9, 12, 16-19, 22</sup> When referring to penicillin resistance, an increased relative resistance is meant, i.e. a higher concentration of penicillin is required for an antibacterial effect than is required for the usual strains.<sup>17</sup>

From a clinical standpoint the emergence of penicillin resistant strains has grave significance. No longer can gonorrhoea be considered lightheartedly as a disease with less disability than the common cold. The twin problems of chronic gonorrhoea and the asymptomatic male carrier—at first considered banished by penicillin—may have returned.<sup>17</sup>

(iv) *The use of outdated penicillin* has the same effect as inadequate dosage of penicillin.<sup>11</sup>

(v) *The presence of penicillinase.* Careful examination of the patient to exclude concurrent staphylococcal infections is required.<sup>11</sup> Cases which at first sight appear to be due to penicillin-resistant gonococci, on investigation often show concurrent infection with penicillinase-producing staphylococci, or infections with bacteriologically similar penicillin-resistant mimeae.<sup>16</sup> The presence of mixed infections, particularly with penicillinase-producing staphylococci, may be an important factor in the failure to eliminate the gonococcus. In such cases it is essential to include another agent directed specifically against the secondary invaders.<sup>19</sup>

(vi) *Infection with mimeae.*<sup>11, 16, 21, 22</sup> Many patients who are thought to have been re-infected, or to harbour penicillin-resistant gonococci, may in actual fact harbour bacteria from the tribe of mimeae. These bacteria closely mimic the gonococcus, hence the name. The majority are penicillin-resistant. It is extremely difficult to distinguish the mimeae from gonococci, and differentiation requires elaborate culture techniques.<sup>11, 22</sup>

Three genera of mimeae distinguished by their abilities to ferment carbohydrates are described (De-Bord).<sup>11, 21</sup> The microscopic pictures of the tribe mimeae and of the genus *Neisseria* may be identical and therefore the identification of *N. gonorrhoeae* by stained smears alone is not justified.<sup>21, 22</sup>

In one series, 34 US military personnel in Naples were investigated for what was thought to be penicillin-resistant gonorrhoea. In 22 cases, the infection was found to be due to mimeae, and 18 were penicillin-resistant.<sup>21</sup> In another study mentioned by Svihus and his co-workers, 216 soldiers were evacuated from overseas in 1946 because of 'penicillin-resistant gonorrhoea'. In 9% of cases infection was due to the gonococcus. In the remaining 91%, the urethritis was due to other organisms, including 'unidentified Gram-negative organisms'.<sup>21</sup> The possibility that some of the latter cases were due to infection with the mimeae must be considered.

#### Points to Consider

Discussion of urethritis owing to the tribe of mimeae, poses 2 questions. Firstly, what is meant by the word 'gonorrhoea'? The Latin-Greek word etymologically means a flow of semen ('urethral discharge without sexual excitement').<sup>21</sup> The term gonorrhoea has been used for many years to denote the clinical picture of a purulent, burning urethral discharge containing intra- and extra-cellular Gram-negative diplococci. Now that mimeae have been shown to cause such a picture, should these infections be labelled 'gonorrhoea', or should the term be restricted solely to urethritis due to *N. gonorrhoeae*?<sup>21</sup>

Secondly, how widespread are infections with the tribe of mimeae? Two studies are mentioned, but the question can only be answered by further studies which should include exact determination of the causative organisms in cases of urethritis, before treatment. Until more is known of the mimeae, care should be exercised in the use of the expression 'penicillin-resistant gonorrhoea'.<sup>21</sup>

Infections owing to the tribe of mimeae are usually responsive to the tetracyclines, or erythromycin, as is the case with many other types of non-specific urethritis.<sup>11</sup>

#### CURRENT TRENDS IN THE TREATMENT OF ACUTE GONORRHOEA

The opinion has often been expressed that the gonococcus may be adapting itself to the chemotherapeutic era. Gonorrhoea now seems a milder disease than was the case in earlier times.<sup>5</sup> Complications are certainly less frequent.<sup>5</sup>

Any antibiotic used to treat gonorrhoea should ideally be therapeutically effective in one easily administered dose, relatively non-toxic, hypoallergenic and reasonable in cost.<sup>16</sup> Except for increasing allergic reactions varying from benign urticaria to severe anaphylaxis and death, penicillin most closely fits the above criteria.<sup>16</sup> Immediate, severe reactions have been reported for all types of penicillin and all routes of administration. For patients with a history of allergy or drug reactions, a 3-10 times higher sensitivity rate to penicillin may be expected.<sup>16</sup>

In patients attending VD clinics, the incidence of penicillin reactions increased from 5.95 per 1,000 in 1954 to 9.71 per 1,000 in 1959.<sup>16</sup> By 1957 it was estimated that 1,000 deaths from anaphylaxis owing to penicillin had occurred in America.<sup>5</sup> In American troops in Korea, Epstein reported that 5% of his cases had mild penicillin

reactions—the chief manifestation being urticaria.<sup>17</sup> In an earlier report from SARMCOL, 1.9% of patients with venereal disease exhibited urticarial penicillin reactions.<sup>2</sup>

#### Penicillin

Despite the possibility of allergic reactions to its use, penicillin is accepted by most authorities as the antibiotic of choice.<sup>4, 7, 11-13, 15, 16, 20-22</sup> Willcox calls it the 'queen of drugs'.<sup>20</sup> Penicillin is non-toxic, and the toxic doses far exceed those required for therapeutic effect.<sup>5</sup>

Kirby suggests one injection of 600,000 units of procaine penicillin, and feels it will cure over 95% of patients both male and female.<sup>20</sup> This dosage is considered too low by most military physicians,<sup>17</sup> but for optimal results, Kirby recommends that the dose be repeated for 2-3 days in males, and 5-7 days in females.<sup>22</sup> At SARMCOL, 3.6 mega units of aqueous procaine penicillin ('distaquaine' BDH) are given over 3 or 4 days.

Laird feels that neither PAM nor aqueous procaine penicillin preparations in a single injection of 600,000 units are able to cure infections with strains whose minimum inhibitory concentration (MIC) with penicillin is 0.25 units/ml. or higher.<sup>7</sup> He uses a combination of aqueous procaine penicillin and crystalline penicillin G in a proportion of 3:1 giving a single injection of 800,000 units to males, and 1.2 mega units to females. In one series, he reports 4 failures out of 91 cases. In 2 of the failures the MIC was 0.5 units/ml.<sup>7</sup>

The WHO recommended a mixture of aqueous procaine penicillin 1.2 mega units, and procaine penicillin G with aluminium monostearate (PAM) or benzathine penicillin, 0.6 mega units in one injection.<sup>5</sup> This provides a sufficiently high peak level for the less sensitive strains, and a sufficiently long serum level for the less easily reached gonococci. It also allows epidemiological procedures to be conducted, without risk of re-infection to the patient before they are completed.<sup>5</sup> Aqueous procaine penicillin is considered by many to be the currently available preparation most suited to the cure of gonorrhoea.<sup>20</sup>

The WHO dosage is essentially similar to that recommended by the US Public Health Service.<sup>12</sup> In females, however, 1.2 mega units of benzathine penicillin are given in addition to the dosage of aqueous procaine penicillin and PAM—the injections are given in 2 sites.

Benzathine penicillin has also been tried alone in doses of 0.3-2.4 mega units. The larger doses will produce a penicillinaemia for over a month. It has been shown, however, that the level obtained is insufficient for some of the less sensitive strains which are encountered. In London in 1957, on doses of 0.3-1.2 mega units of benzathine penicillin, a failure rate of 27.4% was reported.<sup>20</sup> Local pain at the site of the injection is more common, and severe, than with PAM.<sup>20</sup>

In general, it can be said that the maximum advantages of short- and long-acting penicillins can be obtained by the use of mixed penicillins.<sup>20</sup>

Earlier treatment at SARMCOL consisted of 4 daily injections of 1.2 mega units of aqueous procaine penicillin.<sup>2</sup> Preliminary follow-up studies suggested that cure was obtained in all cases. A subsequent follow-up study has been less reassuring however, but is still proceeding.

Penicillin has been given orally and by inhalation in the

treatment of acute gonorrhoea.<sup>20</sup> A semi-synthetic penicillin—alpha aminobenzylpenicillin or ampicillin ('penbritin' Beecham Research Laboratories) was given orally in single doses of 0.5 to 1 G.<sup>23</sup> A failure rate of 13.7% was reported. No advantage in increasing the dose over 0.5 G was found. The results compared favourably with those achieved with single injections of aqueous procaine penicillin, and better than those achieved with phenethicillin and phenoxymethyl penicillin.<sup>23</sup>

#### Retreatment

If the discharge persists for 3 or more days after initial treatment, and smears or cultures are still positive, 1.2 mega units of benzathine penicillin plus 0.9 mega units of PAM may prove effective.<sup>11</sup> An alternative method is to double the original dose of penicillin and give the increased dose in a single injection. This dose may be advantageously repeated over a 3-5-day period until all signs and symptoms have subsided and smears and cultures are negative.<sup>12</sup>

If complications of the initial gonococcal infection occur (e.g. conjunctivitis, arthritis, epididymitis or prostatitis) aqueous crystalline penicillin G, 2.4-10 mega units per day, may be given intramuscularly in divided doses at 2- or 4-hourly intervals.<sup>12</sup> Kirby recommends doses of mixed penicillins, of 10-20 mega units per day until signs and symptoms have cleared up and cultures are negative.<sup>22</sup>

#### Treatment of Contacts

The fact that many women are asymptomatic, or have minimal signs, makes careful follow-up mandatory. A follow-up period of 2-3 weeks is advisable in females.<sup>4</sup> All female contacts of known cases of gonorrhoea should be given prophylactic penicillin even if gonococci are not demonstrated in urethral, cervical or vaginal smears.<sup>11</sup> This applies particularly in areas where laboratory facilities for adequate culture, or FA tests, are lacking. Known contacts of either sex could well be given 1.2 mega units of benzathine penicillin plus 0.9 mega units of PAM or aqueous procaine penicillin in one injection.<sup>11, 12</sup>

Large doses of benzathine penicillin will abort simultaneously-acquired syphilis, and will also prevent early re-infection with gonorrhoea.<sup>20</sup> It is nevertheless advisable for patients with gonorrhoea to have repeated serological tests for syphilis for up to 6 months after completion of treatment.<sup>4</sup>

#### Other Antibiotics

In cases where penicillin sensitivity is a hazard and occasionally in infections with relatively insensitive strains of the gonococcus, other antibiotics may be used.

(a) *Sulphonamides*. It has been shown that many strains of the gonococcus are again sensitive to the sulphonamides.<sup>9, 12, 19</sup> Previous experience has shown, however, that the gonococcus rapidly develops resistance to the sulphonamides, so that these drugs would offer only a short-term solution to the problem of penicillin resistance.<sup>9, 12, 19</sup> The value of combined therapy with a sulphonamide plus penicillin has not been proved, but it is equally questionable whether combined therapy has been given an adequate clinical trial.<sup>19</sup>

(b) *Streptomycin*. Many strains of the gonococcus are sensitive to streptomycin, but resistant strains have been found with increasing frequency where streptomycin has been used. In view of the ease with which other organisms

have developed resistance to streptomycin, it would be inadvisable to place much reliance on this antibiotic as a long-term alternative to penicillin.<sup>9</sup> It has also been reported that streptomycin is unlikely to be effective if penicillin has failed.<sup>7</sup> Streptomycin if used, is given in a single dose of 1-2 G. Its use does not mask, or abort, concurrent syphilis.<sup>12</sup>

(c) *Chloromycetin*. Chloromycetin succinate has been given by injection in doses of 1 G. In a series of 53 patients, Willcox reported a failure rate of 4.5%. Pain was experienced at the injection site in 8 cases, and in 4 was associated with faintness.<sup>22</sup> Chloramphenicol has been given with success in doses of 0.5 G orally every 4-6 hours. Total dosage given was 2-3 G.<sup>11-13</sup>

(d) *Tetracyclines*. 1 strain resistant to penicillin, was also resistant to tetracycline in the series described by Rees.<sup>13</sup> In another trial reported by Brittain-Moore and his co-workers, the failure rate of 3 tetracycline derivatives given orally, was not very different from that of cases treated with a single injection of 1.2 mega units of PAM.<sup>16</sup> The antibiotics they used were:

1. Tetracycline 500 mg. orally every 4 hours. Total dosage 3 G.
2. Tetracycline with amphotericin B, 500 mg. orally every 4 hours. Total dosage 3 G.
3. Demethylchlortetracycline—900 mg. (6 capsules) in one dose.<sup>16</sup>

The results of treatment using the 3 broad-spectrum antibiotics were not significantly different.<sup>16</sup> Oxytetracycline, 0.5 G orally every 4 hours, may be given. Total dosage required is 2-3 G.<sup>11</sup> Erythromycin and oleandomycin are equally effective broad-spectrum antibiotics.

*Penicillin sensitivity* provides a hazard in the treatment of venereal disease. It may be suspected where a history of allergy, drug eruption, or previous penicillin reaction is obtained. Conjunctival, scratch, and intradermal tests may be used before injecting penicillin. These tests are significant when positive, but a negative test is no guarantee against a subsequent reaction.<sup>11</sup> The truth of this statement was demonstrated at SARMCOL, when a negative intradermal test in one patient was followed by immediate anaphylactic shock, prostration, vomiting and diarrhoea, after 0.6 mega units of aqueous procaine penicillin were given by injection.

A newer skin-testing technique, using penicilloyl-polylysine has been described.<sup>11</sup> 3,687 patients at venereal disease clinics were tested. 117 patients with a previous history of penicillin sensitivity and 165 with no history of penicillin sensitivity gave positive skin tests. 20 patients with a previous history of penicillin sensitivity, and 3,385 patients with no history of penicillin sensitivity, gave negative skin reactions, and were given penicillin with no after-effects. The use of penicilloyl-polylysine as a skin-testing preparation seems to be accurate and without apparent danger to the patient.<sup>11</sup>

#### Tests for Cure

In the female, adequate culture techniques or, preferably, FA tests are advocated.<sup>4, 11, 22</sup> In the male, absence of urethral discharge and clear 2-glass urine tests one week after infection are considered adequate by some workers.<sup>4, 12</sup> Laird maintains that males must not urinate

for 3 hours before an examination, and that the prostatic secretion should be examined in all cases.<sup>7</sup> My experience at SARMCOL supports this statement. The follow-up study of cases of gonorrhoea in males at SARMCOL is still proceeding, but it has been possible at this stage to show that approximately one-fifth of our cases exhibit pus cells in the expressate, after prostatic massage.

Chronic prostatitis is the most common of all the sequelae of gonorrhoea.<sup>3,4</sup> It is therefore possible that the prostatitis demonstrated in patients at SARMCOL may be a direct sequel of the attack of gonorrhoea. It is appreciated equally, that a non-specific prostatitis may have been present before the patient presented with acute gonorrhoea, but the fact is difficult to establish with certainty.

#### *Non-specific Urethritis*

A discussion of this difficult clinical entity lies outside the scope of the present article. It is sufficient to mention that non-venereal, and venereal, forms are recognized, and that both forms may follow an attack of gonorrhoea.<sup>4,12</sup> No specific causative organism has so far been incriminated, but many organisms, normally present in the genito-urinary tract, may be found in numbers far greater than normal.<sup>4</sup> The widespread replacement of gonorrhoea by these non-gonococcal infections has created a growing problem in venereal disease control.<sup>4</sup>

This form of urethritis is usually penicillin-resistant, and tetracyclines, streptomycin, erythromycin and sulphonamides are advocated in treatment.<sup>4</sup> Kirby draws a cautionary note into this discussion, when he mentions that a mucoid discharge in males may persist for weeks or months after an attack of gonorrhoea.<sup>22</sup> He suggests it is reasonable to regard the discharge as evidence of subsiding inflammation, which usually disappears spontaneously and requires no specific therapy.<sup>22</sup>

#### *Conclusion*

It is with this difficult clinical condition of non-specific urethritis, and conditions such as Reiter's syndrome in mind, that speculation about Burke's<sup>3</sup> views concerning the gonococcus, and Warden's work which he quotes, become so interesting.

Penicillin and the broad-spectrum antibiotics are known to be very effective in the treatment of acute gonorrhoea. Hirsch and Finland, however, draw attention to the fact that few, if any, of the antibiotics may be expected to act on intracellular organisms.<sup>19</sup> Could this view indicate that the gonococcus is not really in an intracellular position in the leukocytes, but lying applied to their surfaces, as maintained by Burke?<sup>3</sup> This might explain its susceptibility to the effect of the antibiotics used in treatment.

#### SUMMARY

Despite the advent of penicillin and the broad-spectrum antibiotics, the gonococcus continues to wreak havoc. Gonorrhoea

is a world-wide problem, and it is estimated that 60,000,000 cases occur annually. It is frequently seen at the rubber company in Howick. There is general acceptance of the view that gonorrhoea is increasing. This is attributed to increased teenage promiscuity, the appearance of relatively insensitive strains of the gonococcus and, in Britain, to the influx of immigrants. Fortunately gonorrhoea appears a milder disease than formerly, and complications are rare.

Penicillin remains the antibiotic of choice in treatment. The tetracyclines, chloramphenicol, erythromycin, oleandomycin, streptomycin and the sulphonamides are also effective, particularly in penicillin-sensitive patients. Frequent reports of penicillin-insensitive strains of the gonococcus are reported, and therefore the dosage of penicillin has been increased from 300,000 units of PAM to 1.2 mega units of aqueous procaine penicillin, plus 0.6-0.9 mega units of PAM or benzathine penicillin, given at one time. An alternative to the above is aqueous procaine penicillin and crystalline G penicillin, in a 3:1 ratio.

Gonorrhoea in males results in early reporting. In females the condition is usually latent; many women are unaware that they are infected. In females adequate culture techniques or fluorescent antibody tests (FA) are usually required for diagnosis. Careful follow-up is essential. In males, follow-up should include examination of the expressate after prostatic massage.

Gonorrhoeal infection is frequently followed by a non-specific urethritis; the exact causal relationship is obscure. The tribe of mimeae may exactly simulate the effects of the gonococcus. These infections are usually penicillin-resistant, and further studies of their prevalence are desirable.

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