SPIRAMYCIN IN THE TREATMENT OF ACUTE GONORRHOEA*

BY

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Introduction

The treatment of gonorrhoea in Denmark is as yet no serious therapeutic problem, as the majority of gonococcal infections can be cured by penicillin. Nevertheless, in an increasing number of cases a higher dosage of penicillin is required than was the case just a few years ago. At the Dermato-venereological Department of the University Hospital, a single treatment dose of 300,000 units of procaine penicillin is still used in the routine treatment of acute uncomplicated gonorrhoea. With this dose, the cure rate in 1961 was found to be approximately 98 per cent. for patients infected with penicillin-sensitive gonococci (the limit between strains with normal and reduced susceptibility was set at an in vitro concentration of 0.038 μg./ml.), while 300,000 units of procaine penicillin cured only 62 per cent. of those patients who were infected with gonococcal strains of reduced sensitivity (Schmidt, 1962).

Penicillin is still considered to be the drug of choice for the treatment of gonorrhoea, as it is essentially non-toxic, and when used in adequate doses results in a high cure rate. Other treatment schedules have been used, for example, penicillin in larger doses or a combination of sodium penicillin and procaine penicillin, and have given excellent results (Nielsen and Schmidt, 1962). The blood concentration of penicillin can also be increased by the administration of probenecid (Jensen, Kvorning, and Nørredam 1963; Schmidt and Roholt, 1965; Lomholt and Berg, 1965). An increasing number of patients report that they cannot tolerate penicillin, and even though this is presumably not so in many cases, it is preferred to withhold penicillin in such instances. Out of a total of 179 patients, mainly from the younger age groups, who attended the out-patients’ department of the University Hospital in 1961 for treatment of gonorrhoea, there were 8 such patients, i.e. 4 per cent., who reported that they could not tolerate penicillin (Schmidt, 1961). Similar information has been obtained in a survey of a series of approximately 10,000 surgical patients (Foged, 1958). A reduction in the penicillin-susceptibility of gonococci involves the risk of several patients requiring a higher dose of penicillin, so that the appearance of new therapeutic agents is of considerable interest.

Spiramycin NFN, isolated in 1954 by Pinnert-Sindico from Streptomyces anbofaciens, is among the more recent drugs which have been found effective against gonococci. Administered perorally, the substance was found to be effective against infections caused by staphylococci, certain streptococci, and gonococci. Willcox (1956) concluded that
SPIRAMYCIN IN THE TREATMENT OF ACUTE GONORRHOEA

Siboulet and Durel (1961) were the first to test spiramycin clinically as a “one minute treatment” in a high number of cases of acute uncomplicated gonorrhoea—in 784 men and 58 women. The treatment consisted of 10 tablets each of 250 mg., i.e. 2.5 g., administered in the presence of the physician; the cure rate was reported as approximately 97 per cent. in men and approximately 98 per cent. in women. In this series, the diagnosis in the men was made by direct microscopy, and the investigation did not include the culture of discharge. A total of 61 strains had been previously isolated, however, and their in vitro susceptibility to spiramycin was determined; 98 per cent. of the strains required less than 1 μg./ml. for total inhibition (Roiron, Rassetti-Nicod, and Durel, 1961). In 13 patients treated with a single dose of 2.5 g., the serum concentration after 2, 4, and 6 hours was on the average 1–2 μg./ml.

Compared several antibiotics in the treatment of gonorrhoea in males, Clarke (1964) found that spiramycin was superior to penicillin. All of his patients were African negroes. The cure rate after penicillin was found to be 67.4 per cent., as compared with 82.2 per cent. for spiramycin in a single dose of 2.5 g. No culture studies were reported from these cases. Aurangabadkar and Yawalkar (1964) treated 32 males with a single dose of 3 g. spiramycin perorally with a cure rate of 87.5 per cent.

In the autumn of 1963 spiramycin was used routinely in the Dermato-venereological Department of the University Hospital in the treatment of patients with acute uncomplicated gonorrhoea; the purpose was to estimate the properties of the agent, with a view to employing it in patients with penicillin allergy and as an alternative drug in cases where penicillin treatment presented difficulties, such as the occurrence of gonococcal strains with strongly reduced susceptibility.

Material and Methods

During the period August to November, 1963, a total of 96 patients, 30 women and 66 men, with acute, newly diagnosed, uncomplicated gonorrhoea received treatment with spiramycin. The treatment consisted of 10 tablets of 250 mg. taken with two glasses of water in the presence of the physician. The patients were not specially selected, as almost all those in whom the diagnosis of uncomplicated gonorrhoea was made during the period in question received this treatment.

Swabs were taken from the urethra in men and from the urethra, cervix, and rectum in women. The swabs were sent the same day, in Stuart’s medium, to the Neisseria Department, Statens Seruminstitut, where plates were inoculated immediately. Direct microscopy was carried out on methylene blue-stained smears from all the men and from 27 women. When gonococci were found by direct microscopy the above treatment was immediately instituted; otherwise the return of a positive culture report was awaited.

In Statens Seruminstitut, susceptibility tests were carried out on the isolated strains as follows: spiramycin (Rovamycin, M & B), penicillin (penicillin G, Leo), streptomycin (di-hydrostreptomycin, Leo), and tetracycline (tetracycline hydrochloride, Lepeitit), with the aid of the plate dilution method, using two-fold dilution steps for spiramycin, four-fold dilution steps for penicillin and tetracycline, and only one concentration (25 μg./ml.) for streptomycin. The results are given as 50 per cent. inhibiting concentration in μg./ml. medium (IC50). As a rule, 100 per cent. inhibition is obtained by twice as high a concentration (Reyn, 1961a and b; Reyn, Bentzon, and Ericsson, 1963). The precision of the susceptibility tests with regard to spiramycin was examined by repeat determination on the same specimen, and by determination on two different specimens from the same patient. The standard deviation of the difference between the results obtained by duplicate determination on 36 specimens was found to be s4 = 0.13 (log IC50). A determination on two different specimens from 8 patients, 5 of whom belonged to pilot investigations, gave the result s4 = 0.10. The two estimates of the standard deviation are not significantly different. The final estimate was 0.12, which corresponds to the precision with which log IC50 can be determined for other antibiotics, by means of the plate dilution method using two-fold dilution steps (Reyn and Bentzon, 1963).

As a control of the treatment, the aim was to obtain two negative post-treatment cultures in men and three in women. Blood specimens for serological tests for gonorrhoea (GR) were taken on the first visit.

Results

Table I shows the distribution of the 96 patients with regard to age and sex. It is seen that half of the infected women were “teenagers”, while the majority

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Per cent.</td>
<td>No.</td>
<td>Per cent.</td>
<td>No.</td>
<td>Per cent.</td>
</tr>
<tr>
<td>15–19</td>
<td>5</td>
<td>8</td>
<td>15</td>
<td>50</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>20–24</td>
<td>30</td>
<td>45</td>
<td>10</td>
<td>33</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>25–29</td>
<td>6</td>
<td>9</td>
<td>2</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>30 and over</td>
<td>25</td>
<td>38</td>
<td>3</td>
<td>10</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>100</td>
<td>30</td>
<td>100</td>
<td>96</td>
<td>100</td>
</tr>
</tbody>
</table>
of the infected men were in the age-group 20–24 years. A similar distribution was found in Lind's material for 1962 (Lind, 1964).

As stated, cultures were made in all cases to verify or to establish the diagnosis, but where direct microscopy of discharge showed gonococci (methylen blue stain), treatment was instituted immediately. As in previous investigations direct microscopy was positive in the majority of male patients, and in all those cases where direct microscopy gave a positive result (64–97 per cent.), the result of culture was also positive. In the remaining two men microscopy was negative, but the cultures were positive.

Direct microscopy of preparations stained with methylene blue showed gonococci in only 5 of 27 women so tested; in the remaining 22 women the diagnosis was not made until the results of culture were obtained. Direct microscopy thus gave the diagnosis in only about 20 per cent. of the cases, in agreement with the results previously reported from the same clinic (Schmidt, 1962).

**Table II**

**Occurrence of Gonococci on Culture from 30 Women**

<table>
<thead>
<tr>
<th>Site</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethra</td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
</tr>
</tbody>
</table>

Cultures were made from the urethra, cervix, and rectum in all 30 women, and Table II shows the distribution of gonococci from these different sites. In 6 women (20 per cent.) gonococci were demonstrated in the rectum, and in 2 the rectum was the sole site from which gonococci were cultured. In 9 women gonococci were demonstrated in the cervix without being found simultaneously in the urethra; in 2 women gonococci were found in the urethra, and not in the cervix, while in 17, gonococci were present in both urethra and cervix. The serological studies showed that of the 30 women in the series, 6 (20 per cent.) had a positive GR, while 9 of the men (14 per cent.) had a positive GR. Wassermann reaction was negative in all patients.

The series includes 7 infective pairs or so-called "true" partners, who reported each other mutually as contacts (Schmidt and Olesen Larsen, 1962). The susceptibility patterns of the isolated gonococci from both partners are set out in pairs in Table III for the four antibiotics. The figure for the male partner is quoted first in the case of each infective pair.

**Table III**

**Susceptibility Pattern for Spiramycin, Penicillin, Streptomycin, and Tetracycline in Gonococci Isolated from Patient and Contact in 7 True Partners**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Spiramycin</th>
<th>Penicillin</th>
<th>Streptomycin</th>
<th>Tetra-cycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>109</td>
<td>0-141*</td>
<td>0-106</td>
<td>&lt;25</td>
<td>0-28</td>
</tr>
<tr>
<td>119</td>
<td>0-168</td>
<td>0-106</td>
<td>&lt;25</td>
<td>0-40</td>
</tr>
<tr>
<td>121</td>
<td>1-13</td>
<td>0-106</td>
<td>&lt;25</td>
<td>1-6</td>
</tr>
<tr>
<td>163</td>
<td>1-60</td>
<td>0-2</td>
<td>&lt;25</td>
<td>1-6</td>
</tr>
<tr>
<td>132</td>
<td>0-100</td>
<td>0-0066</td>
<td>&lt;25</td>
<td>0-2</td>
</tr>
<tr>
<td>183</td>
<td>0-084</td>
<td>0-0066</td>
<td>&lt;25</td>
<td>0-14</td>
</tr>
<tr>
<td>135</td>
<td>0-168</td>
<td>0-0066</td>
<td>&lt;25</td>
<td>0-14</td>
</tr>
<tr>
<td>155</td>
<td>0-168</td>
<td>0-0066</td>
<td>&lt;25</td>
<td>0-14</td>
</tr>
<tr>
<td>151</td>
<td>0-141</td>
<td>0-075</td>
<td>&lt;25</td>
<td>0-8</td>
</tr>
<tr>
<td>149</td>
<td>0-119</td>
<td>0-106</td>
<td>&lt;25</td>
<td>0-8</td>
</tr>
<tr>
<td>167</td>
<td>0-95</td>
<td>0-30</td>
<td>&lt;25</td>
<td>1-6</td>
</tr>
<tr>
<td>174</td>
<td>0-48</td>
<td>0-30</td>
<td>&lt;25</td>
<td>1-6</td>
</tr>
<tr>
<td>188</td>
<td>0-80</td>
<td>0-30</td>
<td>&lt;25</td>
<td>1-6</td>
</tr>
<tr>
<td>171</td>
<td>0-40</td>
<td>0-42</td>
<td>&lt;25</td>
<td>1-6</td>
</tr>
</tbody>
</table>

* 50 per cent. inhibitory concentration in µg./ml. medium

The Table shows that the greatest variation between the susceptibility patterns for patient and contact corresponds to a two-fold dilution step.

As stated, 96 patients underwent treatment with spiramycin 2·5 g., but 18 patients failed to return to the University Hospital for control. Of the remaining 78 patients who underwent control at the University Hospital 65 were cured (83 per cent.) The difference between the cure rates in females and males (22/23 = 96 per cent. against 43/55 = 78 per cent.) is not statistically significant.

Of the 13 uncured patients, 12 were men and one was a woman. All uncured cases were considered to be relapses. They appeared in the clinic from 3 to 17 days after treatment, and 10 of the 13 failures appeared within the first week after treatment. The susceptibility patterns in one of the male patients should be mentioned in particular, as repeated susceptibility tests suggest that the gonococcal strain in this patient changed its susceptibility to spiramycin during the treatment with this substance, since the patient denied exposure to renewed infection during the period of observation. Table IV shows the susceptibility pattern and treatment in this patient.

**Table IV**

**Susceptibility Pattern and Treatment in 1 Patient**

<table>
<thead>
<tr>
<th>Date</th>
<th>Spiramycin</th>
<th>Penicillin</th>
<th>Streptomycin</th>
<th>Tetra-cycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 1, 1963</td>
<td>0-168</td>
<td>0-21</td>
<td>&gt;25</td>
<td>1·13</td>
</tr>
<tr>
<td>Treatment</td>
<td>2·5 g.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spiramycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>August 13, 1963</td>
<td>1·13</td>
<td>0-21</td>
<td>&gt;25</td>
<td>1·60</td>
</tr>
<tr>
<td>Treatment</td>
<td>2·5 g.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spiramycin: not cured</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
It appears from the Table that the spiramycin susceptibility altered, as IC$_{50}$ on second examination was seven times as high as on first examination. The difference in the logarithmic titre value was 0.85, i.e. 7.1 times the standard error. Unfortunately, no susceptibility determination for spiramycin was made on the third examination, but the susceptibility with regard to the other three antibiotics remained unchanged.

This patient was not cured by treatment with Reverin (Hoechst) 350 mg. daily for 2 days. Cure was finally obtained after treatment with procaine penicillin 1-2 mega units plus sodium penicillin 1 mega unit daily for 3 days.

The final series of 78 patients was first divided into three groups according to the degree of spiramycin susceptibility (Table VI; Groups I, II, III, the limits are arbitrary), and a relationship sought between the degree of spiramycin susceptibility and cure rate. Only a very slight tendency to correlation could be observed, however, and when the material was further divided according to the susceptibility to penicillin, any trace of correlation between spiramycin susceptibility and cure disappeared, as the treatment failed with approximately the same frequency within the three groups showing differing susceptibility to spiramycin. On the other hand, a pronounced correlation was found between reduced penicillin susceptibility and treatment failure. A total of 49 patients who were infected with gonococcal strains of varying spiramycin sensitivity, but all sensitive to penicillin, were all cured with spiramycin (2-5 g). The remaining 29 patients were infected with gonococcal strains possessing reduced susceptibility to penicillin; as mentioned, 13 of these (45 per cent.) were not cured by spiramycin treatment. The correlation between reduced penicillin susceptibility and treatment failure cannot be demonstrated in females, of whom only one did not recover.

In order to estimate whether the IC$_{50}$ values for the various antibiotics examined showed any mutual correlation, the 96 strains isolated were grouped according to their susceptibility to penicillin, streptomycin, and tetracycline (Table VII).

Gonococcal strains from three of the remaining uncured 12 patients were examined twice with spiramycin, with identical results. The sero-reaction for gonorrhoea, which was examined in 11 of these 12 patients, was positive in 4 cases. Table V shows the subsequent treatment which cured 11 of the patients after the failure with spiramycin. One patient defaulted.

### Table V

<table>
<thead>
<tr>
<th>Preparation and Dose</th>
<th>No. of Patients</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine penicillin 0.3 mega units</td>
<td>1</td>
<td>Defaulted</td>
</tr>
<tr>
<td>Sodium penicillin 1 mega unit plus probenecid 1 g. x 4 daily for 3 days</td>
<td>1</td>
<td>Cured</td>
</tr>
<tr>
<td>Sodium penicillin 1 mega unit plus procaine penicillin 0.6 mega units for 3 days</td>
<td>1</td>
<td>Cured</td>
</tr>
<tr>
<td>Sodium penicillin 1 mega unit plus procaine penicillin 1-2 mega units</td>
<td>7</td>
<td>Cured</td>
</tr>
<tr>
<td>Reverin (Hoechst) 350 mg. daily for 2 days</td>
<td>1</td>
<td>Cured</td>
</tr>
<tr>
<td>Dihydrostreptomycin 1 g. daily for 2 days</td>
<td>1</td>
<td>Cured</td>
</tr>
</tbody>
</table>

### Table VI

<table>
<thead>
<tr>
<th>Group</th>
<th>Preparation $\mu g./ml.$</th>
<th>Spiramycin IC$_{50}$</th>
<th>Penicillin</th>
<th>Penicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Defaulted</td>
<td>Cured</td>
<td>Not cured</td>
</tr>
<tr>
<td>I</td>
<td>$\leq 0.050$</td>
<td>2</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>0.059-0.100</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>0.119-0.200</td>
<td>2</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>II</td>
<td>$0.24-0.40$</td>
<td>4</td>
<td>22</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>0.48-0.80</td>
<td>9</td>
<td>22</td>
<td>41</td>
</tr>
<tr>
<td>III</td>
<td>$&gt;0.95$</td>
<td>10</td>
<td>3</td>
<td>9 (25%)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td>7</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td>11</td>
<td>43</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>18</td>
<td>65</td>
<td>13 (20%)</td>
</tr>
</tbody>
</table>

* IC$_{50}$ <0.038 $\mu g./ml.$  † IC$_{50}$ >0.053 $\mu g./ml.$
SUSCEPTIBILITY
The relationship between the results of treatment in women, and the occurrence of susceptibility to spiramycin in gonorrhoea. Other authors have shown that penicillin-resistant gonococci have been isolated from patients with gonorrhoea. The present investigation has likewise shown that the susceptibility pattern in "true" partners is very nearly identical, as the susceptibility of the gonococcal strains in question differs at most by a single two-fold dilution step, thus agreeing with previous reports by Schmidt and Olesen Larsen (1962) and Reyn and Bentzon (1963).

The original aim of the study was to investigate the possibility of using spiramycin as an alternative to penicillin in the treatment of acute uncomplicated gonorrhoea. The results show that the cure rate with spiramycin is considerably lower than that found by other authors (Siboulet and Durel, 1961). This might be due to a difference in the susceptibility of the gonococcal strains in the different series, a point which cannot be clarified, as susceptibility tests are missing in the case of the earlier studies. As mentioned above, in the present study it appears that the cure rate following spiramycin treatment is dependent only on the in vitro susceptibility to penicillin. It might be that the higher cure rates obtained by the French workers were due to the fact that in treating gonorrhoea penicillin has been used to a comparatively low degree in France and in North Africa. The cure rates obtained by Willcox (1956), Clarke (1964), and Aurangabadkar and Yawalkar (1964) with a dosage of 2·5–3 g. spiramycin are of the same order of magnitude as that reported in the present paper.

The present material shows that the cure rate following spiramycin treatment (83 per cent.) does not differ from that found in previous series from the same clinic after a dose of 300,000 units of procaine penicillin. If all those who defaulted were in fact cured, and therefore did not attend subsequently, the figures would be 86 per cent. As this series consists of out-patients, it is possible that the treatment failures were actually due to re-infection in spite of an injunction against coitus during the period of treatment. In one patient, who denied the possibility of reinfection, susceptibility tests were performed twice during the period of investigation and it was found that the sensitivity to spiramycin had altered to a considerable degree. Unfortunately, susceptibility tests were only made in 3 of the other patients who were not cured; the sensitivity to spiramycin had remained unchanged in these patients.

In the present study, no correlation has been demonstrated between the in vitro susceptibility to spiramycin and the results of treatment. The susceptibility of the 96 strains examined (IC₅₀) varied by a factor of 32 from 0·05 μg. to 1·60 μg. Hirsch and Finland (1960), examining 36 gonococcal strains, found an eight-fold variation, namely, from 0·4 μg. to 3·1 μg./ml. Roiron and others (1961) found that the MIC (minimal inhibitory concentration) in 61 gonococcal strains varied by a factor of 10 (0·12–1·0 μg./ml.). As the MIC is approximately twice the IC₅₀, there is quite good agreement between these three investigations. No estimation of the spiramycin concentration in patient sera was made in the present study. Chabbert (1955) found a mean concentration

<table>
<thead>
<tr>
<th>Group</th>
<th>Penicillin</th>
<th>Streptomycin</th>
<th>Tetracycline</th>
<th>No. of Strains</th>
<th>Spiramycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Per cent.</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>56</td>
<td>15</td>
</tr>
<tr>
<td>2a</td>
<td>is</td>
<td>s</td>
<td>s</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>2b</td>
<td>is</td>
<td>s</td>
<td>r₂</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>2c</td>
<td>is</td>
<td>s</td>
<td>ls</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2d</td>
<td>is</td>
<td>ls</td>
<td>r</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>2a–2d</td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>96</td>
<td>38</td>
</tr>
</tbody>
</table>

*Is = less susceptible  **Is** = susceptible  *Ir = resistant

The limits for the various grades of susceptibility are as follows:

IC₅₀ for:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (μg./ml.)</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiramycin</td>
<td>≤0·40</td>
<td>susceptible (s)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>≤0·038</td>
<td>susceptible (s)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>≤0·25</td>
<td>susceptible (s)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≤0·80</td>
<td>susceptible (s)</td>
</tr>
</tbody>
</table>

Br J Vener Dis: first published as 10.1136/sti.41.2.120 on 1 June 1965. Downloaded from http://sti.bmj.com/ on September 3, 2023 by guest. Protected by
in the blood (7 adult patients) of 2·7, 2·8, and 1·6 
µg./ml., one, two, and six hours after the ingestion of 3 g. daily. Siboulet and Durel (1961), as mentioned, 
found a mean value in the serum of approximately 1–2 
µg./ml. during a period of 0–6 hours following the 
ingestion of 2·5 g. spiramycin in a single dose, but 
the individual variation does not appear from their 
study. It is known in the case of other antibiotics 
(particularly penicillin) that the individual variation 
can be high (Juncker and Raaschou, 1951; Andresen, 
1955; Pellerat, Maillard, and Carron, 1961; Jensen, 
Lund, and Marner, 1962; Bond, Lightbown, Barber, 
and Waterworth, 1963; Knudsen and Perdrup, 
1963; Yourassowsky, 1963; Schmidt and Roholt, 
1965). An individual variation of the spiramycin 
concentration in serum of the same order of magnitude 
as the variation in the in vitro susceptibility would 
 obscure any possible correlation between the in vitro 
and in vivo results. The results will also be affected 
by other individual factors.

An observation of considerable interest is that all 
the patients who were not cured were infected with 
gonococcal strains possessing reduced susceptibility 
to penicillin. Thus, the present study would appear 
to show that the outlook for cure following spiramycin 
treatment is dependent only on the in vitro 
susceptibility of the gonococcal strain to penicillin.

A reason for this peculiar phenomenon might be 
that in strains with reduced in vitro susceptibility to 
penicillin, metabolic conditions were present of a 
nature that would also reduce the susceptibility of 
these strains to spiramycin in vivo. The absence of 
any chemical relationship between spiramycin and 
penicillin does not exclude such a condition, sup-
posedly based on genetic changes, that would simul-
taneously involve further metabolic changes (Welsch, 
1955). This might, for example, result in the survival 
of bacteria in closed foci, and thus reduce the 
possibility of their being attacked by the spiramycin. 
Watson (1957), for example, found that spiramycin 
penetrated with difficulty through fibrin membranes. 
Results from the few cases of meningococcal 
meningitis treated with spiramycin have also been 
so poor that the use of the drug is contra-indicated 
for the treatment of meningitis (May & Baker, 
1964). Poor penetration might also explain why the 
present study failed to demonstrate any correlation 
between in vitro susceptibility to spiramycin and the 
result of treatment with this drug in the case of 
strains with reduced susceptibility to penicillin 
(Table VI, last column).

In the case of penicillin, streptomycin, and 
tetracycline, the relation between the in vitro sus-
ceptibility of gonococci to these various antibiotics 
corresponds to what has been previously found in 
this country (Reyn, 1961a, b, 1963a, b; Schmidt 
and Olesen Larsen, 1962). Resistance to strepto-
mycin and reduced susceptibility to tetracycline 
have virtually been found only in strains with re-
suced susceptibility to penicillin. This correlation 
could be explained as a result of a selection in 
treatment, starting with penicillin, and only using 
streptomycin or tetracycline for treatment of those 
cases in which the penicillin treatment failed (cf. 
Reyn and Korner, 1958; Reyn, Korner, and Bentzon, 
1958). In the case of spiramycin, not previously in 
use in Denmark, the results can hardly be affected 
by a successive selection of this nature. In the present 
study, a positive correlation was found between the 
susceptibility to spiramycin and each of the other 
three antibiotics. It is possible that in each case the 
correlation is a reflection of the same factor, the 
result of the mutual dependence of these antibiotics. 
It is worthy of note, however, that a correlation can 
be demonstrated between spiramycin and tetra-
cycline in strains which show both resistance to 
streptomycin and reduced susceptibility to penicillin.

The possibility must be considered that the cure rate 
in the present material might have been in-
creased by using a higher daily dose of spiramycin 
and administration of this drug over a longer period 
of time. A single 24-hour dose of more than 4 g. has 
not been reported. Most previous investigators 
treating gonorrhoea by means of spiramycin have 
used 2·5 g., administered as a single dose, and in the 
presence of the physician, just as in the present study, 
and Willcox (1956) found that 2 g. in a single dose 
was unsatisfactory.

If this dose is increased as a result of repeated 
administration during the course of the day, the 
control which has been achieved by the procedure 
used in this and other studies is lost, namely, the 
certainty that the patient does actually consume the 
drug.

Summary

Ninety-six patients, 30 women and 66 men, with 
acute newly diagnosed, uncomplicated gonorrhoea,
were treated with 2·5 g. spiramycin in a single dose; 
18 defaulted. Of the remaining 78 patients, 65 
were cured (83 per cent.). All the patients who were 
not cured were infected with gonococcal strains possess-
ing reduced susceptibility to penicillin. No corre-
lation was demonstrated between the in vitro 
susceptibility to spiramycin and the result of treat-
ment. Possible reasons for this apparent independence 
between the result of treatment and the in vitro 
susceptibility to spiramycin are discussed.
Grateful acknowledgements are expressed to Messrs. May and Baker Ltd. for kindly providing the spiramycin used in this study.

REFERENCES


La spiramycine dans le traitement de la gonorrhée aiguë

RéSUMÉ

On traita 96 malades, 30 femmes et 66 hommes atteints de gonorrhée aiguë non compliquée, récemment diagnostiquée, par une dose unique de 2,5 g de spiramycine; 18 ne se présentèrent pas pour le contrôle. Parmi les 78 restants, 65 furent guéris (83 %). Tous les malades qui ne furent pas guéris étaient infectés par des souches de gonocoque possédant une sensibilité réduite à la pénicilline. On ne trouva pas de rapport entre la sensibilité du microbe in vitro à la spiramycine, et les résultats du traitement. On discute les raisons possibles de cette indépendance apparente entre les résultats du traitement et la sensibilité à la spiramycine in vitro.