The outcome of a particular infection in the individual patient will depend upon the balance between the pathogenicity of the infecting organism and the natural defence mechanisms of the host. However, these defence mechanisms may be impaired by the presence of a structural or functional abnormality in the host which may then favour persistence and possibly progression of the infection. On the other hand a chemotherapeutic substance may also modify the host-parasite relationship and the effectiveness of such a substance is determined primarily by the sensitivity of the infecting organism to the concentration of the chemotherapeutic agent which can be obtained at the site of bacterial invasion in the tissues or body fluids. The mode of action of the chemotherapeutic substance in terms of bactericidal or bacteriostatic effect and whether it acts upon bacteria in both the resting and the dividing phases is probably also of great importance. As a model for investigating the factors concerned in response to chemotherapy, infection of the urinary tract is in some ways the easiest of infections in the human body to study. Although urine, being a waste product, varies in composition it usually supports the growth of those bacterial pathogens liable to invade the urinary tract and which therefore readily multiply in bladder urine. This and the ease with which satisfactory urine specimens can be obtained, allows accurate quantitative bacteriological analysis to be carried out in order to establish precise criteria for the presence or absence of infection. Furthermore, the urinary tract is accessible to both endoscopic and radiological studies which can demonstrate the presence of even relatively minor underlying abnormalities.

In view of this situation it is surprising that relatively little advance has been made in the last ten years in our knowledge of the fundamental processes governing the response of urinary tract infections to treatment. Following the discovery of the sulphonamides, early reports indicated that these compounds were successful in approximately 80% of patients with urinary tract infections, (Huber 1936, Kenny, Johnson and von Haebler, 1937). Although many antibiotics have since been used, the results of treatment with these compounds have been little better. It was soon recognised that the most important factor determining the outcome of treatment was the presence of an underlying structural or functional abnormality in the patient. A review by Kass (1955) showed that the failure rate in primary uncomplicated urinary tract infections was 10-20% almost regardless of the chemotherapeutic agent used, but when infection was associated with an underlying abnormality, approaching 90% of cases failed. Therefore, the main problem in the treatment of urinary tract infection is to devise more effective methods for treating the 10-20% who fail the initial conventional course of treatment as well as those who have an underlying abnormality. It is important to realise that although the former group will contain a substantial number who may subsequently be shown to have organic lesions, in many no underlying
The Results of Treating 188 Patients with Sulphonamide and Subsequent Investigation of those Failing to Respond to Treatment

<table>
<thead>
<tr>
<th>Number treated</th>
<th>Cure at 6 weeks</th>
<th>Cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>188</td>
<td>130</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70%</td>
</tr>
</tbody>
</table>

Reasons for failure

- Emergence of resistant strain: 10%
- Renal abnormality: 20%
- Re-infection with different organisms: 5%

Total cases where reason found for failure: 32
No reason found for failure: 26
Total failure: 58

* In three cases with renal abnormality the infecting organism developed resistance to sulphonamide during treatment.

Importance of Effective Tissue Levels

A number of antibiotics are largely excreted in an active form by the kidneys with the result that high urinary levels are obtained. Since the normal urinary tract has a tendency to spontaneous eradication of bacteria owing to the dilution and wash out effects of urinary flow, the presence of an antibacterial substance greatly facilitates this process. Failure of treatment when using such an antibiotic can be explained either by an obstruction to the flow of urine or to persistence of a bacterial focus of infection in a tissue site inaccessible to an effective concentration of the antibiotic. It is well established that eradication of bacteria is difficult in the presence of urinary tract obstruction but the part played by tissue involvement in determining the response to the chemotherapy has not yet been clearly defined.

There is no doubt that many patients with urinary tract infections have been successfully treated with urinary disinfectants such as mandelic acid (Rosenheim, 1935) which does not give blood levels but it must be remembered that spontaneous cure of even renal tissue infections is probably not uncommon for by no means all patients suffering from clinically typical acute pyelonephritis in the pre-chemotherapeutic era subsequently had persistent infection. However the importance of blood levels is emphasized by the observation that during treatment with nitrofurantoin clinically obvious pyelonephritis may develop despite the disappearance of bacteria from the urine. (Brumfitt, Percival and Carter 1962). This has also been the experience of others (Richards, Riss, Kass and Finland, 1955).

Turck, Browder, Lindemeyer, Brown, Anderson and Petersdorf (1962) treated groups of patients who had chronic urinary tract infections with kanamycin-3-phenyl salicylate, chloramphenicol and demethylchlortetracycline. It was found that there was persistence of infection by the same organism in a high proportion of patients treated with kanamycin-3-phenyl salicylate which gave only negligible serum levels whereas the initial infecting organism was eradicated in a much greater proportion of patients treated with chloramphenicol or demethylchlortetracycline which do give appreciable serum levels. These findings suggest that persistence of infection in a tissue site may be an important reason for failure of treatment.

One of the main difficulties in assessing response of renal tissue infection to chemotherapy is the lack of a simple method which enables such a lesion to be recognised in the individual patient with significant bacteriuria. This is necessary since a proportion of patients with either no symptoms, or with symptoms referable only to the lower urinary tract, may have clinically inapparent infection of the renal parenchyma. We have found (Brumfitt and Percival, 1964) that patients with renal tissue infection regularly show high levels of serum antibody to the infecting organism whereas when infection is confined to the bladder the antibody response usually is either absent or does not exceed the normal range. Furthermore when women with bacteriuria of pregnancy were treated with an eight-day course of sulphonamide, we found that failure of treatment was twice as common in those with raised levels of serum antibody than in those with levels within the normal range, suggesting that treatment of patients with renal tissue infection is more difficult (Brumfitt, Williams, Leigh and Percival 1964).
Relation of Minimum Inhibitory Concentration of Antibiotics to Attainable Blood Levels

For successful treatment of a renal tissue infection, the concentration in the tissue of the chemotherapeutic agent used should exceed the minimum inhibitory concentration (M.I.C) for the infecting organism. Since very little is known about tissue levels obtained during treatment with antibiotics, it is often assumed that the serum levels are similar if not identi-
Fig. 3.—Relationship of ampicillin blood levels to the M.I.Cs. for *Esch. coli* following a single dose (oral and intramuscular) of 500 mg.

Fig. 4.—Relationship of colistin methane sulphonate (polymyxin E) blood levels to the M.I.Cs. for *Esch. coli* following a single intramuscular injection of 1½ million units.

cal to the tissue levels. This assumption may not always be valid especially in the renal medullary tissues where diffusion from the tubules could theoretically lead to tissue levels higher than those in the serum, since the concentration of antibiotic in the renal tubules may be several hundred times greater than that in the serum. On the other hand, a substantial proportion of some antibiotics is bound to serum protein and may not be available for diffusion into tissues. Therefore, the serum level may give a false indication of the con-
centration of antibiotic available for tissue penetration. However, at the present time, since tissue levels can be measured only with difficulty in experimental animals, and usually not at all in the patient, serum levels are the best indication which we have of tissue levels of antibiotic.

The minimum inhibitory concentration of some antibiotics for various strains of *Esch. coli* in relation to the blood levels attainable on conventional therapeutic dosage are shown in Figs. 1-4. Fig. 1 shows that with sulphamethoxypyridazine most *Esch. coli* strains isolated from women with bacteriuria of pregnancy and patients with symptomatic infections in general practice were inhibited by 40 μg per ml. and blood levels capable of inhibiting growth of the infecting organisms were commonly obtained following standard dosage. Similar results are obtained for tetracycline (Fig. 2) but following a conventional oral dose of ampicillin (500 mg.) a far greater proportion of *Esch. coli* strains isolated from patients with urinary tract infections fall outside the therapeutic range as judged by comparison of the M.I.C. and serum level (Fig. 3). It can be seen that much better levels can be obtained by the parental administration of a similar dose of ampicillin (Fig. 3) or colistin methane sulphonate (Fig. 4). The serum level following parenteral injection is also more predictable as the variation in absorption which occurs following oral dosage is avoided.

These findings which are relevant to the general problem of treatment of systemic infections due to Gram negative bacteria, suggest a reason for the difficulty in treating renal tissue infections since with all the chemotherapy agents so far available the peak serum levels barely exceed the M.I.C. for many of the infecting organisms and often levels above the M.I.C. are not obtained at all. The results expressed in Figs. 1-4 apply to organisms found to be sensitive by conventional paper disc testing and therefore it should be remembered that a proportion of organisms have been excluded by this procedure. In contrast, treatment of systemic infections due to Gram positive organisms presents no such difficulties because the M.I.C. of the effective antibiotics for sensitive Gram positive organisms are so much lower than with Gram negative bacteria (Fig. 3).

**Ampicillin**

Ampicillin is active against many strains of *Esch. coli, Proteus mirabilis* and *Strept. faecalis* (Rolinson and Stevens, 1961) and like other penicillins, it has low toxicity and is bactericidal. The development of resistant variants during treatment is very uncommon (Brumfit and others 1962, Trafford, McLaren, Lillicrapp and Barnes, Houston and Knox, 1962) and activity in the urine is little affected by pH variation (Brumfit and Percival 1962). In our view these properties suggested that ampicillin was a suitable agent for the treatment of urinary tract infections due to sensitive organisms and in particular for those in whom there is infection of the renal tissue. We therefore, decided to assess the value of ampicillin in treatment and have now used it in three different groups of patients.

**TABLE II**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Total</th>
<th>Cure at 6 weeks</th>
<th>Cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Esch. coli</em></td>
<td>30</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>11</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td><em>Paracolon spp.</em></td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total for all organisms</td>
<td>44</td>
<td>36</td>
<td>8</td>
</tr>
</tbody>
</table>

**Ampicillin in Initial Treatment of Urinary Tract Infection**

The results of treating 44 patients from hospital and domiciliary practice with 500 mg. ampicillin eight hourly for five days are shown in Table II. All organisms were sensitive to 10 μg. ampicillin per ml. or less. The overall cure rate, as judged by clinical and bacteriological cure when examined six weeks after the end of treatment, was 82% and similar results have been obtained by others (Trafford et al. 1962, Anderson, Kennedy, Plorde, Shulman and Petersdorf 1964). No attempt was made to follow the eventual clinical progress of the patients who failed or to establish reasons for failure.

**Ampicillin in the Treatment of Urinary Infections which have Failed to Respond to Sulphonamide**

Because of the cheapness, low toxicity and satisfactory serum and urinary levels obtained with sulphonamides and because a high proportion of the infecting organisms in patients from general practice or in women with bacteriuria of pregnancy are sensitive we use the short acting sulphonamide sulphadimidine or the long acting compound sulphamethoxypyridazine initially in these patients (Brumfit et al.)
TABLE III
Results of Treatment using either Ampicillin or Tetracycline in Cases of Urinary Tract Infection which Failed to Respond to Sulphonamide

<table>
<thead>
<tr>
<th>Organism</th>
<th>AMPICILLIN Failure at 6/52</th>
<th>Cure rate %</th>
<th>Failure at 6/52</th>
<th>Cure rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esch. coli</td>
<td>26</td>
<td>11</td>
<td>58%</td>
<td>11</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Paracolon spp.</td>
<td>2</td>
<td>0</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Aerobacter aerogenes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Total for all organisms</td>
<td>30</td>
<td>12</td>
<td>60%</td>
<td>14</td>
</tr>
<tr>
<td>Renal abnormalities</td>
<td>7 (58%)</td>
<td>—</td>
<td>—</td>
<td>2 (30%)</td>
</tr>
</tbody>
</table>

1964). However, if these patients fail to respond a second course of sulphonamide is usually unsuccessful even though the organism remains sensitive. In a series of 10 patients with sensitive organisms who failed to respond to sulphonamide only two (20%) were cleared of infection by a second course of sulphonamide and we have discontinued this regime of treatment.

If sulphonamide failures were treated with ampicillin (500 mg, eight hourly for seven days) the cure rate was 60% which though lower than the 82% when ampicillin was used initially was nevertheless substantial. If blood and urine levels of oral ampicillin and sulphonamide are compared and these results related to the M.I.C. of the organisms treated (Figs. 1 and 3) the reason for success of ampicillin and failure of sulphonamide is not immediately clear since blood levels in relation to M.I.C. are more satisfactory with sulphonamide. The possibility that the better results with ampicillin may have been a reflection of the greater effectiveness of a bactericidal rather than a bacteriostatic antibiotic is not supported by the finding that treatment of sulphonamide failures with tetracycline gave results apparently almost as good as ampicillin (Table III). However, investigation of the patients in whom infection by the same organism persisted despite treatment with sulphonamide and then either ampicillin or tetracycline showed the presence of underlying abnormalities in seven out of 12 failures in the ampicillin group and two out of seven in the tetracycline group (Table III). The abnormalities found included renal calculi and congenital lesions such as calyceal cyst and double ureter and pelvis.

Parenteral Ampicillin
Where it was felt necessary to obtain blood levels in excess of the M.I.C. of the infecting organisms, we have treated a number of hospital patients with ampicillin given by intramuscular injection (500 mg. six hourly for five days).

Patients were divided into three groups according to the presenting features and the groups and results of treatment are shown in Table IV. In eight patients with clinical features of acute pyelonephritis a rapid response was obtained and all patients showed clinical and bacteriological cure at follow-up examination six weeks after the end of treatment. On the other hand, only seven of the 14 patients with persistent infection by the same organism associated with an underlying renal abnormality were successfully treated and five of these successes had become infected by a different organism during the six week follow-up period. The results were somewhat better where persistent infection was not associated with a demonstrable abnormality, six of nine patients being cured but in two of these infection by a different organism had occurred when examined six weeks after the end of treatment.

Conclusions

Initial Treatment of Urinary Tract Infection
If the high incidence of chronic renal disease resulting from urinary tract infection is to be reduced effective treatment of the primary attack is required and because of the unreliability of symptoms as a guide to the presence of infection (Mond, Percival, Williams and Brumfitt 1964) a specimen of urine should be taken before starting empirical treatment and therapy immediately adjusted where the organism is found to be resistant. Patients known to be susceptible to urinary tract infection, e.g. pregnant women, diabetics, should have the urine screened for bacteriuria. Since most patients remain ambulant and a number are at work some form of oral therapy is desirable in the first instance.

As the majority of strains of Esch. coli and Proteus mirabilis which cause spontaneous
infection in domiciliary practice are sensitive to sulphonamide (Mond et al., 1964) we usually recommend this therapy in the first instance and the patient is seen three days later when the results of culture and sensitivity tests are available. If the organism is sensitive to sulphonamide this treatment is continued for a further 5-10 days and the urine re-examined four days after the end of treatment and again six weeks later if clear of infection. Patients with a history of sulphonamide sensitivity are given ampicillin 500 mg. t.d.s., for seven days as primary treatment.

The Treatment of Sulphonamide Failures

Sulphonamides are successful in eradication of primary infections due to sensitive organisms in about 75% of patients. Of those who fail, most are due to the persistence of sulphonamide sensitive strains within the renal tract although development of resistant mutants during treatment occurs in some cases. For treatment of these failures we use oral ampicillin which is bactericidal, there is little tendency to development of resistance and it is little affected by pH variation of the urine. With regard to the blood level found after oral administration, there is evidence that this frequently does not exceed the M.I.C. of infecting Esch. coli strains (Brumfitt et al., 1962; Neumann, 1962). However, the extent of diffusion of antibiotics in the renal tissues is at present unknown but the satisfactory clinical results with ampicillin using dosages which give blood levels which barely reach the M.I.C. of the infecting organism suggests that concentration of the antibiotic may occur in the renal tissues as well as in the urine (Brumfitt, Percival and Williams 1964).

In summary we use oral ampicillin for treating urinary tract infections due to sensitive organisms in the following circumstances:

1. As initial treatment for patients who have a history of hypersensitivity to sulphonamide or when the infecting organism is resistant to sulphonamide.

2. In patients who have typical clinical features of pyelonephritis (indicating extensive renal involvement).

3. Where treatment with sulphonamide has failed.

It must be emphasized that the duration of therapy should not depend upon the relief of symptoms and a minimum of seven days therapy should be given no matter how quickly symptoms subside. Over half the patients in our series who failed to respond to sulphonamide and ampicillin were found to have organic abnormalities which in many cases were amenable to surgical treatment. Therefore failure to respond to both sulphonamide and ampicillin is a clear indication for further investigation by the radiologist and genitourinary surgeon.

Parenteral Ampicillin

The persistence of infection without organic abnormality means that the renal lesion is more inaccessible and parenteral therapy aimed at producing higher blood levels is indicated. The substances available for this purpose are colistin methane sulphonate, streptomycin and kanamycin and parenteral ampicillin. Which of these antibiotics is most effective in treating severe and persistent renal infections remains to be elucidated.

Injections of 500 mg. ampicillin are required at intervals of six hours or less to maintain adequate blood levels and therefore treatment is best given in hospital. We consider the indications for parenteral therapy to be as follows:

(a) For patients who have been given an adequate trial of oral therapy, but infection by the same organism persists in the absence of a demonstrable renal lesion.

<table>
<thead>
<tr>
<th>Group</th>
<th>Diagnosis</th>
<th>Number studied</th>
<th>Immediate Success</th>
<th>Immediate Failure</th>
<th>Follow-up Success</th>
<th>Follow-up Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Acute pyelonephritis needing urgent treatment.</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>Persistent infection with abnormality</td>
<td>14</td>
<td>9</td>
<td>5</td>
<td>7*</td>
<td>7</td>
</tr>
<tr>
<td>III</td>
<td>Persistent infection no renal abnormality</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

*Two patients in group 3 and five in group 2 have become re-infected with a different organism.
(b) For patients with pronounced clinical features of acute pyelonephritis where rapid control to limit renal damage is desirable.

(c) For patients known to have extensive renal damage where there is a danger of infection precipitating renal failure as well as extending the renal lesion.

(d) Post-operative patients where oral therapy is impracticable or where absorption is in doubt.

Finally, we do not wish to claim that ampicillin is superior to all other drugs in the treatment of urinary tract infection. More comparative trials are needed before the superiority of one antibiotic over another can be established.

REFERENCES

TREATMENT OF URINARY TRACT INFECTIONS WITH AMPICILLLIN

Peter Naumann
From the Institute of Clinical Bacteriology and Serology of the University of Hamburg.
(Director: Professor G. B. Roemer).

The therapeutic evaluation of a new antibiotic should not be carried out solely according to clinical criteria. The course of a bacterial infection depends on too many individual factors and imponderables. The therapeutic value of an antibiotic cannot, therefore, always be assessed objectively by comparing clinically cured or improved cases with those who failed to respond. After all, a not inconsiderable number of infections is cured without any or with only inadequate therapy and may then be quoted as evidence in favour of a preparation which actually is ineffective. On the other hand, failure to respond may be wrongly ascribed to an "ineffective" antibiotic, even though the bacterial process has been controlled, or is capable of being controlled, provided the drug is given in adequately high doses. "Clinical cure" is a complex event which depends on the defensive potential of the body as a whole, and it is not always easy to make a true assessment of the part played by the antibiotic—both in the cured case and in that which fails to respond. This applies particularly to infections of the urinary tract, for even after successful eradication of one organism re-infection by an unrelated bacterial strain frequently results in apparent failure of therapy. For this reason assessment of a drug such as ampicillin should not be based on the number of "clinical cures", but primarily on the consideration whether the bacteriological effect has been attained which should be expected from this antibiotic.

Present Series
Using the bacteriological examination of the urine to diagnose the presence of infection, an attempt has been made during 1963
An Assessment of Ampicillin in the Treatment of Urinary Tract Infection
W. Brumfitt, D. A. Leigh, A. Percival and J. D. Williams

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