PENICILLIN TREATMENT OF NEUROSYPHILIS

A STUDY OF FORTY-FIVE CASES THAT HAD PREVIOUSLY RECEIVED CHEMOTHERAPY

LESLIE PAXTON BARKER, M.D.

From Department of Dermatology and Syphilology, College of Physicians and Surgeons, Columbia University, New York and the Department of Dermatology and Syphilology, St. Luke's Hospital, New York

This study has been undertaken as an endeavor to determine the influence of penicillin therapy on late neurosyphilis which has failed to respond to what was once considered "sufficient" chemotherapy. For the past twenty-three months it has been our privilege to treat, observe and record 45 patients, representing virtually all phases of the disease, all of whom had had previous unsuccessful chemotherapy. Presented here, with brief comparisons to other current studies which do not emphasize former treatment, are the clinical and serologic observations of these 45 cases, followed one to two years after penicillin treatment.

It is, of course, evident that at least a decade is required to attempt to evaluate adequately the results of any treatment upon a disease so complex as late neurosyphilis. Penicillin therapy is still in its infancy and while the indications are that its ultimate results may be more satisfying than any preceding treatment, including fever therapy, all that can now be reported of this relatively new drug are careful and comparative analyses of its therapeutic progress. To our advantage, however, are the improvement in the purity and potency of commercial penicillin and the experimentation with various administration techniques. We know now which of the present forms of penicillin is most actively spirocheticidal. And, we have also learned that for favorable results it is apparently unnecessary to obtain, through means of administration, a penicillin level in the spinal fluid. These recent developments have caused some of the earlier reports on penicillin's use to become of questionable value, but enable syphilologists now to draw some conclusions, or at least read a trend of the drug's effectiveness.

Before we report our findings, it is also well to note that the effects of any drug on the clinical manifestations of neurosyphilis are difficult to appraise because there are no acceptable criteria for the quantitative measurements of the clinical improvement of the disease. The degree of clinical betterment is too dependent upon the individual interpretations of the symptoms. The most scientific quantitative evaluation of the effect of a medication on neurosyphilis is the response of the blood and spinal fluid abnormalities. Unfortunately, in neurosyphilis the blood serology on the one hand, and the spinal fluid and symptomatic response to treatment on the other, do not parallel each other.

Our series of 45 cases, analyzed below, include various categories of late neurosyphilis. The group consists of ambulatory clinic patients who were hospitalized

Received for publication November 22, 1947.
and injected intramuscularly with the aqueous solution of sodium penicillin at three hour intervals over an 18 to 21 day period. Total dosages ranged from 8,000,000 to 12,000,000 units. All patients had received more than 15 arsphenamine and at least 15 bismuth and mercury injections, the majority having received many more. Some had had tryparsamide or aldersone as well. Several had been given fever therapy, but not within the two years preceding penicillin treatment. When penicillin was started, because of this previous therapy, only a few of the cases showed spinal fluid abnormalities other than positive spinal fluid serology.

In the more recent published reports (1-4), certain facts on the penicillin treatment of neurosyphilis seem to stand out. Generally, it is agreed that the abnormal spinal fluid responds to penicillin in the following order of frequency:
2. Total protein drops more slowly than cell count—but in many instances will return to normal within 6 to 9 months.
3. The colloidal gold curve does not respond as often or as rapidly as the total protein.
4. Serologic reaction is the last and least likely to respond to treatment, although in many cases it will become normal or decrease in titer as early as 2 to 6 months after treatment.

Current studies (1-4), emphasize, too, that the most striking immediate response which syphilitic patients seem to experience from penicillin is its "tonic" effect. They "feel much better" and often gain weight and strenth quickly and nervousness disappears.

ANALYSES OF RESULTS OF PENICILLIN THERAPY IN 45 CASES OF LATE NEUROSYPHILIS PREVIOUSLY TREATED WITH CHEMOTHERAPY

I. Response of spinal fluid cell count

Eight patients had, at the beginning of treatment, an increase in the spinal fluid cell count ranging from 12 to 88 cells. The pleocytosis occurred in cases who had previously received the least chemotherapy. The cell counts returned to normal within 6 months.

II. Response of total protein

Of nineteen cases with abnormally high total protein in the spinal fluid (chart 1) 10 became normal within 6 months, 13 within 12 months and one at 18 months. Three cases were declining at the end of 18 months. Eight of the 27 patients whose spinal fluid serology was reversed had a high protein at the beginning of treatment. In each instance the total protein became normal before the serology.

III. Response of the colloidal gold test

Only 5 cases (paresis) had first zone type of colloidal gold curves at the time of penicillin therapy. Two of the paretic cases with normal and one with abnormal gold curve had previously received malaria treatment. Three of the abnor-
PENICILLIN TREATMENT OF NEUROSYphilis

171

mal colloidal gold curves became normal 12 months after penicillin treatment. The other 2 abnormal gold curves showed no substantial change 12 to 18 months after penicillin—one of these had had malaria therapy.

IV. Response of spinal fluid serology—various types of neurosyphilis

Taken as a group representing various categories of neurosyphilis (chart 2), 27 patients (60%) had a reversal of the spinal fluid serology, and an additional 12 (26.6%) showed a declining titer at the time the last test was done. Six cases (23.4%) showed no response. Considering the amount of former chemotherapy most of these patients had received, this is a quite remarkable serologic response.

Discussion of chart 2: Stokes et al. (5) reported 52% of their series of 179 cases of all phases of neurosyphilis had a return to normal, or near normal, of the

CHART 1
Total protein response—19 cases

<table>
<thead>
<tr>
<th>MONTHS*</th>
<th>DECLINING</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>No. of Cases</td>
<td>5</td>
</tr>
</tbody>
</table>

* Time required after Penicillin treatment for reduction of spinal fluid total protein.

CHART 2
Spinal fluid serology*

<table>
<thead>
<tr>
<th>REVERSED TO NORMAL</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal serological response</td>
<td>No.</td>
</tr>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td></td>
<td>No.</td>
</tr>
</tbody>
</table>

* Effect of penicillin treatment on spinal fluid serology. All categories of neurosyphilis.

spinal fluid findings and a “striking improvement” in 72% of all cases during the first year after penicillin.

Curtis and associates (6) obtained a spinal fluid improvement in 62% of their 118 cases treated with penicillin alone and 81% improvement with penicillin plus malaria.

V. Response of spinal fluid in relation to duration of post-penicillin observation period

When analyzed from the standpoint of time after treatment (chart 3), it will be seen that the greatest improvement took place in the first 12 months after penicillin. Twenty-three of our 27 cases which showed a reversal of spinal fluid serology did so in 12 months and 9 (additional) cases showed a reduction in serologic titer within the first year after penicillin treatment.

Discussion of chart 3: In the Stokes et al. (7) report of 361 cases of neurosyphilis,
the greatest improvement in spinal fluid findings occurred in the first 120 to 200 days after penicillin treatment (with only a slight tendency to relapse) and continued to the end of second year. These cases showed little added betterment when followed through the third year. Stokes concluded that a levelling-off process in spinal fluid improvement happens after the second year. Curtis and associates (6) among their cases found the most rapid serologic response in the first 90 days after penicillin.

**CHART 3**

*Spinal fluid serologic response*—45 cases

<table>
<thead>
<tr>
<th>MONTHS</th>
<th>NORMAL</th>
<th>IMPROVED</th>
<th>UNIMPROVED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. cases</td>
<td>Per cent</td>
<td>No. cases</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>13.3</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>13.3</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>24.4</td>
<td>2</td>
</tr>
<tr>
<td>18</td>
<td>3</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>1</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Total...</td>
<td>27</td>
<td>60</td>
<td>12</td>
</tr>
</tbody>
</table>

* Spinal fluid serologic response in relation to period of observation tabulated in months after penicillin treatment.

**CHART 4**

*Spinal fluid serology*

<table>
<thead>
<tr>
<th>DURATION IN YEARS</th>
<th>NUMBER OF CASES</th>
<th>Reversed to normal</th>
<th>Improved</th>
<th>Unimproved</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-5</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>5</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>over 15</td>
<td>10</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

* Relation of duration of disease to response of spinal fluid serology (all categories of neurosyphilis).

**VI. Response to penicillin therapy in relation to duration of disease**

All our patients who had had neurosyphilis for less than 10 years showed reversal of the spinal fluid serology while 4 of the 6 cases which did not improve had been diseased for over 16 years. Although the number of cases is admittedly small, results tend to indicate that the more recent the disease, the better is the response to penicillin. (In general, this was also true with former methods of treatment.)

**VII. Response of spinal fluid serology in relation to amount of previous chemotherapy**

Chart 5 demonstrates the spinal fluid serologic response in relation to the amount of previous chemotherapy. Of the 17 patients who had received 15 to
20 injections of an arsenical and an equal number or more of bismuth or mercury, 11 cases (64.7%) had a reversal of the spinal fluid serology. Four cases (23.5%) were reduced in serologic titer and in 2 cases (11.8%) there was no improvement. Of the 28 who had received over 20 arsenical injections and as many or more bismuth or mercury, 16 (57.1%) had a reversal of the spinal fluid serology. Eight cases (28.5%) had a declining titer while 4 (14.4%) showed no change. These figures would suggest that the amount of previous chemotherapy had very little, if any, bearing on the spinal fluid response to penicillin.

**VIII. Response of spinal fluid serology and symptomatic improvement in various categories of neurosyphilis**

**Paresis** (chart 6)

**Spinal fluid response:** Three (37.5%) of our cases had a reversal of the spinal fluid serology while another 3 (37.5%) showed a declining serologic titer, for a total of 75% improved and 25% unimproved.

**Symptomatic improvement:** Six (75%) of our 8 cases evidenced symptomatic improvement, but only 2 (25%) sustained it. It was necessary to hospitalize

<table>
<thead>
<tr>
<th>Previous chemotherapy</th>
<th>Reversed to normal</th>
<th>Improved</th>
<th>Unimproved</th>
<th>Total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-20</td>
<td>11</td>
<td>4</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>over 20</td>
<td>16</td>
<td>8</td>
<td>4</td>
<td>28</td>
</tr>
</tbody>
</table>

*Relation of amount of previous chemotherapy to response of spinal fluid serology (all categories of neurosyphilis). Treatment represents number of injections of an arsenical. All had an equal number, some many more, bismuth or mercury.

and give malaria therapy to one patient who, two months after penicillin therapy, displayed rapid deterioration. Sustained improvement resulted. Another patient (one subject to convulsive seizures, mental fogginess, nervousness and irritability) in the previously improved group, responded remarkably for three months after his first course of 8,000,000 units of penicillin. Then his symptoms recurred and 11,000,000 units were administered over a 21 day period. Symptoms disappeared only to recur again after two months, at which time he was given penicillin and fever. For the six ensuing months, until lost from observation, he remained normal. Two other paretic cases evidenced no symptomatic improvement.

**Tabes dorsalis** (chart 6)

**Spinal fluid response:** Four (44%) showed a reversal of the spinal fluid serology while 3 (34%) declined in titer—a total of 78% improvement and 22% serologic failure.

**Symptomatic improvement:** Of 4 cases with shooting pains, 2 displayed im-
provement and 2 showed none. Two patients with mild paresthesia had sustained and complete relief. Of 3 patients with weakness of the legs, all improved but one, in whom the symptoms returned 6 months later.

Asymptomatic neurosyphilis (chart 6)

Spinal fluid response: Our asymptomatic group showed the most striking serologic response. Seventeen cases (71%) had a reversal and 5 (20.5%) a reduction in serologic titer. Only 2 cases (8%) failed to improve.

Late congenital syphilis (chart 6)

Spinal fluid response: The group of 4 late congenital neurosyphilis all showed improvement in their serologic titer while in 3 cases the spinal fluid serology was reversed to normal.

Discussion of chart 6: There is considerable variance of opinion among the syphilologists as to the efficacy of penicillin in paresis.

Thomas (8) said that his results with penicillin alone were equally as good symptomatically and serologically in all categories of neurosyphilis (paresis included) as with fever. Stokes and his associates (7) claimed that malaria, for

<table>
<thead>
<tr>
<th></th>
<th>PARESES AND TABO PARESES</th>
<th>TABES</th>
<th>ASYMPTOMATIC</th>
<th>LATE CONGENITAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>37</td>
<td>3</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Per cent.</td>
<td>37+</td>
<td>34+</td>
<td>8+</td>
<td>75+</td>
</tr>
</tbody>
</table>

N = Reversed serology, I = Declining titer, U = Unimproved, T = Total number of cases.

Clinical improvement of paresis, was superior to penicillin alone only when compared with the first year or two of penicillin responses, but that the penicillin results rapidly overtook malaria in the second year and equalled it in the third year of observation. Stokes observed that it begins to appear as though penicillin alone may equal malaria in paresis.

Reynolds et al. (9) found that their paretic patients who received penicillin and malaria achieved more rapid improvement in spinal fluid than those who received penicillin alone. Rose and Solomon (10) were of the opinion that penicillin alone is an unsatisfactory method of treatment. O'Leary in his comment on the Rose and Solomon paper stated that he had not seen penicillin alone produce a remission of paresis and that whatever improvements he had observed over and above arrest had been of a transient character, while penicillin-malaria not only achieved complete remission, but 5–10% more cases are benefited by the combination than by the use of malaria alone.

Curtis and associates (6) in treating paresis and tabo-paresis with penicillin obtained 57% clinical and 70% spinal fluid improvement with penicillin alone and 64% clinical and 71% spinal fluid improvement with penicillin-malaria.
In the treatment of *tabes dorsalis*, the majority of syphilologists believe that penicillin alone equals or is more effective than malaria therapy. Lightning pains, weakness of legs, paresthesia seem commonly to respond to penicillin, and gastric crises (4) ataxia and incontinence (7) have been reported to improve.

Curtis *et al.* (6) found spinal fluid improvement in all 23 tabes dorsalis cases treated with penicillin alone. Their cases exhibited no apparent difference in clinical or spinal fluid improvement whether given penicillin alone or penicillin-malaria combination. Conclusions from this study were that penicillin alone is the preferred treatment for tabes dorsalis because it is a simpler and less debilitating procedure than penicillin-malaria.

Stokes (7), however, discovered, in his series of tabes dorsalis cases, that more symptomatic improvement was obtained in the second and third year after penicillin alone than with malaria. The percentage of spinal fluid normality was from one half to twice as great in the second and third years of penicillin therapy as with malaria. When near normals were added to normal fluids, the results obtained with penicillin alone were twice as good by the second year as those reported for malaria.

Findings indicate that in *asymptomatic neurosyphilis*, 40 to 70 per cent of spinal fluids became normal or near normal at the end of three years after penicillin therapy, depending on the duration of the disease and on the degree of positivity of the spinal fluid.

Hahn and his associates (11) pointed out that the more strongly positive the initial spinal fluid examination, the less favorable is the prognosis in asymptomatic neurosyphilis.

Moore and Mohr (4) had 77% reversal in 35 cases of early asymptomatic neurosyphilis and only 18% reversal of spinal fluid serology in 43 cases in the later stage of the disease. Some of their cases, however, were observed for only three months.

**IX. Response of optic atrophy**

Three cases showed no symptomatic improvement although 2 did not progress. There was no betterment in the visual field in any of these cases. While clinical improvement as well as improvement in the visual field have been reported, (4–6, 12, 13), in cases of optic atrophy treated with penicillin alone, it is generally accepted that penicillin-malaria is the preferred treatment.

**X. Response of blood compared with spinal fluid response**

Thirty-five (77.7%) of our 45 cases had positive blood serologies at the start of penicillin treatment. Nine (24.7%) had a decrease in reagin titer of the blood after treatment. Three (6.6%) were reversed to negative. A reduction in titer or reversal of spinal fluid serology was present in 84.4% of the cases.

Of the 27 cases whose spinal fluid serology was reduced to normal 3 (11%) had reversal of the blood serology and 5 (18.8%) showed a decrease in blood titer while 7 (26%) had negative blood serologies at start of treatment.

The 11 cases whose spinal fluid serology was reduced in titer by penicillin
included 3 cases which showed a reduction in blood titer. None was reversed. One of the 6 cases which demonstrated no spinal fluid serologic changes had a reduction in blood titer.

Discussion of chart 7: It is apparent from the above findings that the response of the reagin titer of the blood to penicillin therapy is no gauge to the spinal fluid or symptomatic improvement in neurosyphilis.

In Stokes (7) series 74% of his cases of all types of neurosyphilis showed spinal fluid improvement while only 24% showed improvement of the reagin titer of the blood.

Penicillin reactions in the 45 cases

Three of our series had mild to moderate Herxheimer reactions. Four suffered temperature reactions, in elevations of 1 to 2 degrees on the 4th to 7th days, lasting only 24 to 48 hours. One patient had a delayed anaphylactic reaction similar to the syndrome of delayed serum sickness. The three urticaria reactions which occurred were controlled with Benadryl.

### CHART 7

**Blood and Spinal Fluid Serology***

<table>
<thead>
<tr>
<th></th>
<th>REVISED TO NEGATIVE</th>
<th>DECLINING TITER</th>
<th>UNIMPROVED</th>
<th>TOTAL CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal fluid</td>
<td>27</td>
<td>12</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>Blood</td>
<td>3</td>
<td>6</td>
<td>26</td>
<td>35</td>
</tr>
</tbody>
</table>

*Comparison of blood and spinal fluid serologic response. 35 of the 45 cases had positive blood serology at the beginning of treatment.

**SUMMARY AND CONCLUSION**

With the aim of evaluating the relation of previous chemotherapy and the results of penicillin treatment in neurosyphilis, 45 patients, representing various phases of the disease, were given 8,000,000 to 12,000,000 units of penicillin and followed for one to two years. It was found that a large majority of these cases which had failed to respond to chemotherapy subsequently responded to penicillin treatment and that the amount of former chemotherapy did not alter the responses to penicillin of the spinal fluid cell count, total protein, colloidal gold curve or serology.

In spinal fluid serologic response (various categories of neurosyphilis) 60% of cases reversed to normal, 26.6% declined in titer and 23.4% remained unchanged. The greatest improvement in serologic response occurred in the first twelve months after treatment and generally the more recent the infection, the better were the results of penicillin.

Seventy-five per cent of *paretic* cases showed serologic improvement or reversal and 75% experienced rapid symptomatic progress, but only 25% sustained it. Among the cases of *tabes dorsalis* 78% had serologic betterment, and typical
symptoms (i.e. shooting pains, paresthesia, weakness of legs) were relieved in many instances. The asymptomatic neurosyphilitics had 71% reversal of the serology and 20% reduction of serologic titer. Only 8% failed in serologic improvement. The 4 cases of late congenital asymptomatic neurosyphilis (three of which reversed to normal) all showed serologic improvement. In the three cases of optic atrophy no change, either of symptoms or by examination, took place.

24.7% of the 45 cases had reduction of reagin titer of the blood while 6.6% were reversed to negative, evidencing that blood response is no gauge to the spinal fluid or symptomatic improvement of neurosyphilis.

The reactions to penicillin in the cases here reviewed were: 3 moderate Herxheimers, 4 mild temperature rises, 1 delayed anaphylactic and 3 urticarias. This study also substantiated the fact that penicillin is superior or equal to malaria in treating all phases of neurosyphilis, with the possible exception of paresis. The combination of penicillin and fever is the treatment of choice for primary optic atrophy.

REFERENCES
8. Thomas, E. W.: Personal communication.