The Therapeutic Use of Diethylaminoethyl Ester Hydroiodide of Penicillin G in Chronic Bronchopulmonary Infections. Clinical and Bacteriological Studies*

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Introduction
The treatment of chronic infection of the respiratory tract presents a challenging problem. Except in cases suitable for extirpation of diseased lung tissue, the medical management of chronic bronchitis and bronchiectasis in the pre-antibiotic era attempted for the most part to facilitate drainage of the tracheobronchial tree. Although aerosol therapy with the sulfonamides was accompanied by significant improvement in bronchopulmonary suppuration, including lung abscess,\textsuperscript{1,2} the use of these drugs orally generally proved disappointing except in acute exacerbations of infection caused by a gram positive, sulfonamide sensitive organism. Penicillin by parenteral administration was found to be more effective, but arrest of chronic infection was not achieved in the brief periods in which it was given by intramuscular injection. The use of the broad-spectrum antibiotics was generally followed by prompt and conspicuous improvement, manifested by reduction in sputum and cough and by temporary eradication of infection; the occasional development of new infections with organisms relatively insensitive to antibiotics currently available, observed especially in debilitated patients, indicated the need for careful regulation of prolonged therapy with aureomycin, terramycin and chloromycetin.\textsuperscript{3,4}

The association of bronchial asthma and pulmonary emphysema with chronic lung infection frequently results in serious impairment of ventilatory function due to inflammation of the bronchial mucosa, with hyperemia and edema of the bronchial walls and peribronchial tissue, increased bronchial constriction as well as the tendency towards stag-
nation of purulent material and localized atelectasis. Since gram positive bacteria were responsible for the majority of cases of infection, penicillin has been widely used in these cases.

The clinical effectiveness of penicillin in the treatment of chronic bronchitis and bronchiectasis was found to be enhanced by its administration as an aerosol, since topical deposition on the diseased bronchial mucosa, in addition to the systemic absorption of the drug via the pulmonary capillary bed, was obtained. In recent studies, including a review of the literature, the value of nebulized penicillin seemed dependent on the maintenance of a high penicillin level locally in the bronchial secretions; this was especially manifest in bronchopulmonary infections due to resistant Staphylococcus aureus. In the clinical application of penicillin aerosol, it was noted that bronchospasm at times interfered with completion of therapy in patients with chronic bronchitis associated with either bronchial asthma or pulmonary emphysema. A considerable portion, approximately 20 per cent, developed increasing wheezing following inhalations of penicillin. Because of this complication, it is now customary in our clinic to treat these patients with parenteral penicillin and reserve the use of aerosol penicillin for patients with bronchiectasis, lung abscess, sinusitis and bronchitis or pneumonitis due to resistant Staphylococcus aureus.

The isolation and use of the diethylaminoethyl ester of penicillin by Jensen et al. and the demonstration of appreciable levels of penicillin in the bronchial secretions following the intramuscular injection of this drug prompted this study on its clinical effectiveness in chronic bronchopulmonary infection.

The first esters of penicillin were prepared in an impure state by Meyer, Hobby and Chaffee. The methyl, ethyl, n-butyl and benzhydryl esters, when tested in vitro against a hemolytic streptococcus, were found to have less than one-tenth of the activity of the material from which they were prepared. Subsequently, these esters were found to be highly effective in mice which were capable of hydrolyzing the esters with the slow liberation of active penicillin. Since other animals and man were incapable of hydrolyzing these esters, it was concluded that they possessed no therapeutic value. In 1948 Carpenter prepared the dimethylaminoethyl ester of penicillin which was followed by the synthesis of the diethylaminoethyl ester as the hydrochloride and hydrdiodide salts of benzyl penicillin by Jensen, Dragsted and Dlaer. In their animal and human studies, the intramuscular injection of the ester resulted in a lower level of penicillin in the serum than a comparable dose of sodium or procaine penicillin, but its concentration in lung tissue was five to eight times higher. Furthermore, penicillin was found in the expectoration in effective concentrations ranging between 0.23 to 0.45 units per cc. whereas little or no penicillin was recovered from the sputum after the injection of procaine penicillin.

In an extension of this work, Jensen and his collaborators investigated the clinical effectiveness of the ester on a small group of patients with chronic pulmonary infection. The therapeutic results appeared to be supe-
rior to those obtained with benzyl penicillin. The increased sputum levels following the parenteral administration of diethyaminoethyl ester of penicillin in contrast to sodium penicillin was confirmed in England by Heathcote and Nassau12 who also reported favorable results in the treatment of non-tuberculous bronchopulmonary infections. In preliminary reports by Barach rt al.,13,3,4 a prompt and conspicuous improvement was observed in patients with chronic bronchitis and bronchiectasis as a result of intramuscular injections of the penicillin ester in doses of 1 to 2 million units daily for periods of six to 12 days.

Methods

During the past year, 80 patients received a total of 100 courses of the hydriodide salt of diethyaminoethyl ester of penicillin. Thirty-six in this series had bronchographic evidence of bronchiectasis. The remainder exhibited chronic bronchial or sino-bronchial infection associated with bronchial asthma and pulmonary emphysema. The patients selected for this study, the majority of whom had been followed for five years or more, presented clinical, bacteriologic and radiologic evidence which indicated or suggested chronic bronchitis, with or without chronic sinusitis. Twelve members of this group revealed the presence of chronic pneumonitis at the time treatment was instituted. Six were treated for acute upper respiratory infection which in the past had been a frequent cause underlying the exacerbation of their chronic pulmonary disease. Approximately half were hospitalized while the rest were treated as out-patients.

Prior to administering diethyaminoethyl iodide penicillin, studies in most instances included: (1) daily sputum volumes in hospitalized patients, (2) pus in sputum by gross appearance and microscopic examination, (3) culture of sputum specimens, (4) clinical evidence of infection, cough, wheezing, fever, malaise or weight loss, (5) roentgenograms of the chest. These studies were generally repeated during or after therapy. The duration of remission was evaluated in those patients who returned for follow-up examinations.

Pulmonary infection associated with bronchial asthma and pulmonary emphysema is prone to chronicity, marked by periodic acute exacerbations; this is particularly evident in cases with organic structural deterioration, such as in bronchiectasis and pulmonary fibrosis. The clinical evaluation, therefore, of any therapeutic regimen must be appraised in the light of these factors in the life cycle of chronic bronchopulmonary infection. The degree and duration of improvement were appraised objectively, in terms of cough, character and amount of expectoration, and the bacteriologic analysis of the sputum. Additional factors such as weight gain, a reduction in asthma, relief of dyspnea, increase in exercise tolerance, and a sense of well-being were considered in the final assessment. In a number of cases, principally those patients in the bronchiectasis group, two to four repeated courses of neo-penicillin were administered. Respiratory function tests were followed in a few patients.

The diethyaminoethyl ester of penicillin was supplied as the hydroiodide
salt in the form of a dry, relatively insoluble powder which when reconstituted with sterile distilled water formed a milky suspension having a potency equivalent to 300,000 Oxford units of penicillin per cubic centimeter. The original material 1714-J Formula A, produced considerable foaming when reconstituted. This difficulty has been successfully overcome in the more recent material (Formula D). Neo-penil was administered intramuscularly once or twice daily in doses ranging from 500,000 to 2,000,000 units with average total dose of 9,000,000 units. The duration of therapy varied from three to 18 days, averaging approximately eight days for the 99 courses administered.

A total of 68 sputum specimens were assayed for their penicillin activity. The serial dilution tube method was employed with the Streptococcus hemolyticus strain C203 serving as the test organism. Thirty-three specimens were tested at varying collection periods ranging from two to 24 hours following a single dose of 500,000 units of neo-penil; 15 were assayed following the administration of 750,000 units; and 20 after 1,000,000 units.

Results

The clinical response of patients with chronic pulmonary infection is presented in Table I. Of 100 courses of neo-penil therapy, 81 resulted in a significant improvement, which was moderate in 27 and excellent in 55, in which a complete remission of the symptoms and physical signs of chronic suppuration was obtained; in 18 instances, little or no improvement occurred. It may be noteworthy that 10 of these were patients with long standing bronchiectasis who had for the most part failed to respond to other antibiotic and medical regimens. The most conspicuous results were obtained in cases of chronic suppurative bronchitis, with or without sinusitis. Cough and bronchospasm were markedly relieved or eliminated and the purulent character of the expectorate rendered mucoid in 47 of the 51 members of this group. The duration of remission averaged 8.0 weeks for the group as a whole.

Gross character of the sputum, smears and cultures were studied in 80 patients who received a total of 90 courses of neo-penil. In 90 instances, the sputum appeared purulent or mucopurulent, or pus cells were de-

<table>
<thead>
<tr>
<th>TABLE I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL EFFECT OF DIETHYLAMINOETHYL IODIDE PENICILLIN IN 80 PATIENTS WITH CHRONIC BRONCHOPULMONARY DISEASE</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Courses</th>
<th>Excellent</th>
<th>Moderate</th>
<th>Little or None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Bronchitis</td>
<td>51</td>
<td>30</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>37</td>
<td>20</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Chronic Pneumonitis</td>
<td>12</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100</td>
<td>55</td>
<td>27</td>
<td>18</td>
</tr>
</tbody>
</table>

Duration of Remission: Average, 8.0 weeks; Range, 0.5 to 24.0 weeks.
monstrated on routine smear. Following therapy, sputum became mucoid in 55 instances. In four, expectoration was completely eliminated and no sputum was available for examination (Cf. Table II).

Of the 90 purulent specimens of sputum, 36 became sterile after treatment with neo-penil, as seen in Table III. In 27, gram positive organisms were eliminated with the emergence of gram negative bacilli, predominantly of the B. coli-aerogenes group. In three, yeast organisms of the monilia group were recovered. No change in bacterial flora occurred in 24 cases, with 14 revealing the persistence of hemolytic Staphylococcus aureus, coagulase positive, four B. Proteus, one pyocyanus, five other organisms including Streptococcus viridans.

The penicillin levels in the sputum following the parenteral administration of neo-penil are illustrated in Table IV. Of the 33 specimens obtained after 500,000 units of neo-penil, five showed no detectable levels in eight, 12, or 24-hour collection periods. In 10 subjects, levels ranging from 0.02 units per cc. to 0.08 were obtained. In the remaining 18 patients levels in excess of 0.1 units per cc. were found, with one specimen as high as 1.5 units per cc. Of 15 patients given 750,000 units of neo-penil, 10 showed an average level of 0.055 units per cc. while five had an average of 0.2. In 19 subjects given 1,000,000 units the sputum concentration was between 0.2 and 0.48 units per cc. In this series there seemed to be no definitive correlation between the collection period and the levels obtained. The con-

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**TABLE II**

<table>
<thead>
<tr>
<th>No. of Courses</th>
<th>Sputum Examination*</th>
<th>Before</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>Purulent</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Muco-purulent</td>
<td>40</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Mucoid</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>No sputum</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

*Presence of pus was determined by gross and microscopic examination of sputum.

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**TABLE III**

<table>
<thead>
<tr>
<th>No. of Courses</th>
<th>Sterile</th>
<th>Gram-neg. Bacteria</th>
<th>Monilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>36</td>
<td>27</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sputum Cultures Changed by Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum Cultures Unchanged by Treatment</td>
</tr>
<tr>
<td>Staph. aureus</td>
</tr>
</tbody>
</table>

| Other Organisms |
|-----------------|---|---|---|---|
| Proteus         | 1 | 4 | 1 | 5 |
| Pyocyanus       | 1 | 4 | 1 | 5 |
| Other Organisms | 1 | 4 | 1 | 5 |
centration of penicillin in the sputum generally varied with the dose of neo-penill administered. Other factors modify the penicillin content of the expectoration, such as the development of penicillinase during the period the sputum specimen is exposed to room air, but the results reported are those obtained with routine nurse to laboratory management.

In this group nine untoward reactions were encountered during the course of this study. Two consisted of a mild, transient urticaria. In two cases, a moderately severe rhinorrhea and bronchorrhea were attributed to the iodide radical of neo-penil; this factor also appeared implicated in two cases who manifested enlargement of the salivary glands 24 hours after injection. A systemic reaction, including a low grade fever, occurred in one subject. Syncope associated with bronchospasm and transient fall in blood pressure occurred immediately after the injection of neo-penil in a patient with bronchial asthma. Subsequently, this picture was reproduced in the same subject on re-exposure to the drug. There were two patients with a well-documented history of penicillin sensitivity who were able to tolerate neo-penil without allergic manifestations. On the other hand, swelling of the tongue and tachycardia occurred in one case during the third course; subsequently, a severe but transient asphyxial episode

### TABLE IV

<table>
<thead>
<tr>
<th>GROUP I: Sputum Level, None (5 cases)</th>
<th>Dosage (units)</th>
<th>Sputum Collection Period (hours)</th>
<th>Penicillin in Sputum (units per cc. average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>500,000</td>
<td>8 to 24</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP II: Sputum Level, Slight, 0.02 to 0.08 (21 cases)</th>
<th>Dosage (units)</th>
<th>Sputum Collection Period (hours)</th>
<th>Penicillin in Sputum (units per cc. average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>500,000</td>
<td>8 to 24</td>
<td>0.05 to 0.07</td>
</tr>
<tr>
<td>10</td>
<td>750,000</td>
<td>12</td>
<td>0.05</td>
</tr>
<tr>
<td>1</td>
<td>1,000,000</td>
<td>48</td>
<td>0.07</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP III: Sputum Level, Moderate, 0.1 to 1.5 (42 cases)</th>
<th>Dosage (units)</th>
<th>Sputum Collection Period (hours)</th>
<th>Penicillin in Sputum (units per cc. average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>500,000</td>
<td>12</td>
<td>0.35</td>
</tr>
<tr>
<td>4</td>
<td>500,000</td>
<td>8 to 24</td>
<td>0.25</td>
</tr>
<tr>
<td>5</td>
<td>750,000</td>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>1,000,000</td>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>1,000,000</td>
<td>2 to 4</td>
<td>0.32</td>
</tr>
<tr>
<td>5</td>
<td>1,000,000</td>
<td>28 to 48</td>
<td>0.48</td>
</tr>
<tr>
<td>1</td>
<td>1,000,000</td>
<td>48</td>
<td>0.48</td>
</tr>
</tbody>
</table>
with marked enlargement of the tongue took place in this patient after injection of 500,000 units penicillin-O intramuscularly.

The case histories of 10 patients are recited to portray the individual response to intramuscular injection of diethylaminoethyl iodide penicillin.\footnote{The case histories of five patients are included in the Journal; the remaining five histories will be in the authors' reprints.}

**Case 1:** Female, age 55, had bronchial asthma from childhood. Since 1940 asthma became progressively more severe. Good clinical remissions were obtained at Presbyterian Hospital in 1943 with helium oxygen therapy; with bronchoscopic aspiration under ether anesthesia, in 1944 and 1951. During the previous eight years chronic low-grade fever, 99.0 to 101.0 degrees F. by mouth, persisted. Despite protracted coughing, she was unable to expectorate sputum. Nevertheless, during each bronchoscopy about 60 cc. of thick mucopurulent secretions were aspirated from the bronch. A bronchogram did not reveal bronchiectasis; good filling of the bronchial tree was obtained, with the exception of most of the left lower lobe. On physical examination, the pharynx was reddened and lymphoid follicles were unusually prominent. Coarse rhonchi heard at the bases were accompanied by occasional crepitant rales at the left mid-lung field posteriorly.

Culture of bronchial aspirations revealed streptococcus viridans although pneumococcus organisms had been previously found on throat culture. Five-day courses of terramycin, 2 gms. daily, and chloromycetin, 2.5 gms. daily, had no effect on her febrile state nor on the complaint of soreness of the throat. The first course of diethylaminoethyl iodide penicillin, 800,000 units once daily for 14 days was followed by complete disappearance of fever and decreased redness of the pharynx. The lungs were clear. After an interval of one week, a second similar course for 10 days was followed by virtual clearing of the enlarged lymphoid follicles in the throat and disappearance of soreness of the throat.

**Comment:** A low-grade fever of eight years' duration was terminated as the result of administration of diethylaminoethyl iodide penicillin. A chronic bronchial and pharyngeal infection appears to have been eliminated since she has remained symptom-free, without cough, asthma or sore throat for one year. Among the striking features was the disappearance of the red swollen lymphoid follicles in the pharynx. This was thought to be of special interest in view of the high concentration that develops in lymph nodes following administration of diethylaminoethyl iodide penicillin. Although this patient manifested a surprising inability to expectorate, the complete absence of coughing for one year after treatment suggests a "cure" of chronic bronchitis.

**Case 2:** Female, age 58, had chronic persistent cough associated with many febrile episodes since childhood and consistently productive of purulent sputum which was often blood-streaked. Twenty years ago, following several episodes of pneumonia, she was thought to have bronchiectasis; this was confirmed by lipiodol bronchography in 1941. Systemically administered penicillin produced some improvement in cough, but purulent quality of sputum was more decisively reduced by aerosol penicillin; the latter route of administration was discontinued because it produced wheezing. Terramycin, aureomycin and chloromycetin were each given in courses of five to seven days, 2.0 gms. daily, with marked symptomatic improvement but with recurrence five to 10 days later of purulent sputum and cough. In April, 1951, the positive physical findings were confined to the lungs, which revealed crepitant rales at the left base. An increase in lung markings was seen by x-ray film inspection over both lower lung fields, where a reticulated
appearance suggested bronchectasis. Sedimentation rate and hemogram were normal. Sputum was purulent with staphylococcus viridans predominating.

One million units of diethylaminoethyl iodide penicillin were injected daily for nine days. On the fourth day of administration, the sputum became white and frothy, reduced from 3 ounces to ½ ounce daily. Repeated cultures at termination of this course showed the presence of N. catarrhalis an occasional colony of B. colli. Another chest x-ray film revealed no significant change from the one taken before therapy. However, an excellent clinical remission continued for four months, with little cough and sputum remaining mucoid.

Recurrence of cough and purulent expectoration then took place, associated with acute laryngitis. Sputum culture showed the presence of streptococcus hemolyticus and staphylococcus aureus. She received 1,500,000 units of neo-penil daily for 10 days. By the third day sputum had again become white and mucoid, and cough was much improved. However, sputum began to turn purulent 10 days later, with recurrence of cough which increased considerably three months later. She was given a course of procaine penicillin, 1,200,000 units daily for seven days, without discernible clinical improvement; sputum continued to be yellow and purulent, with staphylococcus aureus on culture. Four days later, neo-penil, 1,000,000 units daily, was given for six days; sputum decreased in amount and became mucoid, with a rare colony of diplococcus pneumoniae on culture. Recurrence of gradually increasing cough and purulent sputum took place three weeks later. The organism isolated from the sputum was staphylococcus aureus. The patient, a school teacher, appeared to catch upper respiratory infections from contact with children. A course of terramycin, 2 gms. daily for five days, was now of no benefit. Chloromycetin, 3.0 gms. daily for eight days, resulted in a remission of cough and purulent sputum for three weeks. During a subsequent one week course of neo-penil, 1,000,000 units daily, purulent yellow sputum appeared, associated with increased cough and Friedlander B. on culture. Chloromycetin was administered again for five days with clearing of pus from sputum. A holiday at this time was followed by improvement in cough but reappearance of small amounts of pus in the sputum took place, with staphylococcus aureus present on culture.

Comment: Frequent courses of treatment with penicillin and the broad-spectrum antibiotics had been previously followed by temporary improvement in this patient with extensive bronchectasis. The administration of diethylaminoethyl penicillin was at first accompanied by more decisive clearing of purulent sputum and more lasting remission than the other antibiotics employed. Elimination of the chronic bronchial infection, due to staphylococcus aureus, was not achieved. Following one of the courses of neo-penil, abrupt cessation of improvement was associated with presence of B. Friedlander in the sputum; at this time, chloromycetin was markedly effective.

This patient illustrates the frequency with which staphylococcus organisms develop resistance to penicillin and other antibiotics. During the last winter exposure to children with upper respiratory infection was apparently a factor in the recurrent exacerbations of infection which she manifested. New measures, such as sleeping with the heat down 16 degrees and bacterial vaccines, will be tried in the attempt to reduce the need for antibiotics in the coming term.

Case 3: Female, age 38, had bronchial asthma for 10 years, initially treated in 1942 at the Allergy Clinic, where she was found to be sensitive to house dust, ragweed and feathers. She was treated with hyposensitization and remained under
fair control until 1944, when she had an increase in cough and sputum. A low-grade fever persisted for four weeks, following which she had a remission from asthma until 1947. After an upper respiratory infection, asthma recurred, accompanied by severe cough and copious, purulent sputum. In six months a weight loss of 20 pounds took place. With elevation in temperature to 103 degrees F. she was admitted to Presbyterian Hospital in July, 1948.

Except for bilateral wheezes, the lungs appeared clear. An X-ray film of the chest disclosed evidence of atypical pneumonia of the right upper lung field. This failed to respond to penicillin therapy but resolved spontaneously by lysis in two weeks.

Since discharge from the hospital she continued to suffer from chronic protracted asthma associated with severe coughing and expectoration of purulent sputum, approximately 400 cc. daily. During a period of three years her sputum remained purulent most of the time, with cultures consistently revealing the presence of hemolytic staphylococcus aureus, at times hemolytic streptococcus and, on occasions, K. pneumoniae. Many courses of the broad-spectrum antibiotics resulted in little if any improvement; inhalation of penicillin and streptomycin aerosols temporarily cleared the infection but increased her bronchospasm. Following a short course of cortisone, she had a partial remission from asthma which lasted one month. In June, 1951, an upper respiratory infection, accompanied by chills and fever, was followed by exacerbation of asthma and expectoration of increased amounts of thick, yellowish sputum. Despite chloromycetin and aureomycin therapy, severe asthma persisted, necessitating hospitalization in November of 1951. She was given 1,000,000 units of neo-penil twice daily for eight days after which the sputum became scanty and colorless; asthma and cough completely subsided. This remission was of six weeks' duration when another upper respiratory infection produced a relapse and sputum again became purulent. She was placed on 2,000,000 units of crysticillin (procaine penicillin) for eight days, which resulted in a partial remission, with the sputum again becoming mucoid, which lasted only 14 days. The administration of neo-penil appeared to be more effective than procaine penicillin, in respect to promptness of relief of infection and subsequent duration of benefit.

Comment: Recurring bronchopulmonary infection, with staphylococcus aureus apparently the significant etiological agent, was not controlled by the broad-spectrum antibiotics employed in this patient. The disappearance of pus from the sputum after administration of diethylaminoethyl iodide penicillin was accompanied by complete disappearance of cough and asthma. More prolonged therapy would appear to be indicated in cases of this type in the attempt to produce more lasting remissions. Following elimination of purulent sputum, after intramuscular injections of this drug, penicillin by mouth in large dosage, one million units on arising and one to two million units on retiring, seems to be a feasible method of continued treatment which deserves further trial.

Case 4: Male, age 65, had chronic cough and shortness of breath of 15 years' duration, increasing in severity during the past three years. In January, 1951, wheezing on slight effort and expectoration of purulent sputum became evident. The positive findings were restricted to the chest, which was emphysematous, with distant breath sounds and high pitched expiratory wheezes heard bilaterally. A vital capacity of 2,700 cc. rose to 3,400 cc. after inhalation of vaponefrin. Sputum showed pus, with staphylococcus aureus and diplococcus pneumoniae on culture. Chest X-ray film revealed an increase in the bronchovascular markings and findings consistent with pulmonary emphysema.

Courses of penicillin by injection, aureomycin and chloromycetin by mouth were
employed in the treatment of his bronchopulmonary infection, with moderate benefit in cough and gradual clearing of purulent sputum. In October, 1951, during an episode of acute respiratory insufficiency following increased infection, he was admitted to Presbyterian Hospital. At this time, examination of the lungs disclosed many wheezes with marked prolongation of the expiratory phase. The diaphragms were immobile, respiration was labored and upper costal. Erythrocyte sedimentation rate was 23 mm. per hour. Venous pressure was 48 mm. H2O; temperature, 101 degrees F. Sputum was purulent, with staphylococcus aureus found on culture. He was placed on neo-penil, 1,000,000 units daily for six days. Decrease in cough, with sputum scanty and mucoid, was observed on the fourth day of treatment. Temperature dropped to normal in 48 hours and all evidence of bronchospasm cleared. This remission in cough and dyspnea was largely maintained for three months. In a follow-up four months later, moderate cough had recurred, but the expectoration was mucoid, and bronchospasm minimal.

**Comment:** A prompt clearing of bronchopulmonary infection took place in this patient with chronic bronchitis following the use of neo-penil, one million units daily, for six days, with striking associated improvement in cough and bronchospasm. Staphylococcus aureus was the organism found on sputum culture. The importance of effective elimination of bronchial infection in patients with pulmonary emphysema was illustrated by the course of this patient. The persistence of improvement was surprising in view of the relatively short period of treatment.

**Case 5:** Female, age 41, had allergic vasomotor rhinitis and polyposis since 1931. In 1947 asthma began, but controlled by a hyposensitization program until 1950 when she was hospitalized on four occasions for status asthma. During the last admission she received 100 mgs. ACTH daily for five days which resulted in a remission lasting 29 days. Asthma gradually recurred and in March, 1951, a siege of severe bronchospasm was treated with cortisone, which resulted in a complete remission for six months, when she was given a second course of cortisone which resulted in a partial remission, aided by bronchodilator medication daily.

In January, 1952, following an upper respiratory infection, her sputum became thick and purulent, with diplococcus pneumoniae present on culture. Severe asthma necessitated use of helium and oxygen, and intravenous aminophyllin. She was given 1,000,000 units neo-penil daily for five days with an excellent symptomatic response, a remission of two months' duration. Sputum culture after neo-penil therapy was sterile. In March, 1952, her asthma again increased in severity after another upper respiratory infection. Sulfonamides were given without benefit. After another course of neo-penil, 1,000,000 units per day for six days, a remarkable improvement in asthma took place, accompanied by a decrease in sputum which changed from purulent to mucoid in character. This improvement has persisted for the past two months.

**Comment:** A prompt control of a pneumococcus respiratory infection, achieved by six days of neo-penil, one million units daily, was accompanied by a striking improvement of bronchial asthma. The response of patients with bronchial asthma to antibiotic therapy is especially favorable only in those cases in which the sputum is frankly purulent, either on inspection or on microscopic examination.

Both the effectiveness of clearing of pus from the sputum as well as the promptness with which improvement was manifested suggested that this drug had a beneficial effect superior to that of benzylpenicillin, and
comparable, in many instances, to the action of inhalation of penicillin as an aerosol. Although three cases were encountered in which inhalation of penicillin resulted in disappearance of purulent sputum due to a resistant Staphylococcus aureus, when previous treatment with neo-penicillin appeared to be less effective, the majority of cases with suppurative bronchopulmonary disease were considered markedly benefited. This opinion, largely based on a previous clinical experience of the two senior authors in this report, must admittedly be accepted as suggestive evidence rather than demonstrable proof. The well-known difficulty of predicting in advance the reaction of a patient with bronchopulmonary disease to antibiotic treatment is admitted; nor does the in vitro sensitivity of the organisms to penicillin and other agents always contribute a decisive aid in this respect. In three patients in whom a B. proteus infection had taken place following elimination of both gram positive and gram negative organisms by multiple antibiotic therapy, the employment of neo-penicillin in dosages of 1,000,000 units twice daily for eight to 12 days was accompanied by a marked reduction in cough and disappearance of expectoration; the sputum was mucoid instead of purulent, despite the fact that the B. proteus organism had been repeatedly found to be resistant to penicillin in vitro sensitivity tests. Later, a second course of benzyl procaine penicillin in the same dosage was followed by a similar striking improvement in two of these cases.

Pharmacologic evidence for a specific favorable effect of neo-penicillin in lung infections is found in the presence of penicillin in the sputum in higher concentrations than that which has been reported following injection of benzypenicillin. In the study of Humphrey and Joules® penicillin was rarely found in the sputum in cases of bronchitis and bronchiectasis after its intramuscular injection; whereas in patients with lobar pneumonia small amounts of penicillin were recovered from the sputum during the active phase of the disease. When the consolidation cleared and a chronic bronchitis persisted no penicillin could be detected after intramuscular injection of penicillin, even though patients continued to have considerable amounts of expectoration. In the studies of Barach et al.¹⁵,¹⁶ Bobrowitz, Edwin et al.,¹⁷ penicillin was rarely found in the sputum after intramuscular injection. On the other hand, in 42 of 68 cases of this series in which sputum concentration was tested after 500,000 units to 1,000,000 units of neo-penicillin, a level between 0.1 and 1.5 units per cc. of sputum was present. These results confirmed the observation made by Jensen et al. and Heathcote and Nassau in which higher concentrations of penicillin in the expectoration were apparent after the injection of diethylaminoethyl iodide penicillin than after the introduction of comparable amounts of benzyl-penicillin. Although aerosol penicillin results in far higher penicillin concentrations, 50 to 1,000 units of penicillin per cc. of expectoration,¹⁴,¹⁸ the demonstration that penicillin is present in bronchial secretions in the majority of cases in a concentration that would be expected to inhibit the growth of gram positive bacteria, except highly resistant Staphylococcus aureus, appears to offer a sound bacteriologically based
argument for the superiority of neo-penil over procaine penicillin in cases of bronchopulmonary suppuration.

The effect of diethylaminoethyl iodide penicillin on the bacterial flora of the sputum indicated the effectiveness of the preparation in patients with chronic bronchitis and bronchiectasis. Of 90 courses of treatment the sputum cultures were sterile in 36. In 27 other cases, only gram negative bacteria were recovered on culture. This finding is to be interpreted as a sign of the potency of the preparation against infection with gram positive micro-organisms, as originally pointed out in the use of aerosol penicillin in cases of this type. Although the broad spectrum antibiotics were found highly valuable for treatment of secondary infections with gram negative bacteria, and for acute respiratory infections, their long-continued employment to obtain an arrest of chronic respiratory infection required certain precautions to avoid the development of invasion with unusual organisms such as B. proteus, B. pyocyaneus, and Monilia. The special considerations involved in the therapy of chronic bronchopulmonary infections have been recently described.

The clinical indications for the use of diethylaminoethyl iodide penicillin include the majority of cases of chronic bronchitis, bronchiectasis and chronic pneumonitis. Effective treatment over a period of six to 12 days may be initiated for exacerbations of chronic respiratory infection, or preoperative and postoperative treatment of bronchiectasis and as a beginning of more long-continued treatment of chronic bronchiectasis and bronchitis. After 12 days of intramuscular injection the attempt to initiate a long-continued arrest of infection may be continued with aerosol penicillin or with penicillin by mouth in larger dosages than had previously been used. In our clinic it has recently been found clinically valuable to give 1,000,000 units of penicillin or arising and 1,000,000 units, at times 2,000,000 units, at night for a period of three weeks to three months or more in the attempt to maintain the patient free from the symptoms and signs of chronic infection. The latter method of administration is altered in those cases in which resistant Staphylococcus aureus organisms appear and are responsible for return of a purulent quality of the sputum. In this event, recourse may be had to inhalation of 600,000 to 1,000,000 units of penicillin daily by aerosol, aureomycin or terramycin, generally administered for periods of five to eight days.

It would also appear reasonable to sanction the employment of diethylaminoethyl iodide penicillin in upper respiratory infections, pharyngeal, sinus and bronchial infection that follow in the wake of the common cold. In patients with infection of the cervical (or other) lymph glands, neo-penil would appear to be especially effective, as suggested by a remarkably favorable response in two such cases in this series. In patients with chronic infection of the respiratory tract, neo-penil as well as other antibiotic therapy is more apt to be followed by prolonged benefit if adequate bronchial and bronchiolar drainage is accomplished. Among the measures that are therapeutically feasible and effective for this purpose are: use of the head-down position, training in diaphragmatic breathing, deliberate cough-
ing after inhalation of broncho-dilator aerosols, manual compression of the abdomen and lower chest, as well as the employment of recently developed physical methods of eliminating bronchial secretions. The portable Exsufflator with a negative pressure attachment, has in some cases been found more efficient in eliminating retained secretions from the smaller bronchi than the natural cough of patients with pulmonary emphysema and bronchial asthma.

SUMMARY

The clinical results of the use of diethylaminoethyl ester hydroidide of penicillin G are reported in 80 patients with chronic bronchopulmonary disease, including chronic bronchitis, bronchiectasis and chronic pneumonitis. Of 100 courses of treatment, an excellent result was obtained in 55, moderate improvement in 27 and little or no benefit in 18.

Of 90 courses in which the sputum was purulent or mucopurulent before treatment, the result after treatment was no sputum in four instances, mucoid in 55, mucopurulent in 19 and purulent in 12. The sputum cultures after treatment were as follows: sterile in 36, gram negative bacteria in 27; Staphylococcus aureus in 14, B. proteus in four, pyocyaneus in one, yeast organisms in three, other organisms, including Streptococcus viridans, in five.

The penicillin concentration of the sputum tested after intramuscular injection of 500,000 to 1,000,000 units of neo-penil, varied between 0.1 and 1.5 units per cc. in 48 of 68 instances. In 19 cases the penicillin level in the sputum after 1,000,000 units was between 0.2 and 0.48 units per cc.

The case histories of patients with bronchopulmonary infections illustrate the effect of this drug on the course of their disease.

The clinical and bacteriological observations made on the use of diethylaminoethyl iodide penicillin in patients with chronic bronchitis, bronchiectasis and chronic pneumonitis suggest that this agent has a markedly effective action in the control of infections due to gram positive organisms. The side effects of the drug have not been of such severity or frequency as to limit its employment; allergic reactions to penicillin and the consequences of iodine sensitivity were among those encountered.

RESUMEN

Se refieren los resultados del uso del ester de yodhidrato de dietilaminaetil penicillina G en 80 enfermos con padecimientos broncopulmonares crónicos, incluyendo bronquitis crónica, bronquiectasia y neumonitis crónica. De 100 series de tratamiento se obtuvo un excelente resultado en 55, mejoría moderada en 27 y beneficio escaso o ninguno en 18.

En 90 series, en las que el esputo era purulento antes del tratamiento, el resultado después del tratamiento fue: ausencia de esputos en 4 casos, Deliberate coughing may be most productive after broncho-dilation has been accomplished by drugs such as aminophylline, grains 5, especially when combined with benzocaine, grains ¼, as an anti-nausea factor, and inhalation of ephedrine compounds, including 2.25 per cent racemic ephedrine, nebulized with a handbulb, or in dilute solution with pressure-breathing apparatus.
muciloide en 55, mucopurulento en 19 y purulento en 12. Los cultivos del 
esputo después del tratamiento resultaron: Esteriles 36; con bacterias 
Gram-negativas en 27; Estafilococo aureo en 14; Bacteria proteus en 4; 
picólanico en 1; micro-organismos de tipo levadura en 3, y otros micro-
organismos, incluyendo estreptococo viridans en 5.

La concentración de la penicilina en el esputo después de inyectar 500,000 
a 1,000,000 de unidades de Neo-penil, varió entre 0.1 y 1.5 unidades por cc. 
en 48 de 68 casos. En 19 casos el nivel de la penicilina en el esputo después 
de 1,000,000 unidades fue entre 0.2 y 0.48 unidades por cc.

Las historias clínicas de los enfermos con afecciones broncopulmonares 
son ilustrativas del efecto de esta droga sobre el curso de la enfermedad.

Las observaciones clínicas y bacteriológicas hechas sobre el uso del yodhi-
drato del dietilaminoetil penicilina, en enfermos con bronquitis crónica, ronquiectasia, y neumonitis crónica, sugieren que este agente tiene una 
acción marcada y efectiva en el dominio de las infecciones causadas por 
gérmenes Gram-positivos. Los efectos colaterales al uso de la droga no han 
sido de una severidad tal que limite su uso fueron observadas reacciones 
alérgicas a la penicilina y consecuencias de la sensibilidad al yodo como 
algunos de los efectos colaterales.

RESUME

Les auteurs rapportent les résultats cliniques de l’utilisation du diethy-
laminoethyl-ester-hydroiodide de pénicilline G chez 80 malades atteints 
d’affections bronchopulmonaires chroniques, comprenant bronchites chro-
niques, dilatations bronchiques, et pneumonies chroniques. Sur 100 malades 
mis en traitement, on peut noter 55 excellents résultats, 27 améliorations 
modérées, et 18 cas dont l’amélioration fut très discrète ou même non 
perceptible.

Sur 90 cas, dans lesquels l’expectoration était, avant traitement, puru-
lente ou mucopurulente, on observa les résultats suivants après traitement: 
4 cas où il n’y avait plus aucune expectoration; 55 cas où l’expectoration 
était devenue mucoide, 19 chez lesquels elle était devenue mucopurulente, 
et 12 chez lesquels l’expectoration était restée purulente. Après traitement, 
la culture des crachats donna les résultats suivants: absence de germes 
dans 36 cas, présence de bactéries gram-négatif dans 27 cas, staphylocoques 
dorés dans 14 cas, proteus dans 4 cas, pyocyaniques dans un cas, des levures 
dans trois cas, et d’autres microbes, y compris le streptocoque viridans 
dans 5 cas.

La concentration de pénicilline dans les crachats, évaluée après injection 
intra-musculaire de 500,000 à un million d’unités de néo-pénil varia dans 
48 cas sur 68 de 0.1 à 1.5 unité par cc. Dans 19 cas, le niveau de pénicilline 
des crachats après l’administration d’un million d’unités se situa entre 0.2 
et 0.48 unité par cc.

Les observations des malades atteints d’affections broncho-pulmonaires 
démontront l’action de cette drogue sur l’évolution de leur affection. Les 
observations cliniques et bactériologiques qui ont été faites sur l’usage du 
produit chez des malades atteints de bronchite chronique, de dilatation des
bronches, et de pneumonie chronique amènent à penser qu'il a une action particulièrement efficace sur les affections dues au germe gram-positif. Cette médication ne semble pas avoir d'inconvénients dont la gravité ou la fréquence puisse limiter son utilisation. Parmi ceux qui furent rencontrés, il faut citer les réactions allergiques à la pénicilline, et les conséquences de la sensibilisation à l'iode.

REFERENCES