Aerosol Antibiotic Therapy in Suppurative Diseases of the Lung and Bronchi

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Inhalation therapy has become very popular both with physicians and the laity. While the use of antibiotics by nebulization is rather recent, the utilization of germicidal mists and therapeutic gases dates back many years. Those interested in a complete review of the historical background for aerosol therapy should read Segal's excellent article on the subject.1

The original report on penicillin aerosolization was made by Bryson and his associates2 in 1944 and was an outgrowth of their work on the physical and biologic properties of aerosol for the Technical Division, office of the Chief, Chemical Warfare Service. Since then, stimulated by their findings, clinicians have made exhaustive trials with this method in pulmonary infection not only with penicillin but also with the sulfonamides, the sulfones and more recently with streptomycin.

While this report is limited to the results obtained in suppurative diseases of the lungs and bronchi by penicillin and streptomycin aerosolization, it should be noted that infectious asthma, pneumonia, laryngotracheobronchitis and pulmonary emphysema associated with infectious bronchitis or bronchiectasis were also thus treated. However, as is the case with reports of others, the number of patients in the latter group is too small to warrant final evaluation.

When one realizes the extensiveness of the inner surface of the lungs there is little wonder that effects similar to that of intravenous injection can be obtained by inhalation. In fact both Bryson3 and Barach4-5 and their associates have demonstrated in the experimental animal and in humans that a more uniform blood level of penicillin can be maintained by the inhalation method than by intermittent intravenous or intramuscular injections. Levine6 has gone even further and has satisfied himself that aerosol penicillin will effect improvement in bronchiectasis when other methods fail.

That aerosolized materials when inhaled penetrate the outer-
most air sacs of the lungs and are uniformly distributed was demonstrated by Krueger, et al,\(^7\) using India ink and radioactive chromic phosphate as indicators. High local or topical concentrations are thus made possible.

The detection of penicillin in the blood and urine after administration of penicillin aerosol is proof of its absorption. However, it does not follow that the blood level necessarily is a measure of its topical effectiveness. It has been shown that satisfactory clinical results can be obtained with low and even no penicillin levels. It is for this reason that Segal\(^8\) and his associates feel that the determination of blood levels is more of academic interest than of practical value. The clinical course is a better criterion of the local effectiveness of penicillin aerosol. Besides, factors other than alveolar absorption determine blood levels. These as listed by Segal\(^9\) are the equipment used, the dosage and types of penicillin given, the absorption variations of accumulated pus and secretion and the technic of determining blood levels.

More recently Bryson\(^{10}\) has shown that the bacteriostatic effect of penicillin and streptomycin aerosol can be enhanced by using

**FIGURE 1: Method of Aerosolization,**
a detergent as the solvent for the drugs. Detergents or wetting agents have the properties of emulsification and of reducing surface tension. These properties serve to break up pus and cellular detritus and in this manner assure better contact between microorganisms and the antibiotic. Already the combination of penicillin with detergent solutions has resulted in reduction of mortality in mice with experimental pulmonary disease as compared with a control series treated with penicillin aerosol alone. Clinical trials are being made and while a final report cannot be given at this time, results indicate that wetting agents likely will play an important role as adjuncts to simple aerosol therapy.

Intrabronchial instillation of penicillin or streptomycin has proved of additional value in some instances in which aerosol therapy was used and according to Slitzbach¹¹ better results than with aerosolization can generally be obtained. The method involves inconvenience to the patient and in my experience is seldom necessary. Furthermore, the use of this method does not obviate the interference offered by pus for contact of the drug with the micro-organisms. I believe that wider use of detergents will increase the efficacy of aerosol therapy without necessitating bronchoscopic or tube intubation instillation of antibiotics.

It has been long recognized that a knowledge of the bacterial content in suppurative pulmonary disease is not of real importance.

FIGURE 2: Microscopic section of a dilated bronchus of an excised lobe untreated prior to operation. Note pus and cellular debris within bronchial lumen.
The introduction of penicillin and particularly streptomycin has changed the picture since it is considered essential to know whether one is dealing with sensitive or resistant organisms. This information is especially valuable if the benefits of multiple antibiotic
Figure 5: White female, aged 33 years, admitted with cough and expectoration of foul sputum. Symptoms of 13 years duration. After 2 weeks of admission, unimproved. X-ray shows changes in the left lower lobe. Figure 6: Same patient after left lower lobe lobectomy. Residual lobe shadows are seen in the right lower lobe. Symptom free.
therapy is sought. Yet, despite what has just been said, I feel that aerosol therapy can be properly carried out without facilities for such determinations. It is nice to have them but from a practical point of view the clinical course is a good therapeutic guide. Our own and the experience of others indicate that the vast majority of patients who respond favorably to antibiotic aerosol therapy do so to penicillin alone.

The response to aerosol therapy is rapid and decisive; in fact in some instances it is dramatic. Fever and toxicity subside, the amount of daily sputum is diminished and in many cases secretions are entirely abolished, if the character of the sputum is foul, the odor is lost, serial roentgenograms of the chest reveal partial to complete resorption of the perifocal infiltrates and gross and microscopic sections of excised lungs show dilated but clean bronchi in contrast to bronchi filled with cellular debris and pus in untreated lungs or in cases which fail to respond to treatment. Those who have followed their cases with bacteriological studies have been impressed with the disappearance of susceptible micro-organisms.

If the above effects of antibiotics were permanent, the management of respiratory disease would indeed be simple. Unfortunately, this is not the case. In suppurative bronchiectasis the best results are obtained in the surgical cases in which penicillin and/or streptomycin aerosol seems to improve the surgical risk for the patient. He comes to the operating table either symptom-free or with minimal cough and expectoration. It is a general observation that thus prepared the patient is anesthetized with little or no difficulty and maintains the anesthetic state for many hours without ill effects and postoperative complications such as pneumonia and atelectasis are minimized.

In the non-surgical cases, the effects of penicillin and streptomycin are temporary and in most instances recurrences take place. But even these patients may sustain their attained improvement for months or longer and if symptoms do return, may again benefit by re-institution of aerosol therapy. In some, supplementary deep x-ray therapy may give more permanent results.

Prior to the introduction of the antibiotics, early incision and drainage was considered urgent in the proper management of acute lung abscess. Amelioration of symptoms such as fever, toxicity, cough and expectoration and obliteration of the abscess cavity followed in only about 15 per cent without surgical intervention. The use of penicillin singly or in combination with streptomycin has reversed the picture in so far as symptomatic relief is concerned. The follow up of "cured" cases has not been sufficiently long to determine whether spontaneous obliteration of
Figure 8: White male, aged 43 years, admitted with cough, expectoration of purulent sputum, and history of repeated hemoptyses. Roentgenogram shows broncho-pneumonia left lower half of lung field and multiple ring shadows in right mid lung region. Duration of symptoms since childhood. — Figure 9: Same patient after one month of penicillin aerosol. Occasional cough not productive of sputum. Bronchogram shows cystic bronchiectasis of both lungs. — Figure 10: Same patient, oblique view. — Figure 11: Same patient. Roentgenogram shows residual lipiodol shadows. Note almost complete resolution of pneumonia in left lung. Symptom free for past ten months.
abscess cavities has been materially increased above the figure given.

One thing is clear, surgery is no longer an immediate issue and when it does become necessary the patient is usually a much better candidate than was the case prior to antibiotic therapy. Moreover, the tendency now is to favor excision of the involved segment of the lung rather than pneumonostomy as it is believed that in many cases dilatation of the radicles of the bronchus draining the abscess cavity exists either at the time the lesion is discovered or develops later. As in bronchiectasis so in lung abscess, the preoperative preparation of the patient can be made more ideal and postoperative complications minimized by aerosol therapy.

Toxic effects such as sore tongue or stomatitis, edema of the lips or mucosa of the mouth, generalized urticaria and dyspnea have been reported. In the series of cases herein presented, sore tongue was encountered twice and dyspnea in two other instances; the latter in the group comprising infectious asthma and fibrosis with emphysema. Stomatitis is readily controlled by proper oral and dental hygiene and rinsing of the mouth with warm saline solution at the completion of each treatment. The allergic reactions mentioned above are easily managed by any of the antihistamine drugs. If dyspnea develops, discontinuing the drug brings about early relief. Subsequent re-institution of inhalations may not bring about return of the complaint. In one case, however,.

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<th>LUNG ABSCESS</th>
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<tr>
<td><strong>Type of Surgery</strong></td>
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<tr>
<td><strong>PNEUMONOSTOMY</strong></td>
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<tr>
<td>1 case</td>
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<tr>
<td><strong>PNEUMOSTOMY</strong></td>
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<tr>
<td>+ lobectomy</td>
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<td>2 cases</td>
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<td><strong>LOBECTOMY</strong></td>
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<td>3 cases</td>
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<tr>
<td><strong>NON-SURGICAL</strong></td>
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<tr>
<td><strong>FOUR</strong></td>
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<td><strong>CASES</strong></td>
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<td>2 patients improved and awaiting surgery.</td>
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<td>2 patients obtained spontaneous closure of abscess cavity. In one, cavity has remained closed two years; in the other, recent recurrence has taken place after 6 months of closure. Latter patient awaiting surgery.</td>
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Figure 12: White diabetic female, aged 32 years. Admitted from another hospital with cough and expectoration of foul sputum. Despite parenteral penicillin and sulfa therapy for 2 months prior to admission, improvement failed to take place. Roentgenogram shows large abscess cavity in the left upper lobe. Figure 13: Same patient after 10 weeks of penicillin, aerosol therapy. Note disappearance of cavity leaving residual infiltration. Symptoms minimal at this time. Figure 14: Same patient after four months of aerosol therapy. Note complete resolution of residual infiltrate shown in Figure 13. Symptom free.
the aerosol therapy had to be discontinued permanently because dyspnea returned each time aerosolization was re-established.

Various methods of nebulization are in use. The fundamental principle is that the nebulizer be so constructed as to emit small particles, 5 microns in diameter or less, if penetration of the

FIGURE 15

Figure 15: Same patient. Bronchogram showing absence of bronchiectasis.

FIGURE 16

Figure 16: Same patient 1 year after discharge. Note absence of any abnormal change in the left lung. Has been symptom free since discharge.

BRONCHIECTASIS

<table>
<thead>
<tr>
<th></th>
<th>Pneumonectomy</th>
<th>Lobectomy</th>
<th>Lobectomy plus Lingulectomy</th>
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<tbody>
<tr>
<td><strong>SURGICAL</strong></td>
<td>18</td>
<td>6</td>
<td>9*</td>
</tr>
<tr>
<td><strong>CASES</strong></td>
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*One patient had right middle and lower lobes excised.

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<tr>
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<th>Symptoms Abated</th>
<th>Symptoms Reduced</th>
<th>Recurrences</th>
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<tbody>
<tr>
<td><strong>NON-SURGICAL</strong></td>
<td>3*</td>
<td>15**</td>
<td>In 3 instances all derived from &quot;Symptoms Reduced&quot; group. In each instance severity and character of symptoms as existed prior to aerosol therapy, returned. Two have responded favorably to re-institution of previous therapy.</td>
</tr>
<tr>
<td><strong>CASES</strong></td>
<td>18</td>
<td></td>
<td>*Only 6 months Follow-up.**Followed from 3 months to 2 years.</td>
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</tbody>
</table>
smallest bronchioles and the alveoli is to be expected. Larger particles are impinged by convection in the nose, throat and upper respiratory passages and are undesirable. Nebulization is generally accomplished by employing a stream of oxygen from a high pressure cylinder to a serviceable nebulizer. In the beginning of our work a Y tube was attached to the rubber connection between the regulator of the oxygen tank and the nebulizer. During inspiration the open end was closed by a finger which was released during expiration resulting in the escape of oxygen during this phase of respiration. More recently the Y tube has been replaced by a demand valve which saves the oxygen that used to be lost in the expiratory phase. To minimize the loss of the antibiotic during expiration a rebreathing bag is attached to the nebulizer. A flow of 6-10 liters per minute of oxygen may be employed. Either normal saline or distilled water is used as the diluent.

Patients too ill to cooperate with the demand valve arrangement described above, may be given penicillin or streptomycin either parenterally for several days when sufficient improvement takes place to switch to aerosol or through an oronasal meter mask by attaching the nebulizer to the latter. Patients with dyspnea and/or cyanosis who require oxygen in addition to aerosol therapy may be given both through a head tent. This method is particularly useful in children. Prigal\textsuperscript{12,14} described a combined steam generator and aerosolizer which produces a warm moist aerosol capable of giving high therapeutic blood levels of penicillin. He claims it is more economical to operate and the small size makes it convenient for use at home, in the office, or in the hospital.

The results in 36 cases of bronchiectasis and in 10 of lung abscess are tabulated below. No further explanatory remarks are necessary except to stress that the figures amply support the statements made above regarding the clinical and anatomical effects of aerosol therapy in bronchopulmonary suppuration. Finally, it is to be noted that in only three instances was penicillin supplemented by streptomycin.

Since the paper was submitted for publication, we have utilized a small bedside or table pump for nebulization instead of oxygen. Pumps by a number of manufacturers are now on the market at very reasonable cost. For patients who have obtained the initial improvement hand bulb nebulizers which produce a fine mist are now available for continued therapy at home.

**SUMMARY**

1) The results in 46 cases of bronchopulmonary suppuration treated by aerosolized antibiotics are reported.
2) Methods of nebulization are briefly reviewed.
3) It is stressed that the local concentration and the topical effectiveness of the antibiotics judged by the clinical and anatomical course of the disease are more important criteria than the blood level.
4) Penicillin and/or streptomycin aerosol therapy usually brings about appreciable clinical and anatomical improvement and therapy minimizes the operative risk in patients able to meet requirements for excisional surgery.
5) In non-operative cases of bronchiectasis attained improvement may be maintained for months or longer although recurrences are frequent. Favorable responses to aerosolization may be repeatedly obtained.
6) With the use of antibiotics surgical drainage is no longer an emergency in lung abscess. Because bronchiectasis not infrequently complicates lung abscess, extirpation of the involved lung segment is favored.
7) Whether the number of lung abscesses which heal spontaneously has increased cannot be stated unequivocally at this moment.
8) Antibiotics by nebulization are more convenient for the patient and their effectiveness equal, and in some instances more definite, than parenteral administration.

RESUMEN

1) Se informa sobre los resultados obtenidos en 46 casos de supuración broncopulmonar tratados con aerosoles de antibióticos.
2) Se repasan brevemente los métodos de nebulización.
3) Se recalca que la concentración local y la eficacia tópica de los antibióticos, a juzgar por la evolución clínica y anatómica de la enfermedad, son criterios más importantes que el nivel sanguíneo.
4) El tratamiento con aerosoles de penicilina o estreptomicina, o de ambas drogas, generalmente causa apreciable mejora clínica y anatómica y reduce al mínimo el riesgo operatorio en pacientes que satisfacen los requisitos para la cirugía de excisión.
5) En casos de bronquitecasis que no pueden ser operados es posible mantener la mejora obtenida por periodos de meses o más, aunque son frecuentes las recidivas. Pueden obtenerse repetidamente las respuestas favorables a la terapia con aerosoles.
6) Gracias al uso de antibióticos, la canalización quirúrgica ya no es una emergencia en el absceso pulmonar. Como quiera que con bastante frecuencia complica la bronquitecasis al absceso pulmonar, se favorece la extirpación del segmento pulmonar invadido.
7) Al presente no se puede declarar en forma inequívoca si ha
aumentado el número de abscesos pulmonares que se cicatrizan espontáneamente.

8) La administración de anti-bióticos nebulizados es de más conveniencia al paciente y su eficacia iguala, y en algunos casos supera, a la administración parenteral.

REFERENCES

1 Segal, M. S.: "Progress in Inhalation Therapy," Modern Medicine, April 1946.
3 See reference (2).

Discussion

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Nebulization therapy is effective in providing at least temporary reduction of pulmonary secretion in most patients who have non-surgical bronchectasis. Primary bronchial dilatation is not affected. The patients are still subject to the hazards of a deformed bronchial tree. It is strongly recommended that they continue therapy at home.

In asthma caused by susceptible micro-organisms, aerosol penicillin and/or streptomycin are indicated whether the chronic or