The Endoscopic Treatment of Parenchymal Tuberculosis

(A Pilot Study in the Human)

A. ALBERT CARABELLI, M.D., F.C.C.P.
Trenton, New Jersey

To date the therapy of pulmonary tuberculosis has been more or less confined to three main categories: compression, extirpation, and chemotherapy. There have been many variations of each procedure and frequently any of the three have been used in combination. The selection of the particular type of therapy or combination has been more or less standardized and to date one sees pneumothorax on the wane; extirpation on the rise; and chemotherapy predominant.

With respect to chemotherapy, review of the literature shows that the trend is towards the almost universal use of isonicotinic acid hydrazide (INH) in combination with streptomycin (SM) or para-aminosalicylic acid (PAS). Dosage of these drugs has been commonly accepted at 4 mg/K, 1-2 grams/week, and 12 grams/day, respectively.

It is interesting to review the literature to date on the chemotherapeutic results in parenchymal tuberculosis, pointing out the salient features and the gross averages in results. All the authors reviewed1, 2, 3, 4, 5 have used INH alone or in combination with SM or PAS in the dosage indicated above. The period of treatment varied from one to 32 months. Sputum conversion was from 5-100 per cent with any increase more or less proportionate to the length of time treated. In all cases the determination of negativity depended on expectorated spittles or on gastric studies. With respect to the constitutional symptoms all authors are in accord with the usual increase in weight, subsidence of toxic manifestations, and the general beneficial effect of INH on the body and psyche. With respect to the x-ray film changes there is reported an over-all improvement in about 60 per cent of cases. Cavity closure was noted in about 30 per cent and diminution in size in 21.5 per cent. Clearing of the exudates was recorded at 24 per cent. There is general agreement that fibrous lesions, calcified areas, thick-walled cavities and old fibro-caseous focii remained unchanged; and that, in many instances, little change is noted in the x-ray film status of the lesion in spite of the conversion, weight gain and sense of well-being. Most of the improvement, often with dramatic clearing, is noted in the recent lesion of an exudative nature. Another axiom in the roentgen observations is that if any im-

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**Chief of Thoracic Medicine, St. Francis Hospital, and Consultant in Thoracic Medicine and Bronchoesophagology, Trenton General Hospital, Trenton, N. J. Formerly Associate in Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.
provement occurs, this takes place in the first three months and then such changes become progressively fewer and of lesser degree.

The following study concerns the exploration of an entirely new approach in the chemotherapy of parenchymal tuberculosis: namely, the endobronchial route. This concept is relatively new and few references are to be found in the literature. Before going into the details of its clinical aspects, however, it is important to outline certain basic anatomicophysiological as well as pathological phases of the fate of particulate matter within the lung. Special reference is made to the tubercle bacillus as well as the antituberculosis characteristics of several drugs for a better understanding of the rationale of this type of therapy.

Studies of the fate of particulate substances including the tubercle bacillus introduced into the respiratory channels show a definite reaction on the part of the host to such invasion. The portion of this matter not immediately removed by cough penetrates the air passages and is carried to their finest subdivisions where it is subjected to reactions brought about by the protective forces indiginous to normal tissues. Phagocytosis is the first to function but is limited to particles less than 10 microns in size. The larger particles are not engulfed; they are promptly removed through the airways by the usual excretory function of entrapment in mucous secretions, ciliary motion, molding by the spiral bronchial musculature, and the expellent force of cough. Three cells—the polymorphonuclear leukocyte, the mononuclear alveolar cell, and the mononuclear cell which is believed to come from the blood—are the phagocytes concerned in removing particulate matter from the parenchyma; and this is done by way of the lymphatics. One mechanism is by way of the superficial lymphatics, which follow the first radicle of the pulmonary vein from the center of the primary lobe to its periphery and then course outward to join the subpleural plexus which in turn unite to form the lymph vessels that empty into the hilar nodes. The second is by way of the deep lymphatics, which follow the bronchial and vascular channels towards the hilar lymphnodes. Still a third method of excretion through the alveolar ducts, bronchioles, and bronchi exists but does not concern us in this study since it is non-contributory to the concentration of the drug in the parenchyma or lymphatics.

Once started, the lymphatic removal of particulate matter is rather rapid as can be seen following the introduction of graphite in the trachea when this substance will appear in the paratracheal nodes in about an hour. Tubercle bacilli similarly introduced have been culturally recovered from various organs 12 hours after introduction.

The superficial lymphatic route may be demonstrated by the presence of cells crowded together into irregular, ill-defined groups spaced at irregular, intervals along the course of the radicles of the pulmonary vein and in the subpleural lymphatic tissues. In these situations permanent lesions develop as anatomic tubercles when the foreign substance is the tubercle bacillus. The route of the deep lymphatics may be similarly traced by the temporary and permanent grouping of the phagocytic cells
along their course and also by observing the bronchial lymph follicles through and around which the lymphatics course. Often these vessels are crowded with degenerated phagocytic cells being carried out of the lung.

These observations would indicate that the introduction of particulate matter of antituberculosis activity directly into the bronchi would follow the same route taken by the tubercle bacillus and thus introduce bacteriostatic or bacteriocidal agents directly into focii usually involved by tuberculous infections. With such a portal of entry several advantages are obvious: firstly, a very high focal concentration of the drug may be possible which would remain in the lobe for an indefinite period (oily suspension); secondly, phagocytes loaded with engulfed drug particles are made the bearers of the noxious agent to the tuberculous focii proper and, with their death, release a therapeutic bomb; thirdly, bacilli-laden phagocytes will transport only non-viable bacilli to new focii since INH,

FIGURE 1: Upper lobe instillation with the Pentascope. This figure shows the instrument being used for biopsy. In instillation techniques a flexible woven catheter is substituted in lieu of forceps. Note possibility of segmental bronchus visualization and catheterization. In this case the apical segmental bronchus of the right upper lobe has been entered.
unlike SM, readily penetrates cell membranes in effective bacteriostatic or bacteriocidal concentration.\textsuperscript{10-11}

From the experimental animal and human studies\textsuperscript{10-11} it may be concluded that the oral administration of INH results in its concentration in the body fluids and plasma in direct proportion to any given dose whether in single or chronic administration; and that its retention is non-cumulative since it is rapidly excreted from the urine, faeces, and saliva. The same studies indicate that the safe dose for chronic administration in man is an oral dose of 3-4 mg./K per day, which will result in a plasma concentration of 1.3-3.4 gamma/ml. The incidence of toxic reactions above these levels seems to be in direct proportion to the increased dosage.

It is obvious, that with the conventional oral dose, we are distinctly limited as to the amount of the drug which can be used safely. If we attempt to increase the dose on the supposition that a higher plasma concentration will have a stronger anti-tuberculosis effect, we are faced with a therapeutic frustration. Now, if the lung proper could be used as a therapeutic portal, we might be able to increase the concentration of the drug at the site of the disease without saturating the body as a whole and thus avoid any systemic toxic reactions. Such a concept might be feasible if a slowly absorbed preparation could be used which would saturate the lobe or lobes and still be ineffective in raising plasma levels to toxic thresholds. Herein lies the concept of lobar or multi-lobar rather than body saturation.

In the lung we have an anatomic cul-de-sac not equipped by nature for the rapid absorption or the chemical alteration of foreign substances as is the case with the intestinal tract. Physiologically the lung is highly specialized for gaseous exchange only; and for these purposes has a tremendous surface area. It also has a great potential for phagocytosis because of its richness in capillaries and lymphatics. It has been possible to instil substances of low absorption characteristics such as penicillin in oil into these passages with considerable clinical success (12); and it has long been known that such substances as lipiodol remain in residence for many months without any harm to the parenchyma proper or detectable impairment to the lobar physiology.

From the technical point of view it is presently possible to instrumentally reach many of the segmental and certainly all of the lobar bronchial levels for practical instillation of such substances.

It is interesting, on a purely gross theoretical basis, to calculate the drug concentration in one milliliter of lobar fluid when 10 cc. of an oily suspension containing 500 mg. of INH is introduced into a lobar bronchus. Using 991 grams as the average weight of the human lungs (33) and then considering the presence of six lobes by assuming the lingular division as a separate lobe, we arrive at an average lobar weight of 165 grams. Assuming that 90 per cent of this tissue is liquid matter, we could have a total of 148.5 mls. which eventually pick up 500 mgm. of INH. This would be equivalent to 3367 gamma/ml. of the drug. Again, on the assumption that 75 per cent is lost through the alveolar ducts, bronchioles, and bronchi, as well as dissipated to other organs and tissue fluids by
the blood stream, there might be, at any one time, a potential level of saturation of 842 gamma/ml. in the lobe concerned, uniformly disseminated according to the laws of osmosis, mass action, and phagocytosis. When this concentration is compared with the normal ranges of 1.3-3.4 gamma/ml. (plasma) obtained by standard oral medication, we can readily see the advantage of such a therapeutic portal if the clinical findings, host, and parenchymal tolerance, could justify such a procedure.

Another interesting observation in this respect is that animal studies indicate that INH is broken down into isonicotinic acid and ammonia by enzymatic action in most organs, but that is not true in the lung (rat). If a parallel situation holds in the human, we have this added advantage to the use if the lung as a therapeutic portal.

**Selection of the Drug of Choice**

The fact that the preponderance of the literature in the chemotherapy of pulmonary tuberculosis centers about INH indicates that this particular

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**FIGURE 2:** H. G., a white female, age 21, with a history of right-sided pulmonary tuberculosis treated successfully with pneumothorax from 1950 to 1952, when pneumothorax was discontinued. Patient well and on full duties until 1954 when she developed a recurrent far-advanced ipsilateral lesion. Bronchial aspirate was positive for tubercle bacilli. Note very rapid clearing of the lesion within an interval of 5 weeks following the instillation of endobronchial INH. This patient was on concomitant oral INH and PAS in full doses, but in spite of this she developed a cavitational lesion 2 months following the complete regression of the original massive lesion. The cavity disappeared completely in 1½ months following a second endobronchial instillation. Note complete restitution to normal of the parenchyma except for the basal diffuse cloudiness which represents pleural thickening following the abandonment of the original pneumothorax.
drug has definitely proved its antituberculosis effect clinically. It has the advantage of low toxicity even when administered over a long period of time. With respect to strains resistant to SM it is more effective because of its ability to penetrate the cell membrane in effective concentration which is not true of SM.\textsuperscript{10,11} For example, a concentration of 0.05 gamma/ml. of INH will prevent the growth of H37Rv strains when compared with 25 gamma/ml. in the case of SM. This latter concentration is therapeutically not possible.

Resistance studies\textsuperscript{8} indicate that most strains of the tubercle bacillus become resistant to INH in from two to four months, which probably accounts for the rather dramatic initial systemic as well as roentgen changes which taper off as the time of its use is increased. When combined with PAS, however, resistance is much longer in developing and much longer than when combined with SM. In the present study this combination was not used as it was the intent to study only one drug.

Following study of the various available preparations of INH, a lyophilized form manufactured by the Panray Corporation of New York was found most suitable. This preparation comes in sterile vials containing 1 gram of the drug. The addition of 20 cc. of sterile olive oil and shaking well resulted in the basic suspension used in this study. This suspension is easy to work with and readily instilled with the catheters and instruments devised. A 15 or larger gauge needle facilitates aspiration into a standard syringe. The radiopaque suspension, the use of which will be described later, is made by adding 10 cc. of sterile olive oil and 10 cc. of Dionosil to the 1 gram vial of INH.

\textit{Bronchographic and Bronchoscopic Observations on Behaviour of Oily Substances in the Lung}

General observations in the use of oily contrast and therapeutic media in the lung indicate that such substances have little deleterious effect on the parenchyma (not true of mineral oils); and furthermore, that such preparations may remain safely in residence for many months as can be appreciated from the study of films following lipiodol bronchography. These media have the property of clinging to the bronchial mucosa by capillary attraction in thin films and readily enter the alveoli when used in excessive amounts; or when of low viscosity. Admixture of the basic suspension with Dionosil confirmed a parallel behaviour for this suspension. From these considerations it is assumed that such media will remain \textit{in situ} long enough to be phagocytized and otherwise distributed throughout the lobe.

Retention of oily media in the lungs with anesthetized bronchi depends on the absence of the cough reflex and the suction action of inspiration which exceeds the expellent effort of expiration. This phenomenon is constantly seen in bronchography when the oily contrast medium is seen to make jerky progress towards the periphery of the lung with each inspiration. This inspiratory pull is quite forceful since it functions anti-gravitationally as can be seen when upper lobes fill when the catheter
is juxtaposed at an upper lobe orifice even when the patient is erect. Bronchoscopically this retention is confirmed following introduction deep into a lobe, when prolonged waiting will not reveal the presence of the medium at the mouth of the orifice.
Lipoid granulomas following the instillation of peanut oil based contrast media have been reported. Personal experience with similar media in 297 recorded five-lobe bronchograms and 70 penicillin (peanut oil base) instillations would indicate, at least in the author's experience, that such incidence is comparatively rare. None were encountered in the above cases. In the present study 71 instillations were made with the basic suspension with no evidence of such granulomas. An excellent opportunity was present to detect them since all patients had weekly chest films taken following instillation and later at monthly intervals throughout the period of observation. In none of the series was there any indication of alien shadows which could be interpreted as granulomas.

Toxic Manifestations of INH Suspension

Preliminary studies with the basic suspension indicated that this medium was well tolerated by the parenchyma as well as the host with the exception of a transient pneumonitis which occurred soon after the introduction into the lobe. The typical reaction, as observed on x-ray film study, consisted of an over-all blurring when compared with the original film and a suggestion of a severe exudative process, which made one believe that the lesion had undergone a precipitous aggravation. With the exception of a slight pyrexia systemic reactions or symptoms did not occur. This process cleared rapidly within the space of one week but recurred following subsequent instillations though not to the same extent. No permanent effect on the parenchyma was noted. In the cases studied only one was considered severe, one moderately severe, and four slightly so. In the others no appreciable change could be detected.
Figure 4: J.S., a white male, age 45, with a negative bronchial aspirate and bilateral far-advanced fibro-caseous lesions with a large cavity in LUL. History of recent sanatorium care for over 1 year on conventional therapy with INH, PAS, and SM. In the serial x-rays note the rapid decrease in the size of the cavity following INH institution as well as the resolution of the associated infiltrates. Cavity proper actually closed in 7 weeks. (See text 4.6, on facing page.)
Clinical Material Used in the Study

The patients studied in this series were not selected but were treated as they appeared in sequence. All were ambulatory and only the more severely ill were confined to bed until the acute symptoms had subsided; but in no case longer than two weeks. They are classified on the basis of x-ray film findings and the severity of this involvement. All but two were on concomitant oral INH with conventional dosages. Two pregnancies, two diabetics and one far-advanced unilateral bronchiectasis were the non-tuberculous associated findings in the series. Two had complicating pleural effusion. In addition two had persistent cavities with pneumothorax failure. One had tuberculous bronchostenosis of the left side with a destroyed lung. Two were post-surgical positives—one a lobectomy with exudative spread and the other an ivalon sponge plombage. The others ranged from acute exudative to the chronic fibro-caseous and fibroid types though in some these phases were combined. Many cavities were encountered in the series—some single and others multiple in the same patient.

Technique of Secretion Studies

It was decided for the purpose of this study to use a refinement of the standard technique for the detection of the tubercle bacillus. This method yields a higher percentage of positives than is possible with the expectorate and reduces the number of false negatives. It has been the author's impression for some years that the usual sputum and gastric search for tubercle bacilli is rather coarse, tedious, and prone to many false negatives; furthermore a positive expectorate usually connotes fairly advanced disease and waiting for such a finding may make us temporize in specific therapy.

All the patients were bronchoscooped and the secretions obtained directly from the infected lobe or lobes by a special tubercle bacillus collector designed by the author. All initial aspirates were studied by smear,
culture, and guinea pig inoculation whenever possible and the same was done when a persistent negative smear was obtained. The initial aspirate was generally sufficient for all three studies; though subsequent aspirates were found extremely scanty and frequently only a sufficient amount was obtained for a smear.

**Technique of Laryngotracheobronchial Anesthesia**

Proper anesthesia is a *sine qua non* as without it the procedure becomes a waste of time and effort. The cough reflex must be completely abolished not only in the involved bronchus but in all the others as well. The author has devised a method of anesthesia for bronchoscopy and bronchography which is safe and effective for these purposes and has been used in all the patients of this series. Special attention must be paid in this technique, however, to spraying the trachea and lobar bronchi with an endobronchial atomizer prior to attempting the instillation of the basic suspension. It is wise to spray these structures and then wait about five minutes before instilling. If abundant secretions are present, it is necessary to completely aspirate the entire tracheobronchial tree as surface anesthesia is relatively ineffective in their presence.

**Various Methods and the Instruments Used for the Instillation of INH Oily Suspension in the Lung**

1. **Instillation with the Standard Bronchoscope**:

   For instillation of the basic suspension into the lung bronchoscopically a new instrument had to be devised so that this could be done accurately and effectively. Since most of the lesions existed in the upper lobes, a problem arose when the standard bronchoscope was used. This instrument is generally best used for instillation purposes in the bronchial axis, when an ordinary metal catheter with a Luer-lok tip may be used. The designing of a special catheter made possible upper lobe instillation with little difficulty. This instrument consists of a monel tube of proper length whose tip was protected with a hollow ball and its terminal portion bent at an angle which was sufficient to permit passage through a 7 mm. lumen. Its proximal end was equipped with a Luer-lok adapter with a directional index bead in the plane of the curve. With this equipment the bronchoscope is placed opposite the upper lobe to be instilled and the patient's head and neck rotated to the opposite direction. The bronchoscope lip is then engaged in the lobar bronchus spur and the special catheter manipulated to enter the lobar bronchus which is now almost in the bronchoscopic axis. Care must be taken that the catheter end is not placed into a segmental bronchus which may then be filled to the exclusion of other diseased segments. This is particularly true of the anterior segment of the right upper and the lingular division of the left upper lobes. In practice, it is sufficient to introduce the suspension only into the lobar orifice as it will automatically be aspirated into the various segments of the lobe if the respiratory physiology is not too impaired. Accurate segmental localization is not necessary, except for
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special reasons, since it is rather difficult to decide on x-ray observations alone how many segments are involved in a tuberculous process.

2. Instillation with Special Optical Catheterizing Bronchoscope (Pentascope): (Fig. 1)

A more accurate technique for instillation is with the use of an optical catheterizing bronchoscope designed by the author for this specific purpose. With this instrument it is possible to instil accurately into any lobar orifice under direct vision and even into segmental bronchi.

3. Instillation by Bronchographic Technique:

To extend this study for the benefit of those skilled in bronchography a technique of instillation has been worked out by the addition of Dionosil to the basic suspension which renders its adequately radiopaque. The

FIGURE 5: R. T., a white female, age 31, with positive bronchial aspirate. Note rapid clearing of the super-imposed tuberculous infiltrate revealing a hidden cavity. The cavity closed and the lesion almost completely regressed in 1 month. In 5 months there is complete clearing of the lesion with restoration to normal of parenchymal markings.
The author prefers a bronchoscopic approach even when using this modified suspension for reasons of proper diagnosis, detection of obstructive or stenotic lesions, proper aspiration and adequate surface anesthesia; as well as for the progress detection of tubercle bacilli in the aspirate. The bronchographic catheter is introduced through the bronchoscope to the side desired and the latter withdrawn leaving the catheter in place. The catheter used for this purpose is a standard 12 F woven ureteral catheter, non-graduated, non-x-ray (C. R. Bard, Inc., Summit, New Jersey) (No. 302), which has been modified by the insertion of a snugly fitting two inch monel tube in the tip so that it occludes the second orifice. The tip over the metal tube is bent at an angle which still permits passage through a 7 mm. lumen bronchoscope. The proximal end was equipped with a special Luer-lok adapter and small tubular insert which prevents closure of the lumen when the adapter is tightened over a plastic or rubber tubular sleeve. The original length of the catheter is adequate for working over a fluoroscopic screen and the terminal curve and single aperture permit accurate localization of the suspension within the lobar orifice to be filled. Simple rotation at the carina permits easy shift from one main stem bronchus to the other. The terminal metal insert renders the tip constantly visible during fluoroscopy.

Lately it has been found advantageous to use the radiopaque suspension with all of the above techniques since hidden cavities and bronchiectatic areas become visible and obviate the use of tomography. An excellent film record can be obtained for verification of the degree and extent of filling. Another innovation has been the routine complete filling of all five lobes at the same sitting after the known diseased lobes have been filled. This takes care of latent or non-detectable infection in the other lobes and to date has not been found harmful.

No matter which of the above techniques is used instillation should be gentle, deliberate and slow. Most of the lobes will usually tolerate 10 ccs. of the suspension. It must be remembered that aspiration into the branch bronchi from the lobar bronchus takes some time and that flooding of the lobar bronchus too quickly will evoke a cough reflex no matter how adequate has been the surface anesthesia. The phenomenon may be explained by the pressure of air retained in the bronchioles and alveoli eliciting a distension cough reflex not controlled by the anesthesia.

**Positioning of the Patient for Instillation**

For bronchoscopic techniques instillation is originally made with the patient in the standard bronchoscopic position though immediately following this the patient is placed in more advantageous positions to take advantage of gravitational forces.

For upper lobe work the patient is placed in an oblique position with the side filled downward and the table inclined 5 or more degrees cephalad for about 15-20 minutes. For middle lobe the position is face down with the table in the horizontal position. For lower and lingular branch instillations the patient lies on his back with the table tilted 5 degrees
caudad. The Ritter electric hydraulic table with the modified head rest is excellent for these purposes as well as for general endoscopic work. Following the 15-20 minute rest, the patient is removed to bed or couch and the same position duplicated except for tilting. He is admonished not to cough. For multiple lobe filling a compromise position is arranged so that the flow will gravitate to the lobes filled. For example, when both upper lobes have been instilled the most favorable position will be flat on the back with the table tilted cephalad.

For five lobe filling with the bronchographic technique the patient lies on the radiographic table on his back. The more involved lobe or lobes are filled first by proper postural techniques. Oblique positioning to the right or left will almost completely fill the tracheobronchial tree of any particular side though a cephalad tilt while the patient is in this oblique position will take care of the upper lobes. The middle lobe fills best and spontaneously with the patient face downward with the table in the horizontal position. A good procedure to follow is to fill first the upper lobe with a tilt, the lower lobe with the table horizontal or tilted caudad. The same is then done with the other side. The patient is then placed on his face for automatic filling of the middle lobe. Experience will acquaint the operator with the time intervals needed for each side. Following instillation the patient rests on the radiographic table for 15-20 minutes prior to removal to bed or cough. It has been noted that once the suspension has penetrated the bronchioles and alveoli it remains there even after the cough reflex returns; though the patient still is exhorted not to cough.

Results

The results obtained in this study are summarized in Tables I, II and III. With respect to conversion, 86 per cent of the patients became and stayed negative during the period of observation. The shortest interval was 21 days and the longest 11 months. These figures, however, are not too accurate since the conversion interval was determined from the first positive to the first persistent negative; though in many cases bronchoscopic aspiration was not done until some time after the lesions had cleared or became stationary. The actual conversion time could have been much shorter. The average period of tabulated conversion was 96 days.

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>CONVERSION STUDIES WITH ENDOBRONCHIAL INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Cases</td>
<td>18</td>
</tr>
<tr>
<td>No. Positive</td>
<td>14 (78 per cent)</td>
</tr>
<tr>
<td>Average Instil./pnt.</td>
<td>4 (500 mg. each)</td>
</tr>
<tr>
<td>No. Converted</td>
<td>12 (86 per cent)</td>
</tr>
<tr>
<td>Average Time for Conversion</td>
<td>96 (days)</td>
</tr>
<tr>
<td>Failures: Lobect., Plombage</td>
<td>2 (14 per cent)</td>
</tr>
</tbody>
</table>
TABLE II
X-RAY CHANGES FOLLOWING INH ENDOBRONCHIAL INSTILLATION

<table>
<thead>
<tr>
<th>No. Cases</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Instil./pnt.</td>
<td>4 (500 mg. each)</td>
</tr>
<tr>
<td>Complete Clearing</td>
<td>10 (59 per cent)</td>
</tr>
<tr>
<td>Exudate Clearing</td>
<td>14 (100 per cent)</td>
</tr>
<tr>
<td>Cavity Closure</td>
<td>10 (100 per cent)</td>
</tr>
<tr>
<td>Time to Clear/Close</td>
<td>55 days average</td>
</tr>
<tr>
<td>Time Remaining Static</td>
<td>14 months average</td>
</tr>
<tr>
<td>No Change:</td>
<td>4 (22.2 per cent)</td>
</tr>
<tr>
<td>2 Fibroid, 1 Plombage</td>
<td></td>
</tr>
<tr>
<td>1 Destroyed Lung</td>
<td></td>
</tr>
</tbody>
</table>

The x-ray film findings were rather striking with complete clearing of visible lesions in 10 of the series and complete closure in 10 separate patients with cavitation. Closure was effected in cases of single as well as multiple cavities. The time for clearing of the lesions as well as closure of the cavities was also remarkable with the shortest interval 14 days and the longest 120 days with an over-all average of 55 days. Complete clearing of the lesions was noted in 59 per cent of the series.

Weight gain varied from two to 29 lbs. The two diabetics, however, because of their dietary regimen lost six and 10 lbs. Two patients neither gained nor lost. With these exceptions the average weight gain distributed amongst the remaining 14 patients was 13 lbs.

The maximum sedimentation rate (MSR, Cutler technique) was usually proportional to the rate of clearing and systemic improvement. The greatest drop, prior to treatment, was 15 mm. and the lowest 0.5 mm. with the average of 6.0 mm. Following treatment the highest was 7.0 mm. (bronchiectatic case) and the lowest 0.5 mm. with an average of 2.2 mm.

An attempt was made to compare the findings in this pilot experiment with the gross results as obtained from a compilation of the figures found in the literature (Table III). Comparison is of course only relative because of the small number of cases in this pilot experiment. It will be noted

TABLE III
RESULTS OF PILOT STUDY COMPARED WITH AVERAGES IN THE LITERATURE

<table>
<thead>
<tr>
<th></th>
<th>Literature Per Cent</th>
<th>Pilot Study Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversion</td>
<td>48</td>
<td>86</td>
</tr>
<tr>
<td>Gen. x-ray improv.</td>
<td>60</td>
<td>82.5</td>
</tr>
<tr>
<td>Exudate Clearing</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>Cavity Closure</td>
<td>30</td>
<td>100</td>
</tr>
</tbody>
</table>

*References 1 to 5
that the conversion rate is rather high (86 per cent); the x-ray improvement moderately higher (82.5 per cent); and the clearing of the exudates and cavity closure 100 per cent.

Discussion

It would seem from the results obtained in this pilot study that the theoretical considerations which made it possible were justified. Apparently the airways may be safely used as a portal of therapy with antituberculous agents in oily suspension and that the concept of lobar or multilobar rather than body saturation is a feasibility. It is also evident that to be effective the lobar physiology must not be too grossly impaired. With this type of therapy as well as with all others the need for early detection is still in order.

It is important to note the specific lytic action of the suspension on the tuberculous foci as seen on the serial x-ray films with the tendency to restoration to normal of the parenchyma. The onset of a transient INH pneumonitis should not be interpreted as an aggravation or failure of the procedure as following the apparent exacerbation, the foci begin to clear with disappearance of the exudates, visualization of hidden cavities, and reappearance of the parenchymal components. Cavity walls become better defined, thinner and the cavity itself soon becomes distorted or collapsed due to external pressure on its weakened walls; or it may diminish in size weekly with eventual complete closure. In the series complete disappearance of good-sized cavities usually occurred in six to seven weeks.

A question may arise on the relative value of the endobronchial therapy per se since it was combined with oral therapy of INH and PAS in many of the patients. An attempt was made originally to confine the therapy only to the endobronchial instillation and this was actually done in two of the patients by mutual consent; the others insisted in adjuvant therapy once the diagnosis of tuberculosis was made. These two patients (CS and JM) had excellent response with the endobronchial medication and cleared completely with only one instillation. One (J.S.) had been in a sanatorium for over one year on full doses of INH, PAS, and SM with a persistent large cavity. One endobronchial instillation closed the cavity in seven weeks. Several others of the series had complete regression of the lesions following a first instillation but had cavitational recurrences in different locations in spite of the fact that they were on continuous oral medication in full doses. A second instillation promptly resolved the lesions and there has been no further recurrence. Apparently oral medication in these particular patients was not effective in controlling or preventing recurrences of lesions.

From these observations it may be stated that the endobronchial therapy for pulmonary tuberculosis is indeed specific and apparently independent in its action from any effect of oral therapy.

The rapid disappearance of fluid in the two cases of effusion complicating the pulmonary lesions would indicate that this treatment is also effective against tuberculous effusions. Bronchoscopic observations with
respect to secretions show that these are considerably reduced in quantity and modified in character following INH instillation; and in many of the patients stopped completely within a short interval. Papanicoloau smears showed a rapid disappearance of the leukocytes with reversion to a normal cytogram.

Dosage schedules, because of the pilot nature of this study were more or less arbitrary and instillations were generally repeated when it was considered that an additional instillation would further effect the regression of the lesion. For the same reason accurate spacing could not be determined since the time intervals of effective change and quantitative response of the lesion were unknown factors. In general, it would now seem that from one to four instillations are necessary for maximum therapeutic effect spaced at 20 day intervals. This arrangement, however, is a mere guide and, if the lesions persist or recur, a second instillation is in order at any particular time.

The amount of the suspension used was generally 10 cc. per lobe and for these purposes the lingular division is considered as a separate lobe. Multiple instillations, when indicated, are made at the same time. With the five lobe bronchographic technique as much as 25-30 cc. of the radiopaque suspension may be used.

Resistance of the tubercle bacillus as judged clinically has not been a factor in this study when using the endobronchial instillation; though it may be expected when the scope of this technique is enlarged to a greater number of cases.

NOTES:

The INH preparation used in this series was the 'Lyophilized Isoniazid 'Panray,'" which was kindly supplied for this study by the Panray Corporation, New York, New York.

All the bronchoscopic instruments mentioned as well as the optical catheterizing bronchoscope (Pentoscope) and the special catheters are presently being manufactured by the George P. Pilling and Sons Company, Philadelphia, Pennsylvania, to whom the author has given originals which were personally designed and made.

SUMMARY

1. A series of 18 cases of pulmonary tuberculosis of various types and degrees of severity has been treated by the endobronchial instillation of an oily suspension of isonicotinic acid hydrazide as a pilot experiment.

2. This study would indicate that, with this new portal of therapy:
   a. The conversion rate becomes high and is obtained in rather short intervals.
   b. Complete disappearance of the lesion, its improvement and cavity closure incidence is higher and shorter in time intervals than with conventional oral therapy alone.
   c. INH in oily suspension endobronchially introduced has a pronounced specific lytic action on tuberculous foci.

3. The medication and the techniques described are safe and free from any detrimental parenchyma or constitutional effects.

4. The clinical and roentgen results appear to be permanent and not of short duration.
5. *Lobar or multilobar drug saturation* is proposed as a new concept in the chemotherapy of pulmonary tuberculosis.

**RESUMEN**

1. Como un experimento piloto, 18 casos de tuberculosis pulmonar en varias formas, se han tratado con instilaciones de una suspensión aceitosa de hidracida del ácido isonicotínico.
2. El estudio indicaría:
   a. La proporción de conversiones se hace elevada y es obtenida a corto plazo.
   b. La desaparición completa de la lesión, su mejoría y el cierre de cavidades es más elevada y se obtiene más pronto que el método oral.
   c. INH (isoniacida liofilizada) en suspensión oleosa endobronquialmente tiene una acción lítica pronunciada en los focos tuberculosos.
3. La medicación y la técnica descritas son seguras e incapaces de dañar el parénquima y de causar daños al estado general.
4. Los resultados clínicos y radiológicos parecen ser permanentes y no de corta duración.
5. *La saturación lobar o multilobar* se propone como un concepto nuevo en la quimioterapia de la tuberculosis.

**RESUME**

1. A titre d’essai expérimental, une série de 18 cas de tuberculose pulmonaire de type et de gravités différentes a été traitée par instillation endobronchique d’une suspension huileuse d’hydrazide d’acide isonicotinique.
2. Cette étude indiquerait que, avec ce nouveau mode de traitement:
   a) le taux de négativation est élevé, et est obtenu en un temps relativement court;
   b) la disparition complète de la lésion, son amélioration et la fréquence de la fermeture cavitaire est plus élevée et survient dans un intervalle de temps plus court qu’avec le seul traitement buccal conventionnel.
   c) L’INH (isoniazide lyophilisé) en suspension huileuse administré par voie endobronchique a une action lytique spécifique prononcée sur les foyers tuberculeux.
3. La médication et les techniques décrites sont sans effets secondaires nocifs sur le parenchyme ou sur l’état général.
4. Les résultats cliniques et radiologiques semblent être stables et de longue durée.
5. *La saturation médicamenteuse lobaire ou multilobaire* est proposée comme un nouveau procédé de la chimiothérapie de la tuberculose pulmonaire.

**ZUSAMMENFASSUNG**

2. Diese Untersuchung vermag zu zeigen, dass mit diesem neuen Zugang der Therapie:
   a. Die Ziffer der Bazillenfreiheit gross und in ziemlich kurzem Zeitabschnitt erreicht wird.
   2. Komplettes Verschwinden der Herde, ihre Besserung und das Vorkommen von Kavernenverschluss ist häufiger und erfolgt in kürzeren Zeiträumen als durch die übliche orale Therapie allein.
   b. INH (lyophilisiertes INH) in öliger Aufschwemmung endobronchial eingeführt hat eine ausgeprägte Lytische Wirkung auf tuberkulöse Herde.


5. Lobäre oder multilobäre Arzneimittelsättigung wird als ein neuer Begriff in der Chemotherapie der Lungentuberkulose vorgeschlagen.

REFERENCES


