Surgical treatment of coccidioidomycosis is recognized as a proved method of curative therapy. However, there is not universal agreement as to the specific method of management. The decision regarding management is made on personal experience and judgment and this varies with the individual surgeon. In general, the division on methodology hinges on an opinion regarding administration of amphotericin B (Fungizone). There are those surgeons who do not use it in any circumstance. Some reluctantly agree that it may have a place for treatment of complications. The latter insist their complications are few and their use of amphotericin B is therefore minimal. They believe amphotericin B is an extra hazard to surgical therapy. A second group of surgeons uses amphotericin B in specific circumstances, but prefers to avoid its use if at all possible. The third group, and the one to which the authors adhere, believe that amphotericin B has a definite place in surgical methodology. The specifics for its use have been detailed in other publications, but reference to a suggested dosage of this drug will be made later in the paper. The justification for its use is based on the demonstrated decrease in complications when two groups of surgical cases are compared. In one group, surgery was performed without amphotericin B; the other group received amphotericin B. The complication rate decreased from 20.4 per cent to 4.2 per cent.

It has been of significant importance to us to have support in our opinion and conclusions from a separate parallel unrelated study. Evans and the late Dr. William Winn reached identical conclusions as to the merits of amphotericin B. This was summarized in a statement by Dr. Winn, "the judicious use of amphotericin B in preparing cavitary coccidioidomycosis for surgery is of enough protection in safeguarding surgical results as to far outweigh any objections that might be raised as to amphotericin B toxicity." A similar difference of opinion regarding the use of amphotericin B in the surgical treatment of histoplasmosis has been recorded. Support for the value of amphotericin B in this disease will be found in articles by Beatty, Furcolow, Gryboski and their co-workers. Ahn et al have recently reported their experiences in surgical therapy of cavitary pulmonary histoplasmosis. They recommended both preoperative and postoperative use of amphotericin B because of a remarkable reduction of complications of the surgery when this regimen is followed. Levene and colleagues give lukewarm but obvious support of its use, but fail to mention dosage used. The non-advocates of amphotericin B are Diveley, Furcolow, and Mendenhall and Sealy. It would seem, therefore, that the neophyte in this field, whether concerned with coccidioidomycosis or histoplasmosis, will be torn between fact, opinion, experience, medical and surgical contacts and personal judgment. All this is further influenced by the geographic location of the practice.

It should be emphasized that amphotericin B is not recommended for every case of pulmonary coccidioidomycosis coming to surgery. Until we know a good deal more about this disease, we cannot make any statement as to why certain cases of pulmonary coccidioidomycosis are tame and somnolent and not given to causing trouble. The solid nodule is one of the latter lesions. Other lesions (cavities in particular) are wild, dangerous, capricious and unpredictable. We can only emphasize that in the latter case, which we try to identify herein, amphotericin B is often obligatory. It is most important to identify the cavitary “fissure jumper.” This type cavitary lesion is recognized by those experienced in this disease. The “why” of transgression of both visceral and parietal pleural boundaries remains a mystery. Tuberculosis does not act in a like manner.

The indications for surgical therapy of pulmonary coccidioidomycosis are listed in Table 1.

The pulmonary coin lesion requires special attention. Coccidioidomycosis as a geographic endemic...

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*From the College of Medicine, University of Arizona, Tucson.
**Phoenix, Arizona.
Table 1—Indications for Surgical Therapy

<table>
<thead>
<tr>
<th>1. Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Giant cavity (over 5 cm)</td>
</tr>
<tr>
<td>b. Infected cavity</td>
</tr>
<tr>
<td>c. Ruptured cavity</td>
</tr>
<tr>
<td>2. Probable</td>
</tr>
<tr>
<td>a. Enlarged cavity</td>
</tr>
<tr>
<td>b. Cavity with hemorrhage</td>
</tr>
<tr>
<td>3. Possible</td>
</tr>
<tr>
<td>a. Coin lesion</td>
</tr>
<tr>
<td>b. Persistent cavity</td>
</tr>
</tbody>
</table>

factor reduces the incidence of malignancy in the coin lesion from 30 per cent to 5 per cent. The responsibility for making the decision for or against removal of any coin lesion remains a diagnostic difficulty of no small magnitude to Southwestern thoracic surgeons.

In the past, surgery of pulmonary coccidioidomycosis has been fraught with a significant complication rate. This rate has varied with each surgeon—a high of 26 per cent was reported by Hyde in 1960, a low of 5 per cent by Cotton in 1965, and an overall average of 13 per cent in a collective review of 400 cases by Melick in 1958. It is interesting that the series of Evans and Winn was also attended by a complication rate of 13 per cent. In 1965, Marks reported a series of 256 cases in which the complication rate was 6.7 per cent. The fact that 159 of his cases were of the nodular form may have greatly influenced his statistical finding of minimum complications, as we believe the type of disease process for which surgery is performed is a major contributor to the complications. In those cases with complications, amphotericin B has been a comfort. For those physicians who want to be so comforted the following will be pertinent: Most patients tolerate amphotericin B in a dosage of 500 mg without any difficulty whatsoever. The majority of the patients can tolerate twice this dosage without any serious difficulty. The administration of 2000 mg of amphotericin B is not considered excessive, but does fall at the lower level of what might be termed "reasonable safety." Furthermore, 5000 mg is believed to be within the realm of "relative safety." Close monitoring of the patient with regard to bone marrow response, kidney, and liver function, is an absolute must when therapy with amphotericin B is undertaken.

We advocate amphotericin B as preoperative therapy in a dose of 600 mg, increasing the daily dose from 10 to 15 mg per day to 50 mg per day on about day five. We believe 400 mg to be the absolute minimal dose in preparation for surgical intervention.

Report of Surgical Experience

In a recent series of 92 pulmonary resections for cavitary coccidioidomycosis by Grant and Melick, a comparative analysis was made between 44 resections accomplished without the use of amphotericin B and 48 resections with the use of amphotericin B (Table 2).

Of significance was the large number of segmental resections performed in the early group in contrast to the significant increase in lobectomies in the later group. Of prime importance, however, was the overall complication rate of 20.4 per cent in the group not receiving amphotericin B in contrast to the 4.2 per cent complication rate in the group which did receive amphotericin B. The series also emphasized that the highest incidence of complications occurred in the segmental resections. This was especially true when amphotericin B was not utilized.

We would be the first to state that it is impossible to delineate an absolute indication for the use of amphotericin B. There are many reported cases wherein surgery without amphotericin B was accomplished without complications. This may lead some surgeons to be overly optimistic and may result in the unwarranted assumption that coccidioidomycosis is a benign disease. One complicated case in the hands of these optimists will usually make believers out of them.

Complications Related to Cavitary Coccidioidomycosis

A detailed consideration of cavitary coccidioidomycosis is pertinent to an understanding of surgery in this disease. Complications are always higher in cavitary coccidioidomycosis. Why this is true is unclear to us, but it may be the fact that viable hyphal elements of Coccidioides immitis are more easily identified in cavitary lesions. We have concluded this is evidence of a more active stage of the disease.

Table 2—Statistical Analysis of the Operative Procedures

<table>
<thead>
<tr>
<th></th>
<th>Without Amphotericin</th>
<th></th>
<th>With Amphotericin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complications</td>
<td>%</td>
<td>Complications</td>
<td>%</td>
</tr>
<tr>
<td>Wedge</td>
<td>1</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Segmental</td>
<td>36</td>
<td>26.6</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>23</td>
<td>18.7</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Lobectomy and segment</td>
<td>3</td>
<td>23.3</td>
<td>3</td>
<td>33.3</td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>44</td>
<td>20.4</td>
<td>48</td>
<td>4.2</td>
</tr>
</tbody>
</table>
CLASSIFICATION OF CAVITIES

A. Primary cavity—this type cavity is seen in acute pneumonic phase. As the lesion clears, the cavity disappears (usually in one or two months). The cavity, however, may persist as a residual.

B. Secondary cavities

1. Thin wall cavities—a cavity is considered to have a “thin wall” if it measures less than 3 mm.

2. Thick wall cavities—the wall measures more than 3 mm.
   a. Concentric cavity—very thick wall.
   b. Eccentric cavity—thick wall with a meniscus pattern.
   c. Abscessing coccidioidomycosis.

3. Filled-in cavity.

The classification of cavities as outlined above by Winn has served us well over the years. It allows a point of departure for discussion. Surgery must be based on an understanding that cavitary coccidioidomycosis exhibits a necrotizing phase characterized by an invasiveness. This necrotizing ability causes a pathologic process that might be termed “perforating extension” or “perforating invasiveness.” This confronts the surgeon with three hazards at the time of thoractomy: a) perforations across fissures, “fissure jumpers;” b) perforations across both the visceral and parietal pleurae and into the chest wall. The ribs are invaded as well as the intercostal muscles; c) perforation of the lung with pneumothorax which may or may not be complicated by empyema.

No one can be absolutely sure, in any given cavitary situation, what residuals of the disease may remain as foci of satellite seeding. The satellite lesions are of such importance that the characterization of them as “silent daughters of danger” should bring about the respect that is due them.

The following detailed description of cavities is believed paramount to a proper surgical understanding of the disease.

A. Location of cavity

1. A cavity near the visceral surface or near a fissure demands consideration for early surgery. Amphotericin B should be used.

2. A cavity in the outer cortex of the lobe but well removed from the fissure, and well removed from the hilar area, may be treated conservatively. If surgery is decided upon, amphotericin B coverage is not obligatory. The decision to avoid amphotericin B is justifiable only if one can be certain that no satellite seeding has occurred.

B. Size of cavity

1. Giant cavities—amphotericin B coverage is indicated because it is impossible to determine whether more than one lobe is involved. Further, the amphotericin B will bring about reduction in size of the giant cavity. The operation will thereby be less difficult technically.

2. Cavities of over 5 cm in diameter usually require surgery. The use of amphotericin B will be predicated on factors previously mentioned and to be mentioned hereafter.

3. Cavities below 4 cm may be treated conservatively, depending upon the location as previously described. This cavity may close without therapy. It may allow for avoidance of amphotericin B in certain situations.

C. Behavior of cavity

1. Enlarging cavity: amphotericin B coverage plus surgery.

2. Decreasing size of cavity—this is a unique characteristic of coccidioidomycosis. One is sometimes deceived in watching a large cavity decrease in size and concluding it will continue only to find that it reverses itself and becomes larger. The alternating size of the cavity is probably an indication for surgery. Amphotericin B may be avoided if conditions as outlined permit.

One intriguing question now seems settled. Cavitary can and do close, and not only close but heal securely. This has been noted on serial chest x-ray films, both with and without the use of amphotericin B therapy. The real difficulty comes in attempting to determine which cavities may close and which cavities will not close. It is believed that such a determination may be possible in the future on the basis of preoperative and postoperative studies combined with a correlation of the x-ray appearance, gross and microscopic tissue examination, plus cultural and chemical characteristics of the cavity contents. It may be within the purview of some experts to declare “this cocci cavity will close spontaneously,” but the hazard of being such a prophet is replete with pitfalls.

D. Status of lung surrounding the cavity

1. This is often hard to determine unless early chest x-ray films are available. A large pneumatic infiltrate may eventually clear but leave behind a small, persistent cavity.
Knowledge of the previous pneumatic infiltrate is presumptive evidence of seeding and granulomata will be found in the peri-cavitary tissue. Amphotericin B coverage is indicated.

2. Occasionally there will be unequivocal evidence of x-ray peri-cavitary nodulation. This indicates the presence of daughter granulomata and amphotericin B coverage is considered obligatory.

E. Complicating secondary disease.
1. Diabetes—amphotericin B coverage is indicated.
2. Tuberculosis—differential diagnostic difficulties may arise. It is the considered opinion of the authors that both antituberculosis therapy and anti-fungal therapy will have to be considered if this dilemma is to be solved.
3. Diseases requiring corticosteroids should be covered by amphotericin B if surgery is contemplated.
4. There is a recognized danger of dissemination in primary coccidioidomycosis infection in the last trimester of pregnancy. If one is forced into surgical intervention (i.e., ruptured cavity, empyema) then amphotericin B coverage is indicated.

F. Complement fixation blood titer—if a titer of 1:32 or above is recorded, then this has been considered an indication for amphotericin B by some surgeons. One might qualify this to recommend a course of amphotericin B plus conservative therapy and see what happens. Follow up chest x-ray examinations plus repeated complement fixation blood titers might bring one to a more favorable situation and lessen the risk of complication if surgery is performed.

A NEW CONCEPTUAL APPROACH TO DIFFERENTIAL Diagnosis AND Therapy FOR THE COMBINED Diseases OF Pulmonary Coccidioidomycosis AND Pulmonary Tuberculosis

Tuberculosis and coccidioidomycosis as concomitant infections are common. It can be extremely difficult to make an unequivocal diagnosis between the two.16-18 To administer prolonged antituberculosis therapy on a presumptive diagnosis only is a disservice to the patient. The psychologic stress of the presumed diagnosis may also be complicated by physiologic stress to the point of physical disability. It goes without saying that an individual denied antituberculosis therapy as a result of a mistaken diagnosis of coccidioidomycosis falls within the realm of mismanagement, as well as misdiagnosis.

In an effort to illustrate the problem of this differential diagnosis and to formulate a rational therapeutic approach, a selected series of 22 surgical cases has recently been analyzed. In 19 of the 22 cases with an original diagnosis of tuberculosis, coccidioidomycosis was the final diagnosis in 11 (Table 3). In three other cases, combined disease was found in two and tuberculosis alone in one.

Our inclination to be unduly influenced by laboratory reports has changed to one of skeptical inquiry for the following reasons. The coccidioidin skin test was negative in seven of the 11 pure cases of coccidioidomycosis (1:100 strength repeated at 1:10). Further, the coccidioidin skin test gave negative results in three of the eight cases of concomitant disease. This is an overall false negative reading for the coccidioidin skin test of 52.8 per cent. The sputum was cultured in all cases, but only four gave positive results of C. immitis. Complement fixation titer was positive in only one. Precipitins were negative in all cases.

In two cases, we were influenced to make a presumptive diagnosis of coccidioidomycosis by negativity in both the intermediate and second strength tuberculin skin tests plus the fact that repeated sputum cultures did not grow tubercle bacilli.

A recounting of the above would lead the reader to believe our laboratories need help, advice and a review of their procedures. No matter how excellent the laboratory may be, the vagaries of these two diseases should always make one wary of too great a dependence upon laboratory reports.

We must also state that the chest x-ray films of these individuals were also difficult to evaluate. There were many roentgenologic paradoxes. Some experts may be able to make an etiologic determination in pulmonary caviation, but eventually a mistake will bring caution to bear.

In Figure 1, the roentgenogram reveals a left apical infiltrate and a small cavity. This patient exhibited a positive tuberculin skin test and a negative coccidioidin skin test and a negative coccidoidal complement fixation test. This chest x-ray film was thought to show tuberculosis. The pathologic diagnosis proved to be coccidioidomycosis.

Another patient (Fig 2) had classic, proved bilateral far-advanced tuberculosis. Thoracoplasty was performed. He died. Post-mortem examination revealed his death to be due to tuberculosis and disseminated coccidioidomycosis. A large cavity
Figure 1. Roentgenogram of patient with left apical infiltrate and cavity interpreted as tuberculous, but shown by histopathologic examination to be coccidioidal despite negative coccidioidin skin test and serology.

diagnosed as pulmonary coccidioidomycosis is shown in Figure 3. The pathologic specimen contained only tubercle bacilli. Recheck of the preoperative laboratory findings revealed consistently negative acid-fast sputum reports.

Another chest x-ray film (Fig 4) revealed a thin wall cavity in the right lower lobe. The specimen revealed spherules of coccidioidomycosis. The cul-

Figure 2. Patient with proved bilateral tuberculosis treated, in part, by thoracoplasty. Subsequently he died and was found to have combined tuberculosis and disseminated coccidioidomycosis.
tture of the cavity was positive for both tubercle bacilli and C. immitis.

The preoperative medication in these patients is of interest. In the 19 "tuberculosis" patients, 12 received antituberculosis medications. Five others received combined antituberculosis medications and amphotericin B. In those cases diagnosed as coccidioidomycosis, two received amphotericin B. One had tuberculosis and two had both diseases (Table 3). In the last of the three cases, tuberculosis was the presumptive diagnosis. Streptomycin was used for therapy resulting in permanent vestibular injury. The specimen produced by surgical extirpation revealed coccidioidomycosis. The patient did not have tuberculosis. Table 3 points up the dilemma in no uncertain terms. To resolve this confusion we

Figure 3. Patient with large cavity diagnosed as coccidoidal. The excised specimen contained only tubercle bacilli.

Figure 4. Thin walled-cavity which was found, after excision, to contain viable tubercle bacilli and Coccidioides immitis.
now advocate a "surgically oriented" approach. We allow eight weeks for diagnostic evaluation. We believe that a definite diagnosis must be forthcoming. During this interval and depending upon the presumptive diagnosis, either an anti-fungal or anti-tuberculosis regimen should be instituted. If the eight-week, "target date" is reached without a positive diagnosis, then a "double disease" drug regimen is instituted in preparation for definitive surgery. This is scheduled for 30 days later. This gives three months of antituberculosis therapy which affords adequate basic "umbrella" protection in surgery for tuberculosis. The addition of one month of amphotericin B allows protection to the patient in case coccidioidomycosis is also present.

SUMMARY AND CONCLUSIONS

1. Surgical treatment of pulmonary coccidioidomycosis may be accompanied by complications in the range of 13 per cent to 26 per cent. The judicious use of amphotericin B as adjunctive therapy should result in a decrease in the complication rate to 5 per cent or below.

2. Lobectomy is the operation of choice. In certain cases, less than lobectomy may be permissible, but failure to use amphotericin B will greatly increase the chances for complications.

3. Careful attention to the exact location of the cavity will allow for a better delineation of surgical technique and obviate complications. It may also preclude the need for amphotericin B in certain situations as specified.

4. To resolve diagnostic confusion and to offer a rational approach to the problem of isolated coccidioidal or tuberculous disease or a combination of the two diseases, a two-month diagnostic "target date" is advocated. Treatment is given depending on the weight of evidence in favor of the presumptive diagnostic impression. If the diagnosis still remains obscure, a "double disease" drug regimen is carried on for an additional 30 days and thoracotomy is then performed.

Table 3—Changes Between Preoperative Diagnosis and Postoperative Diagnosis

<table>
<thead>
<tr>
<th>Postoperative Diagnosis</th>
<th>Combined Tb</th>
<th>Tb plus Coed</th>
<th>Coel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis believed to be the primary diagnosis</td>
<td>19 cases</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Coccidioidomycosis believed to be the primary diagnosis</td>
<td>3 cases</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

REFERENCES

2. Winn, W. A.: Personal communication.

Reprint requests: Dr. Melick, University of Arizona College of Medicine, Tucson 85721.