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Flexible Fiberoptic Bronchoscopy and Fluoroscopically Guided Transbronchial Biopsy in the Management of Solitary Pulmonary Nodules

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In our experience with fluoroscopically guided flexible fiberoptic bronchoscopy (FFB), transbronchial biopsy, bronchial brush, bronchial washing (BW) and sputum cytology (SC) in 101 patients with solitary pulmonary nodules (SPN) less than 6 cm in diameter (without endobronchial tumor), a specific diagnosis was reached via FFB in 36 cases. The diagnostic yields in primary lung malignant lesions (PLM), metastatic lesions and benign SPN were 58 percent, 28 percent and 10 percent, respectively. Size affected diagnostic efficiency considerably, with a 12 percent yield in lesions under 2 cm, a 40 percent yield in lesions 2 to 4 cm and a 63 percent yield in lesions over 4 cm. BW and SC (prebronchoscopic) did not contribute enough information to justify their cost. FFB directly affected therapy in 17 patients who were not thoracotomy candidates and may have influenced the decision for surgical treatment in another 19 patients diagnosed as having PLM. In 65 patients results of FFB were negative and the procedure did not appear to directly affect subsequent management because malignancy was not ruled out.

ESTABLISHING THE CAUSE of the solitary pulmonary nodule (SPN) remains a problem to clinicians. Numerous articles have attempted to establish guidelines for systematic handling of the SPN. Some authors[1-3] advocate an organized approach using various clinical criteria (that is, age, growth rate, roentgenographic appearance) and nonsurgical diagnostic means (sputum cytology, nuclear scans, bronchial brush cytology, needle aspiration) to distinguish benign from malignant lesions. Other authors[4] caution that these procedures not only lead to delay in the treatment of potentially curable malignant lesions but add considerable morbidity, discomfort and hospital cost and, in some circumstances, may disseminate tumor cells.

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ABBREVIATIONS USED IN TEXT

BB = bronchial brush
BW = bronchial washing
COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in one second
FFB = flexible fiberoptic bronchoscopy
FVC = forced vital capacity
PLM = primary lung malignancy
SC = sputum cytology
SPN = solitary pulmonary nodule
TBB = transbronchial biopsy

Whether or not these studies produce positive or negative findings, thoracotomy is still indicated unless a specific benign process is found.[5]

The applicability of these diagnostic techniques to the SPN appears to depend on their accuracy and relative safety. Numerous articles[3,6-8] address these two aspects of the nonsurgical diagnostic tools. In the final analysis the usefulness of any diagnostic technique is determined by its therapeutic implications to patients.

Fluoroscopically guided flexible fiberoptic bronchoscopy (FFB) in conjunction with transbronchial biopsy (TBB), bronchial brush (BB) or bronchial washing (BW) cytology has given physicians an additional procedure for nonsurgical diagnosis of the SPN. Several articles[9-15] have presented data on the diagnostic accuracy of these methods but none have addressed the ultimate effect of FFB on patient care and the cost to this group of patients.

We report the diagnostic accuracy of FFB in 101 consecutive cases of SPN evaluated at the University of Oklahoma Health Sciences Center and the Veterans Administration Medical Center in Oklahoma City from April 1, 1978, to December 31, 1979. In addition, we have assessed the effect of TBB, BB and BW on therapy and hospital cost in these patients.

Methods

We reviewed the records and roentgenograms of 103 patients bronchoscoped to establish the cause of their SPN. Two patients with SPN and endobronchial malignancy were excluded from this series because we wished to examine the yield of "blind" (nondirect visualization) bronchoscopic procedures. Of the remaining 101 patients, 92 were men and 9 were women. The mean age of the group was 60 years (range 29 to 89 years). A total of 88 were smokers with a mean pack-year history of 58. The radiographic criteria used for SPN were those of Steele[16] and patients with symptoms were also included in our study. All lesions were 6 cm or less in diameter.

Of 92 patients in whom spirometry was done, 66 had evidence of airways obstruction based on a greater than 20 percent reduction in forced expiratory volume in one second (FEV_1) and an FEV_1 versus forced vital capacity (FVC) of 70 percent or less. The mean FEV_1 for the obstructed group was 1.88 liters (range 0.62 to 3.88 liters), while the mean FEV_1 for the entire group tested was 3.18 liters. Four patients in whom spirometry was not done were diagnosed as having chronic obstructive pulmonary disease (COPD) based on clinical history and roentgenographic findings. Twenty-three patients had symptoms attributable to the SPN (weight loss, hemoptysis, chest pain) and 12 had previously resected primary tumors (six had lung tumors, four had tumors of the head and neck and two had tumors of the colon).

The technique for FFB, TBB and cytology collection has been previously described in detail.[9,17] The bronchoscope (Olympus BF-B2) was introduced transnasally after local anesthesia had been achieved with lidocaine. Fluoroscopically guided TBB was carried out in 118 of the 120 bronchoscopies done. TBB was prevented in two cases because of lack of fluoroscopic visualization and bronchospasm. A variety of cytologic specimens (including sputum, bronchial brush and bronchial wash with 60 ml of normal saline) were collected in all cases. All cytology specimens were handled in the routine cytopathology laboratory and final interpretation was made by one cytopathologist.

A histologic diagnosis of nonspecific fibrosis or chronic inflammation was considered to be nondiagnostic even when the final diagnosis proved to be a benign process. These nonspecific entities are often found in TBB taken near malignant disease and do not alter the course of the diagnostic workup.[18] Anatomic location of the SPN was determined using standard anteroposterior and lateral chest roentgenograms, tomograms when available, and fluoroscopy at bronchoscopy and surgical procedure when these were carried out. A modified scheme of ten anatomic segments was used to classify the SPN location: right and left upper lobe anterior segments, right and left upper lobe apical-posterior segments, right middle lobe, lingula, right and left lower lobe superior segments and right and left lower lobe basilar segments (Figure 1).

Size and anatomic location of the SPNs were compared with success at establishing a specific diagnosis by FFB using one-way analysis of variance. SPN size by group (up to 1.9 cm, 2 to 4 cm, 4.1 to 6.0 cm), radiographic shape, margin characteristics and anatomic location were compared with success at establishing a bronchoscopic diagnosis using chi-square analysis.

Results

A definite diagnosis was ultimately established in 89 of 101 patients (Table 1). In 36 cases a diagnosis was established by bronchoscopy and in 32 by a major surgical procedure (mediastinoscopy, left second interspace exploration or thoracotomy). The final diagnosis in 16 patients was established on clinical grounds—five by findings of mycobacteria on sputum cultures and radiographic response to antituberculous drugs, eight by resolution roentgenographically of the SPN without specific therapy and three by the subsequent appearance of new pulmonary nodules and discovery of a primary carcinoma. In five patients a definite diagnosis was established by other means —two by rib biopsy under local anesthesia, one by needle biopsy, one by subsequent endobronchial biopsy following tumor spread and one by pulmonary artery angiography showing an arterial aneurysm.

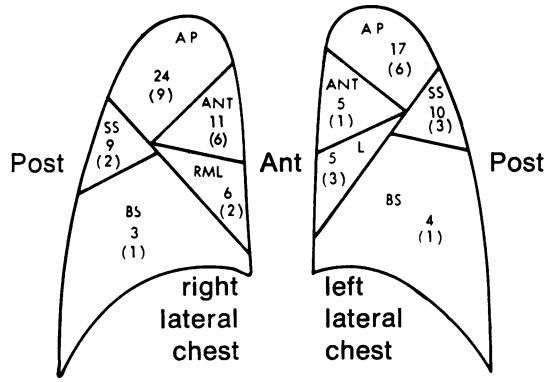

Figure 1.—Schematic representation of lateral view of both lungs (Post = posterior; Ant = anterior) showing the anatomic location (top number) and the number of nodules diagnosed by flexible fiberoptic bronchoscopy in that segment (number in parentheses). AP = apical posterior segment, upper lobe; ANT = anterior segment, upper lobe; L = lingula; RML = right middle lobe; SS = superior segment of lower lobe; BS = basilar segments of lower lobe.

FFB gave specific tissue or cytologic diagnosis in 36 cases (Table 1). Bronchoscopy provided correct identification in 31 of 53 proved primary lung malignant lesions (Table 2) but only two of seven metastatic nodules. Thus, the sensitivity (true-positives versus true-positives plus false-negatives) for bronchoscopy in diagnosing malignant SPN was 55 percent. The specificity (true-negatives versus true-negatives plus false-positives) was 100 percent for malignant lesions because no false-positives were found in this study. Of 29 nonmalignant SPNs, 20 had a definite diagnosis established by sputum culture or histology. Only 3 of these 20 were confirmed by FFB, a sensitivity of 15 percent. Again, there were no false-positives, giving a specificity of 100 percent.

Specific diagnosis was determined more often

TABLE 1.—*Methods of Establishing a Definite Diagnosis*

	Bronchoscopy		*Surgical Procedure*			
	*TBB**	*Cytology†*		*Clinical*	*Other*	*Total*
Primary lung carcinoma						
Squamous cell	14	3	6	..	2	25
Adenocarcinoma	8	1	5	..	..	14
Large cell	2	..	6	..	1	9
Oat cell	1	..	1	..	..	2
Alveolar cell	2	..	1	..	..	3
Metastatic lesion	2	..	1	3	1	7
Tuberculoma	1	..	3	5	..	9
Benign infiltrate	..	..	..	8	..	8
Fungal disease	..	..	4	..	..	4
Lung abscess	2	..	1	..	..	3
Pulmonary dirofilariasis	..	..	1	..	..	1
Pulmonary artery aneurysm	..	..	..	..	1	1
Amyloidosis	..	..	1	..	..	1
Lymphomatoid granulomatosis	..	..	1	..	..	1
Necrotizing granuloma, no apparent cause	..	..	1	..	..	1
TOTALS	32	4	32	16	5	89

*Transbronchial biopsy.
†Including brush, wash and postbronchoscopy sputum.

by TBB than by cytology. Of the 36 correctly identified lesions 32 were diagnosed from the TBB tissue. A total of 511 specimens for cytology (an average of 5.05 per patient) collected by the various methods yielded a specific diagnosis in only 25 cases (bronchial brush 18, bronchial wash 2, prebronchoscopy sputum 1, postbronchoscopy sputum 4) (Table 3). In four cases where cytology was the only diagnostic source, bronchial brushing yielded the necessary tissue in two cases and postbronchoscopy sputum in the other two.

Nineteen patients were bronchoscoped a second time when the first procedure failed to yield a specific diagnosis. Six of these repeat bronchoscopies provided a diagnosis, five by TBB and one by cytology (BB) (Table 2). All three benign lesions in which FFB was successful were diagnosed on the second bronchoscopy.

There was a positive correlation ($P<.0001$) between radiographic size of the SPN and establishment of a specific diagnosis by FFB. The mean size of successfully diagnosed lesions was 3.55 cm while undiagnosed lesions averaged 2.45 cm (Table 4). Chi-square analysis showed no evidence that anatomic location (Figure 1), radiographic shape or character of the margin affected the success rate of FFB.

At the termination of this study a final diagnosis had not been established in 12 patients. Of these 12, 3 had radiographically stable lesions after 12, 18 and 22 months, respectively. Subsequent films showed enlargement in three cases suspected of being malignant. Four patients proved to have malignant primary lesions and the SPNs were believed to be slow-growing metastasis. Two patients were lost to follow-up immediately after discharge and had no subsequent roentgenograms.

In a total of 120 bronchoscopies that were carried out, ten patients had complications associated with the procedure. Five had pneumothoraces (three of these required closed chest tube drainage), one had severe bronchospasm and four had apparent substantial bleeding (lobar infiltrate or persistent hemoptysis). Bleeding resolved in all four of these patients within 48 hours and no transfusions were required.

TABLE 2.—*Diagnostic Accuracy of Bronchoscopy*

Final Diagnosis	*Number of Procedures*	*Successful on First Bronchoscopy*	*Successful on Second Bronchoscopy*	*Total Yield (percent)*
Bronchogenic carcinoma	53	28	3	58.5
Metastatic tumor	7	2		28.5
Benign disease	29	0	3	10.3
TOTAL	89			

TABLE 3.—*Yield of Sampling Method in Bronchoscopy**

Method	*Number of Procedures*	*Positive Yield (percent)*
Transbronchial biopsy	118	27.0
Bronchial brush	116	15.5
Bronchial wash	54	4.0
Sputum cytology		
Prebronchoscopy	179	0.5
Postbronchoscopy	162	2.4

*120 bronchoscopies in 101 patients. Suspicious cytologies were considered negative.

TABLE 4.—*Bronchoscopic Yield by Nodule Size*

Size cm	*Number of Procedures*	*Diagnosed*	*Yield (percent)*
<2	32	4	12.5
2-4	50	20	40.0
>4	19	12	63.1

Discussion

This study considers SPNs in predominantly older male smokers. Previously published data[1,2,16] suggest that a large proportion of these would be malignant. In our study, all malignant nodules were found in patients aged 45 years and over. Because of the high incidence of malignancy in this group, there was a significant probability that a major surgical procedure would be needed whether or not the diagnosis was made beforehand by FFB. The only way bronchoscopy could prevent thoracotomy in operative candidates was to show a benign lesion, endobronchial disease, vocal cord paralysis or widening of the carina, which would preclude curative resection.

We examined several factors that might have predicted benignity of the SPN. The presence or absence of symptoms was not helpful in that 12 patients with benign lesions were symptomatic, as were eight patients with malignant nodules. The absence of a smoking history was not predictive; four of the nine nonsmokers had primary lung tumors (two had adenocarcinoma, one had squamous cell and one had alveolar cell). Although larger sizes correlated significantly with malignancy, it was of no benefit in predicting individual cases as 9 of 32 lesions smaller than 2 cm were malignant.

Our overall diagnostic yield with FFB was 35.6 percent. This result is lower than that of other published series (Table 5) because of the unse-

TABLE 5.—*Published Results of Flexible Fiberoptic Bronchoscopy With Transbronchial Biopsy in Evaluating Solitary Pulmonary Nodules (SPN's)*

	Number of Patients	Overall Diagnostic Yield percent	Number of Patients	Diagnostic Yield in Primary Lung Neoplasm (percent)
Ellis[9]	65	75	44	67
Stringfield et al.[10]*	27	48	27	48
Hanson et al.[11]	56	53		
Schoenbaum et al.[12]	18	77	10	80
Radke et al.[13]	97	56	62	66
Zavala[14]*	169	64	120	70
Mark et al.[15]	60	31	32	53
Present study	101	36	53	58

*Malignant SPN's only, others include benign lesions.

lected nature of the cases and the requirement of specific findings on histology to be considered diagnostic. The overall yield in one of the studies[9] drops from 75 percent to 55 percent if histologic findings termed "acute and chronic inflammation" are not considered diagnostic. Because both inflammation and fibrosis may be found in association with malignant processes, this finding in TBB tissue does not rule out malignancy. Of 26 patients in our study whose TBB recovered tissue showing nonspecific fibrosis and inflammation, ten patients eventually proved to have a malignant nodule. Thoracotomy, needle biopsy or roentgenographic follow-up is still necessary to confirm or refute benignity. If only nodules that require specific histologic findings (such as primary lung malignancy) are considered, our diagnostic yield of 58 percent compares favorably with the yield in other studies (Table 5).

In some cases, bronchial brush and sputum cytology (postbronchoscopy) complemented the results from TBB by providing the diagnosis. Specimens from BB showed definite malignancy in 18 of 116 specimens but BB was necessary for the diagnosis in only two cases where results of both TBB and BW were negative. Bronchial washing was diagnostic in 2 of 54 specimens but TBB also gave positive findings in both cases. Cytology of sputum collected before bronchoscopy added nothing to the information obtained by TBB. Postbronchoscopy sputum cytology had a low yield (2.4 percent) but did give a diagnosis in two cases where the findings on TBB were negative.

The total cost of the 511 cytology specimens in this study was $8,176. Of the four methods of collection, BB had the highest positive yield (15.5 percent) per number of specimens. Its yield-cost ratio was 0.68. Sputum cytology (postbronchoscopy) had a yield-cost ratio of 0.07 but was necessary for diagnosis in two cases. This low yield-cost ratio may have been due to the large number of specimens collected (162). In general, if the first postbronchoscopy sputum was positive, so were subsequent specimens. BW and prebronchoscopy SC added nothing to information collected by other means, yet accounted for 45 percent of the cost of cytology. These data suggest that BW and SC were not cost effective. Kvale and co-workers[19] reached a similar conclusion. Postbronchoscopy sputum cytology may be useful but should probably be limited to one specimen.

Because of the clinical suspicion of a benign SPN or because of a high operative risk, we repeated bronchoscopy in 19 patients. Six of these attempts were diagnostic (31 percent) and three of the six showed benign disease (two showed lung abscesses and one tuberculosis). Eleven of the 19 patients proved to have a malignancy and 9 of these had thoracotomy. The indications and results of second attempts at FFB are not discussed in the literature. We felt that a second attempt was indicated if the SPN was strongly suspected of being benign (for example, when a patient was a nonsmoker) or when a patient was at a high surgical risk and a diagnosis was needed to initiate chemotherapy or radiation therapy. At other centers an alternative nonsurgical procedure after the first attempt at TBB failed would have been transthoracic needle aspiration.[15,20]

It is important to consider what effect FFB had on patient management and to evaluate the diagnostic yield and clinical usefulness of this procedure (Figure 2). Of 101 patients with an SPN, FFB did not give a precise diagnosis in 65. Since negative results from TBB and BB do not exclude malignancy from the differential diagnosis, the decision to excise, treat nonsurgically or follow clinically could not be made on the basis of bronchoscopic results. Thoracotomy was required for diagnosis of the nodule in 32 patients while 33 were not operated on for various reasons that included underlying lung disease, poor general health, clinical suspicion of a metastatic nodule or refusal of thoracotomy by a patient. Of the latter 33 patients, 21 had final diagnoses made by nonbronchoscopic, nonsurgical methods and appropriate therapy was instituted. It could be argued that in these 65 patients, bronchoscopy was useful in ruling out endobronchial disease.

Although this aspect of FFB is important to the thoracic surgeon, it could be accomplished at a lower risk and cost to the patient by a simple bronchoscopic examination (open tube or FFB) without TBB immediately before thoracotomy.

Of 36 patients in whom a definite diagnosis was made by flexible fiberoptic bronchoscopy, 17 benefited directly from the procedure by receiving antibiotic medication or radiation therapy or by the establishment of a diagnosis even though therapy was refused. Nineteen patients had thoracotomies from which histologic diagnosis of a malignant SPN was confirmed. In this group, knowledge gained from bronchoscopy that a malignant nodule was present may have influenced the decision to operate. It also may have altered the surgical approach by eliminating the need for a wedge resection or frozen section before lobectomy. At the same time all 19 patients would have been strongly considered for resection (based on age, sex, smoking history, radiographic findings and adequate pulmonary function tests) had bronchoscopy been negative or not been done. In these cases, bronchoscopy may have been an additional, unnecessary procedure. We could not answer this question based on data from this study.

We examined data to see if bronchoscopy influenced the decision to operate on SPNs in 21 high surgical risk patients with underlying lung disease as determined by spirometry (FEV_1 of 1.3 to 1.8 liters).[21] In this group, four out of a total of eight patients with nodules diagnosed as malignant by FFB later underwent resection. Of 13 similar patients in whom bronchoscopy was unsuccessful, 7 had exploratory thoracotomies. Thus, factors other than diagnosis by bronchoscopy appeared to influence the decision to operate, to follow clinically or to treat medically.

We concluded that FFB with TBB and various cytologic methods played a major role in therapeutic decisions in 17 of the 101 SPN patients bronchoscoped. It may have been of value in an additional 19 percent or been an unnecessary procedure. It did not influence therapy in 64 percent of our patients based on lack of diagnostic tissue recovered.

A conservative estimate of the cost of fiberoptic bronchoscopy at our institution is $550 per patient per procedure, which includes a one-day stay in hospital, laboratory tests before the procedure, pathology and cytology fees, fluoroscopy time and bronchoscopist's fee. The total estimated cost of the 120 bronchoscopies was $66,000; this estimate does not take into consideration hospital stays longer than one day or cost of chest tubes and so forth. However, bronchoscopy obviated the need for 13 diagnostic thoracotomies, which saved

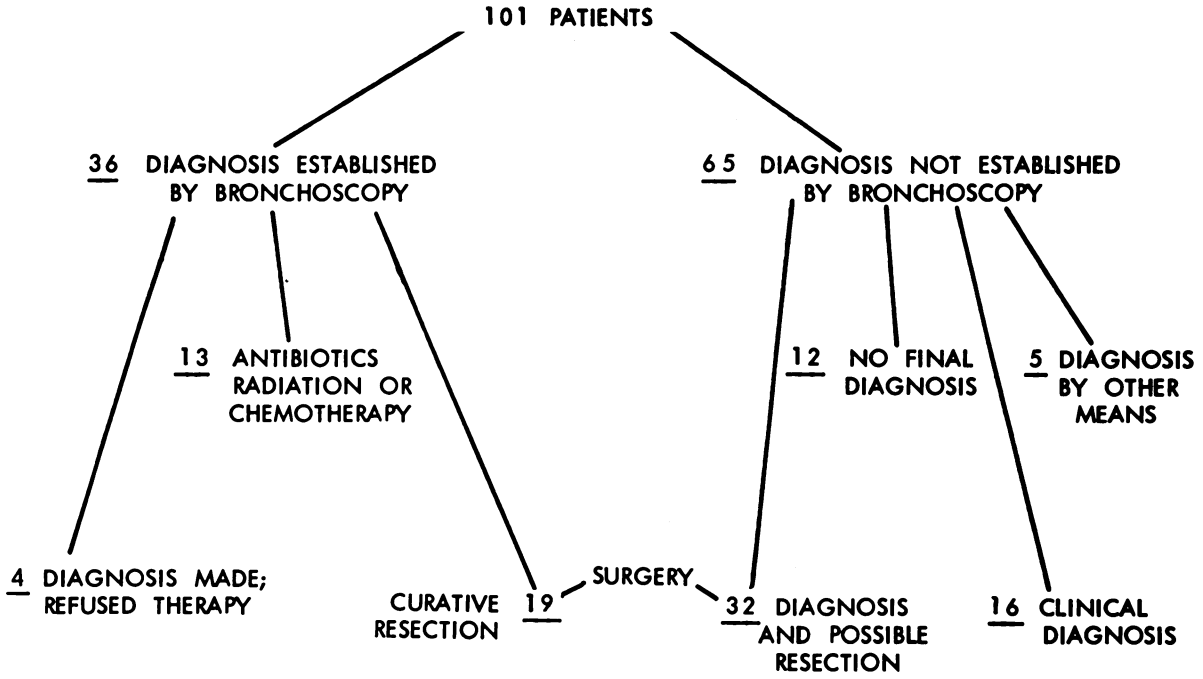

Figure 2.—Diagram showing the effect of flexible fiberoptic bronchoscopy on patient management. See text for details.

considerable cost and substantial patient morbidity. Although expensive, we are left with a useful diagnostic procedure that may have a definite effect on the management of a third of patients with SPN.

Clearly, the answer to this dilemma lies in selecting which patient with an SPN should be bronchoscoped and which should have thoracotomy. The broad application of FFB and TBB with cytology to this population (predominantly male smokers over age 45) may not be justified on a cost-effective basis, as benign lesions have a low diagnostic yield and malignant lesions often are removed surgically because they are frequently the most resectable form of lung cancer. In this particular population of patients with SPNs, data suggest a relative benefit from FFB for the following patients: (1) those in whom lung resection has been ruled out but a tissue diagnosis is needed for radiation or chemotherapy, (2) those in whom lung metastasis is suspected, (3) those who refuse thoracotomy unless a definite diagnosis of cancer is made and (4) those whose lesions are over 2 cm in diameter.

In our review of these cases we found at least four examples where follow-up chest roentgenograms taken two to four weeks after bronchoscopy showed partial or complete resolution of the solitary nodule. These nodules were usually very small (less than 0.5 cm) and had nondiscrete borders. It is conceivable that withholding bronchoscopy two to four weeks when these small "soft" nodules are discovered would allow time for small localized infectious processes to resolve. Also, sputum cultures for acid-fast bacilli should be available and reported as negative before bronchoscopy or before a surgical procedure in patients with a past history of tuberculosis or predisposing factors to the development of tuberculosis.

The data further suggest that bronchial washing and sputum for cytology add little to the information obtained by TBB and bronchial brush and therefore these procedures are not cost effective.

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