

Investigators, Publication	Design	Treatment	Dose per patient (Source & Purity of Talc)	Age, mean (range)	Tumor Type	# Evaluable/ # Entered (# procedures)	Success	Success Definition	Symptom (sx) Relief
FOREIGN STUDIES									
Bal & Hasan Int Surg 1993;78 (4):324-7	Retrospective review of pts with (n=197) MPE & (n=16) PE	T insufflation by thoracoscopy	not reported, single dose, (not reported)	(41-90)	Adenoca. 148, Lymphoma 7, Squamous cell ca. 13, MST 21, Undifferential ca. 6 (patient # discrepancies)	197*/213	184/197	symptomatic improvement, second pleurodesis not required	170 Grade I ^a 14 Grade II ^b
Boniface & Guerin Rev Mal Resp 1989;6:133-9	Retrospective study of pts with (n=48) PE and (n=254) MPE	Thoracoscopy and T instillation followed by aspiration drainage for 4-8 days	5 - 10 mls, single dose, (Luzenac, sterile; "pure")	(23-93)	in French	270*/302 (n=254 MPE) (n=48 PE)	251/270 ^{d, f}	absence of any recurrence of the PE at the drainage site;	82 ± 7.4% (dyspnea)
Bouchama et al Chest 1984; 86 (5): 795-7	Case report of 1 pt. with PE	T instillation under pleuroscopic guidance	2 Gm, single dose, (purified)	40 yrs. old	N/A	N/A case report of 1 patient	1/1	N/A	not given
Canto et al Res Surg 1991; 3/1: 46-8	Retrospective report of pts. with MPE (n=208)	T insufflation under thoracoscopy with biopsies taken	5 Gm, single dose, (sterile)	57 (16-88)	Lung 44, Breast 40, GI 35, MST 15, Lymphoma 15, Genitourinary 14, Miscellaneous malignancies 8, Unknown 37	204/208	189 CR; 15 PR*	CR: only pleural thickening without reaccumulation of liquid evidenced on CXR 1 month later. PR: reaccumulation is so small that new thoracentesis or tube drainage is not required	not given
Ladjimi, et al Rev Mal Resp 1989; 6:147-50	Retrospective report of pts. with MPE (n=218)	T insufflation under thoracoscopic control	2-3 cm ³ , single dose, (pure, non-iodized, sterile, de Luzenac)	not reported	Underlying malignancies were bronchopulmonary and ovarian in nature; no further data provided	not reported/218	170/218	not reported	not given
Ohri, et al Ann Thorac Surg 1992; 53: 1038-41	Retrospective review in pts. with MPE (n=28), PT (n=15), and chylothorax (n=1)	T insufflation at thoracoscopy & lung reexpansion	2-5 Gm, single dose, (not reported)	not reported for MPE pts.	MST 17, Adenoca of unknown primary 14, Squamous of unknown primary 4, Breast 1, Lung 1, Pancreas 1, Chylothorax secondary to NHL 1	not reported/44	42/44	not reported	28/30 f/u cases, no sx recurrence

a = 197 pts. diagnosed with malignancy; b = Grade I: asymptomatic of dyspnea, Grade II: exertional dyspnea; c = MPE and PE pts. included; d = CR in 93% ± 3% of MPE pts. and 97.7% ± 4.5% of PE pts.; e = included the 4 pts. that died within 1 mos. post-procedure; f = "at the end of 6 mos, no recurrence in 81% of cases, 19 (7% ± 3%) early failures, 25 (percentage not given) late failures"
 N/A = not applicable; MPE = malignant pleural effusion; PE = pleural effusion; PR = partial response with no new thoracenteses or tube drainage required; pts = patients

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FOREIGN STUDIES (cont.)									
Pearson & MacGregor J Thorac Cardiovasc Surg 1966;51:732-8	Retrospective report in 17 pts. with MPE	T poudrage*	not reported, single dose, (sterile, USP)	52.1 (22-74)	Breast 9, Lung 4, Malignant MST 3, Fallopian tube 1	17/17	15/17	no recurrence	14/19 (dyspnea) 1/17 (dyspnea/cough)
Rodriguez-Panadero, et al Am Rev Respir Dis 1989;139(3):663-7	Retrospective study of prognostic factors in treatment outcome in 62 pts with MPE	T pleurodesis at thoracoscopy	not reported, single dose, (pure, sterile)	not reported	Lung 19, Breast 14, MST 13, Unknown 13, Lymphoma 10, Kidney 3, Ovary 3, Colon 1, Uterus 1	60/62	48/60	no evident PE present after 30 days with no thoracentesis required after pleurodesis had been performed;	not given
Sanchez-Armengol, et al Chest 1993; 104(5): 1482-5	Cohort analytic prospective study in 125 pts with MPE	Thoracoscopic T poudrage	not reported, single dose, (not reported)	not reported	Lung 48, Breast 30, Unknown 18, GI 11, Ovary 6, Kidney 6, Uterus 3, Thyroid 1	119/125	82/119 CR 22/119 PR	CR: no clinical or radiological recurrence during entire follow-up, PR: small recurrence seen on CXR but symptomless; PR: small recurrence seen on CXR but symptomless with no new thoracenteses or tube drainage required	not given
Scarbonchi, et al Poumon 1981; 37: 283-9 (French article, abstract in English)	Retrospective report of 77 pts with MPE	T poudrage at thoracoscopy	4 - 5 ml, single dose, (pure, asbestos-free, de Luzenac)	59.8 (PE from metastasis) not reported for MST pts.	Unspecified MPE 57, MST 20	77/not reported	70/77	not provided	not given
Todd, et al Chest 1980; 78: 542-3 (Abstract)	Retrospective report in 178 pts. with MPE	T insufflation via multiple methods ^c	not reported, single dose, (asbestos-free)	not reported	Breast 94, Lung 43, MST 11, Genitourinary 11, Hematologic 7, GI 4, Miscellaneous 8	(163/197)	153/163 ^b	"satisfactory control of the effusion"; relief of dyspnea	148/163 (dyspnea)
Weissberg Poumon-Coeur 1981; 37 (5): 291-4	Retrospective report	T insufflation or instillation via trocar or at pleuroscopy	up to 2 Gm per procedure, up to 2 administrations, (sterile, BP, asbestos-free)	not reported	not reported	77/83 (30 via trocar) (47 at pleuroscopy)	23/30 CR; 3/30 PR 41/47 CR; 5/47 PR	CR: "excellent results" with no further description PR: "fair results" with no further description	not given

a = technique of poudrage was either single/two trocar or thoracotomy; b = includes 5 pts. that did not experience relief of dyspnea; c = 158 via multiple trocar technique, 30 via thoracotomy, and 9 in conjunction w/decortication; MPE = malignant pleural effusion; CR = complete response; PR = partial response; MST = mesothelioma; BP = British Pharmacopeia; USP = United States Pharmacopeia; pts = patients

10.2 ADVERSE EXPERIENCES

10.2.1 TABLE OF ADVERSE EXPERIENCES PER TRIAL

Author No. Patients	Treatment	Dose (Source & Purity of Talc)	Adverse Experiences	Chest Tube Drainage Time (days) & Time of Insertion	Amount of Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
UNITED STATES STUDIES						
Adler and Sayek n = 41MPE (44 procedures)	Intercostal tube thcpy w/ bx, then Talc instil	10 Gm in 250 ml sterile saline; (USP, Sterile)	hypotension and tachycardia 2/41(on long term steroids), hypovolemia 2/41; fever ^b	4 to 5; prior to thcpy	not provided	29 survived 1-41mos.; 12 survivors at publication time 2-27 mos.
Aelony et al n = 41 (11 PE, 28 MPE; evaluable pts. only) (42 procedures)	T poudrage at thcpy w/ bx then chest tube insertion	5 ml (2.5 Gm); (USP asbestos-free; sterilized; Spectrum Medical Manuf. Corp.)	fever (37.5 to 39°C; 0-7 days) 21/41; discomfort 39/41; hemoptysis 1/41; cellulitis at drainage site 1/41	2.7 (1 to 9) ^a , after thcpy and T poudrage	not reported, most of pleural fluid drained prior to thcpy	3 died 6-16 d post-treatment; f/u until death (1-61 mos.); survivors followed for 16-69 mos(mean 34 mos)
Camishion et al n = 34 MPE	T poudrage, thmy w/bx and chest tube insertion	2-3 test tubes; (USP, sterilized)	not reported	2 -3, after thmy and T poudrage	not reported, most of pleural fluid drained at thmy	3 died 1-14 d; 16 survived 2-6 mos.; 10 survived 8-16 mos.; 5 survivors at publication time 2-13 mos.
Chambers n = 20 MPE	T instillation/ intercostal intubation	2-4 drams *; (USP, sterilized)	pain 20/20; pulmonary fistula ^b	1 - 3, prior to T instillation	not reported	10 survived 1-6 mos.; 8 survived 8-26 mos.; 2 survivors at time of publication 19&20 mos.
Colt & Dumon n = 21 (12 MPE, 9 PT)	T insufflation and thcpy	4 Gm in MPE; (asbestos- free, sterile Bryan Corp.)	fever 7/21	not reported	not reported	1 year ^c ; 90 d ^e ; survival data not reported
Daniel et al n = 40 (20 PE, 20 PT)	T poudrage and thcpy (bx some pts)	up to 10.5 Gm.; (USP, Humco Laboratories, asbestos-free, sterilized)	pulmonary embolism (fatal) 1/40	5.2 (2-24) ^{aa} 4.6 (3-10) ^{aa} at thcpy after T poudrage	not reported, most pleural fluid drained prior to thcpy	2 deaths (1 support withdrawal at pts. request); up to 1 mo f/u
Factor n = 1 (bilateral MPE)	Thoracenteses & Q; then T instillation w/thmy	400 mg (Q) not reported (T). (not reported)	granulomatous pneumonitis due to Q & T crystals within pulmonary parenchyma; empyema; fever	until death, after Q instillation	1900 ml during Q instillation	died 2 months after admission from a massive acute MI
Haupt et al n = 19 MPE	T poudrage, bx, and insertion of intercostal tubes	not reported; (USP, sterile)	not reported	2-3, after T poudrage	1000 ml & 2500 ml reported for 2 pts respectively, prior to T poudrage & CT insertion in both pts	10 survived 2-6 mos.; 4 survived 8-13 mos.; 5 survivors at time of publication 1-26 mos.
LoCicero n = > 40 MPE	T instillation during video-assisted thcpy w/bx	5 Gm; (sterile, asbestos free)	not reported	≤ 48 hrs, at thcpy prior to T instillation	not reported, most pleural fluid drained to dryness at thcpy w/CT inserted for additional drainage	not reported

a = mean (range), b = exact number of occurrences not reported, c = pneumothorax group, d = pleural effusion group, further breakdown not provided, e = MPE group
 * = unclear if unit of weight is in Apothecaries' (60 grains or 1/8 ounce) or Avoirdupois (27.3 grains or 1/16 ounce) system; Q = quinacrine; instil = instillation, bx = biopsy taken, thmy = thoracostomy, thcpy = thoracoscopy, d = days,
 mos = months, pts = patients, USP = United States Pharmacopeia, PT = pneumothoraces, PE = pleural effusion, CT = chest tube

Author No. Patients	Treatment	Dose (Source & Purity of Talc)	Adverse Experiences	Chest Tube Drainage Time (days) & Time of Insertion	Amount of Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
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UNITED STATES STUDIES (Cont.)

Prorok & Nealon n = 29 MPE	T poudrage and limited thtmy (unclear bx)	not reported, (not reported)	superficial wound infection 3/29; abscess of pleural cavity 1/29	not reported	not reported	4 died 2-14 d; mean survival of 7 mos. ranging up to 18 mos.; 8 survivors at publication time 4-18 mos.
Rinaldo, Owens & Rogers n = 3 MPE	Intrapleural T instillation	10 Gm in 250 ml Normal Saline; (not reported)	adult respiratory distress syndrome (1 fatal) 3/3	not reported; case 1&2 not reported case 3: 1 day prior to T instil.	case 1&3: 2700 ml & 1800 ml respectively, prior T instil.; case 2: not reported	1 died of respiratory failure (1 mo. post-treatment)
Sheldbalkar, et al n = 28 MPE	T pleural symphysis	not reported, (not reported)	empyema 1/28	not reported	not reported	3 died 8-23 d; 13 survived 1-6 mos.; 7 survived > 6-22 mos.; 5 survivors at publication time >4 mos. - >9mos.; average survival 7 mos.

FOREIGN STUDIES

Bal & Hasan n = 213 total (197 MPE)	T insufflation by thcpy w/bx	not reported, (not reported)	"chest infection" 3/197; SC emphysema* 1/197; bleeding 2/197; empyema 2/197 (total of 8 pts with complications)	not reported	not reported	5 (2.3%) died post-operatively ^{ab} ; mean survival 19.3 wks (range 3-67 wks)
Boniface & Guerin n=300 (254 MPE; 48 PE) ^c	Thcpy w/bx and T instillation	5 - 10 mls; (pure, sterile; de Luzenac)	pain (# unknown); fever 270/302; empyema 6/302; cancerous nodules down drainage line 10/302	4 - 8; not reported	not reported	15 (5%) deaths during pleural drainage period; 6 mos. follow-up
Bouchama et al n = 1 PE	T instillation under pleuroscopic guidance and bx	2 Gm; (purified)	minor bleeding; fever x 10 days; malaise; acute pulmonary distress; bilateral interstitial infiltrates on CXR; 2nd degree atrioventricular block on EKG; 1 LFTs; pulmonary embolism	not reported; after T instillation	not reported	alive at 14 mos.
Canto et al n = 208 MPE	T insufflation under thcpy and bx	5 Gm; (sterile)	slight pain 125/208; severe pain 5; SC emphysema 3/208; fever (high) 2/208; fever (in most patients) ^d ; pulmonary edema 1/208; empyema 4/208	not reported; during thcpy	not reported	4 deaths within 1 mos.;
I. adjimi, et al n = 218 MPE	T insufflation under thcpy control	2-3 cm ³ ; (pure, non-iodized, sterile; de Luzenac)	not reported	3 (7 cases had drains for 10-15 days); not reported	up to 12 liters or more	symphysis lasted a mean of 19 ± 8 mos.

a = survival time not reported; b = 19 pts. were lost to follow-up; c = unclear why authors reported 300 pts. total and 302 in demographics; d = exact number of occurrences not reported; * = severe, requiring tube thoracostomy; mos. = month; wks. = weeks; CXR = chest roentgenogram; bx = biopsy taken; thtmy = thoracostomy; thcpy = thoracoscopy; d = days

Author No. Patients	Treatment	Dose (Source & Purity of Talc)	Adverse Experiences	Chest Tube Drainage Time (days) & Time of Insertion	Amount of Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
FOREIGN STUDIES (Cont.)						
Ohri, et al n = 44 (28 MPE, 15 PT, chylothorax 1)	T insufflation at thcpy and bx	2-5 Gm; (not reported)	"post-op chest infection" 2/44; post-op atrial fibrillation 1/44; bronchopleural fistulas 2/44	not reported; at thcpy	not reported; most pleural fluid drained at thcpy	6-31 mos. follow-up ^a ; mean survival 17.7 wks. (2-60 wks.) ^b ; 5 pts. survived ≥ 12 mos.
Pearson & MacGregor n = 17 MPE (19 procedures)	T poudrage ^c	not reported; (sterile, USP)	pain 17/17	mean 2 - 3, prior to T instillation	not reported	3 early mortalities (≤ 1 mo., 1 operative death); 8 survived an average of 8.5 mos.; 6 survivors at publication time with 12.5 mos. mean survival (5 pts. without recurrence of effusion)
Rodriguez-Panadero, et al n = 62 MPE	T pleurodesis at thcpy with bx	not reported; (pure, sterile)	not reported	mean 3 days, not reported	not reported; aspiration performed after T administration	until death or 1 mo.; 2 died within 1 mo.
Sanchez-Armengol, et al n = 125 MPE	Thcpy T poudrage with bx	not reported, (not reported)	not reported	not reported	not reported	until death or close of study (1- 29 mos); 1 pt. lost to follow-up; early deaths ^d 8 pts.
Scarbonchi, et al (French article with English abstract) n = 77 (57 PE from metastasis, 20 MST ^e)	T poudrage at thcpy	4 - 5 ml; (pure, asbestos- free, de Luzenac)	pain ^f ; fever (38 - 39°C) x 2-3 d (8) ^g ; "infection" ("treated by local instillation of antibiotics") 1/77	3 - 6	not reported, after thcpy and T insufflation	until death; mean survival 395 ± 55 d
Todd, et al (Abstract) n = 178 MPE (197 procedures)	T insufflation via multiple methods ^h	not reported; (asbestos- free)	empyema 5/178; respiratory failure and/or pneumonia 7/178; pulmonary embolism 2/178; myocardial infarction 2/178	not reported	not reported	10 deaths due to reported adverse experiences; 17 deaths > 2 wks post-treatment
Weissberg n = 83 ⁱ (30 via trocar) (47 at pleuroscopy) reported on evaluable pts.	T insufflation or instillation via trochar or at pleuroscopy	up to 2 Gm per procedure; (sterile, BP, asbestos-free)	not reported	usually 3 - 4, after T insufflation	not reported	6 early deaths ^j

a = includes 37/42 pts only; b = includes 30 pts, 7 lost to follow-up; c = technique of poudrage includes single/double trochar or thoracotomy; d = early death not defined; e = exact number of occurrences not reported;

f = 8 pts had a fever between 38.5 and 39°C; g = survival time not reported;

mos = month; wks = weeks; bx = biopsy taken; thcpy = thoracoscopy; d = days; pts = patients; USP = United States Pharmacopeia; BP = British Pharmacopeia

10.2.2 TABLE OF ADVERSE EXPERIENCES ACROSS NONCOMPARATOR STUDIES

ADVERSE EXPERIENCE	TALC - 17 Studies* (1263 patients)	
ADVERSE EXPERIENCES IN ≥ 5% OF PATIENTS		
Fever	313/1263	(24.8%)
Pain	208/1263	(16.5%)
ADVERSE EXPERIENCES IN < 5% OF PATIENTS		
INFECTIONS		
Empyema	19/1263	(1.5%)
Cellulitis	1/1263	(0.08%)
Abscess	1/1263	(0.08%)
Infection	9/1263 chest 5 = 0.4% wound 3 = 0.2% "infection" 1 = 0.08%	(0.7%)
RESPIRATORY DISORDER		
Respiratory failure &/or pneumonia	7/1263	(0.6%)
Pulmonary embolism	4 (with 1 fatality)/1263 1 fatality = 0.08%	(0.3%)
Adult respiratory distress syndrome	4 (with 1 fatality)/1263 1 fatality = 0.08%	(0.3%)
SC Emphysema	4/1263	(0.3%)
Abnormal GXR	4/1263	(0.3%)
Dyspnea	3/1263	(0.2%)
Hemoptysis	1/1263	(0.08%)
Granulomatous pneumonia	1/1263	(0.08%)
Pulmonary edema	1/1263	(0.08%)
Bronchopleural fistula	2/1263	(0.16%)
CARDIAC DISORDERS		
Tachycardia	3/1263	(0.2%)
Myocardial infarction	2/1263	(0.16%)
Hypotension	2/1263	(0.16%)
Hypovolemia	2/1263	(0.16%)
2nd degree atrioventricular block	1/1263	(0.08%)
Atrial fibrillation	1/1263	(0.08%)

OTHER		
"Cancerous nodules"	10/1263	(0.8%)
Bleeding	3/1263	(0.2%)
Malaise	1/1263	(0.08%)
Increased LFT's	1/1263	(0.08%)

* = 17 studies reported presence or absence of adverse experiences (n = 1263)

10.3 SUMMARY AND EVALUATION OF DATA

The sponsor submitted 24 articles reporting on intrapleural use of talc in a variety of clinical settings ranging from a report of a single patient to retrospective reviews of 302 patients, all without a comparator. The articles report the use of talc for a variety of conditions: malignant pleural effusions in 19 studies; both malignant and benign pleural effusions in 2 studies; malignant pleural effusions and pneumothoraces in 2 trials; and malignant pleural effusions, chylothorax and pneumothoraces in 1 study.

The total number of patients reported in the 24 articles was 1784, which excluded 2 studies. Haupt 1960 was 1 study of 3 that were performed in a series (Haupt 1960, Camishion 1962, & Prorok 1968) and would have resulted in double counting (Camishion 1962 included Haupt in its update). The study performed by LoCicero and colleagues was also excluded due to the uninterpretable manner in which data on the patient numbers were reported. The total number of patients with malignant pleural effusions was 1577. Responses were reported variably as patients or procedures, variably separating whether they occurred in patients with malignant or benign diseases. This, in conjunction with the uncontrolled nature of the studies, does not lend itself to reliably collapsing the data for efficacy (see Table 10.1 for individual reports). Seventeen studies reported presence or absence of adverse experiences (n=1263).

Method of talc administration was at thoracoscopy in 12 studies, via thoracostomy in 4 papers, intercostal intubation in 2, under pleuroscopic guidance in 2 trials, and via thoracotomy in 2 studies. It was unclear what method was employed in 2 trials.

Of the 24 articles, 7 did not provide information on the source or purity of the talc used. USP-grade, asbestos-free, sterile talc was reported in 2 studies and BP-grade, asbestos-free, sterile talc in one other. Five studies reported USP-grade, sterile talc, but did not address whether it was asbestos-free. Three studies used _____ with 1 of these articles specifically stating that the talc was asbestos-free. Two studies described the talc as asbestos-free, 2 studies described their talc as "pure" and 2 as sterile.

Of the 24 articles, 9 did not report the dose of talc administered, 2 reported their doses in volume (5-10 mls and 4-5 mls) with no concentration information, and 3 studies reported the dose as: 2-3 cm³, 2-3 test tubes, or 2-4 drams. The remaining 10 studies reported administering up to 2 Gm (1 study), 2-5 Gm (6 studies), 10 Gm (2 studies), and up to 10.5 Gm (1 study).

Fever (313 cases) and pain (208 cases) were the most frequently reported adverse experiences in 11 studies. Of the 313 reported cases of fever, 294 (93.9%) had biopsies taken at time of talc administration. The 2 studies that reported biopsies at time of talc pleurodesis also reported more than half (139 out of 208) of all adverse experiences of pain. Twelve cases of empyema (63.2% of cases) were reported in studies that had simultaneous biopsies. Five of the 9 reported cases of infection (55.6%) had biopsies at time of procedure.

The following case reports cited serious or life-threatening adverse experiences in administering talc in 5 patients: Factor 1975, Rinaldo 1983, & Bouchama 1984. Factor reported 1 patient with bilateral malignant pleural effusion who received quinacrine (400 mg) then talc (dose not given) within a few days due to recurrence. The patient was reported as having suffered granulomatous pneumonitis due to quinacrine and talc crystals. The patient died 2 months after his hospital admission from a massive acute myocardial infarction.

Bouchama et al reported one case of talc instillation (2 Gm) for pleural effusion that resulted in acute respiratory distress (fever, malaise, an abnormal chest roentgenogram, pulmonary embolism, and abnormalities on EKG). The patient survived the episode and died 14 months post-treatment. In none of these cases is the causality definitely related to talc.

Rinaldo and colleagues reported 3 cases of ARDS (1 fatality, 1 month post treatment) with talc (10 Gm per patient, per procedure) administration for the management of malignant pleural effusion. Pain (2 patients), fever (3 patients), abnormal chest roentgenogram (3 patients), and tachycardia (1 patient) were among the adverse experiences noted. Two patients recovered without further sequelae.

Forty-four patients were reported in 2 studies that administered the highest doses, i.e., 10 Gms of talc. Tachycardia and hypotension occurred in 2/41 patients under general anesthesia in Adler and Sayek's article, which they attribute to underlying disease. Both patients had been on long-term steroids, had misleading obesity, and were considered hypovolemic in retrospect. All 3 patients in Rinaldo et al's article had ARDS, 1 fatal. A third article by Daniel et al reported 40 patients treated with "up to 10.5 Gms" with one patient dying of a pulmonary embolus. The literature does not report patients treated with higher doses. The only other case of ARDS reported is in Bouchama et al in which a patient treated with 2 Gm developed ARDS associated with a pulmonary embolus. The patient survived the episode and died 14 months later.

11.0 LONG-TERM SAFETY DATA

The sponsor submitted two publications (Chappell, et al 1979 and Lange, et al 1988) reporting long-term follow-up data on patients treated with talc or a related mineral kaolin, in order to provide chronic safety data unable to be collected in patients with terminal cancer.

Chappell and colleagues retrospectively identified a total of 210 patients from 3 hospitals that

had received intrapleural talc (147 patients, from 2 hospitals) or kaolin (63 patients, from the third hospital) before 1961. The intent was to investigate potential delayed carcinogenicity resulting from talc administration. Eighty-eight patients were treated 15-30 years previously and 75 were treated 30-40 years previously. The authors believe that asbestos-free talc was most likely used in 2 institutions. Methods of collecting data included direct written approaches to patients, physicians, family practitioner committees, the Office of Population Censuses and Surveys, foreign embassies, and visits to check the present state of index cases. Of the 147 patients that received talc, 107 were alive and well, 11 were untraceable, and 29 were dead (3 from lung cancer). They found no cases of mesothelioma and the incidence of lung cancer was not greater than expected for the population.

Lange and others assessed 114 consecutive patients treated for first episode of idiopathic spontaneous pneumothorax at 2 chest clinics in Copenhagen with talc poudrage or simple drainage 22-35 years previously. The objective was to assess effect on lung function. Sixty patients received talc and 54 patients received simple drainage via an intercostal tube (no talc). Twenty patients from the drainage only group relapsed and subsequently received talc poudrage (80 total). All patients were traced through the population register. Seventeen patients had died (3 from lung cancer, contralateral in 2 cases and unknown in the third), 2 had emigrated, 75 underwent an interview and physical examination, 14 completed a questionnaire, and 6 failed to respond. Fifty-one of 75 patients undergoing chest radiograph showed pleural thickening. Although there was no significant difference in the incidence of pleural changes between the talc and drainage groups, two talc patients had more extensive pleural thickening with calcification. The mean total lung capacity (TLC) was 89% of predicted in the talc group and 96% in the drainage group. Differences in VC and FEV₁ were not significantly different. Fourteen patients (12 lifelong heavy smokers, 2 non-smokers) had airflow limitation (5 severe). Source and purity of talc was not discussed in the article. No cases of mesothelioma were reported with an observation time of 22 to 35 years.

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11.1 OVERVIEW TABLE OF ARTICLES WITH LONG-TERM FOLLOW-UP

Investigators, Publication	Design	Treatment	Dose Source & Purity of Talc	Age, mean (range)	Patient Population	# Evaluable/ # Entered	Success	Symptom (SX) Relief
FOREIGN STUDIES								
Chappell, et al Br J Dis Chest 1979; 73: 285-8	Retrospective study of pts receiving T or kaolin	intrapleural T (147 pts) or K (63 pts)	not provided; iodized; BP likely; possibly asbestos-free	not provided	T pts: bronchiectasis & non-malignant disorders; ≥ 50% pre-lung resection K pts: spontaneous pneumothorax in pts with chronic bronchitis, emphysema, & pneumoconiosis	136/147 ^{b,c} 63/63 ^d	not provided	not reported
Lange, et al Thorax 1988;43:559-61	Retrospective study of pts receiving T or CT drainage	T poudrage with CT drainage or CT drainage alone	not given	99pts <41yr		108/114 60 (T) ^e 54 (CT) ^e	78/80 (T) ^f 34/54 (CT)	not reported

K = kaolin; T = talc; BP = British Pharmacopeia; T = talc; pts = patients; CT = chest tube
 a = mean in years; b = patients receiving T; c = 11 patients lost to follow-up; d = patients receiving K; e = initial breakdown; 20 CT pts relapsed and were then treated w/T;
 f = includes the 20 CT pts who relapsed

11.2 TABLE OF ADVERSE EXPERIENCES

Author (Location in NDA) No. Patients	Treatment	Dose, Source & Purity of Talc	Adverse Experiences	Chest Tube Drainage Time (days)	Amount of Pleural Fluid Drained	Length of follow-up (f/u) (post procedure)
FOREIGN STUDIES						
Chappell, et al. n = 210 (147T/63K)	intrapleural T (147 pts) or K (63 pts)	iodized; BP likely; possibly asbestos-free	not given	not given	not given	up to 39 yrs (88 pts followed for 15-30 yrs, 75 pts followed for 30-40 yrs) ^a ; 47 deaths total (36 deaths within first 15 yrs) to include 3 from lung cancer ^b (survival 18 mos-32yrs); no increased incidence of lung cancer; no cases of mesothelioma
Lange, et al. n = 114 (80T/34 CT)	T poudrage or simple CT drainage	not provided	T group had restrictive impairment of lung function with mean TLC of 89% predicted; extensive pleural calcification with TLC of 58% predicted and some lung fibrosis in 1/80 (T); CT group had 96% predicted	not given	not given	22 - 35 yrs via interview & PE (75 pts) or questionnaire (14 pts); 17 deaths (3 from lung cancer); 8 lost to f/u; no cases of mesothelioma

K = kaolin; T = talc; BP = British Pharmacopeia grade; TLC = total lung capacity; pts = patients; PE = physical examinations
 a = includes the 11 pts lost to f/u, but believed to be alive; b = patients receiving T;

11.3 EVALUATION AND SUMMARY

Chappell and colleagues reported no increased incidence of lung cancer (3 patients) and no cases of pleural mesotheliomas in this study which retrospectively collected data on 88 patients 15 to 30 years after pleurodesis and 75 patients 30 to 40 years after pleurodesis. Response rates and immediate adverse experiences following pleurodesis were not discussed.

Lange et al collected data on 114 patients (80 treated with talc and 34 drainage only) who were followed-up 22 to 35 years post-procedure. Twenty patients in the drainage only group (37%) had relapsed. The talc group had a response rate of 78/80 (97.5%) and a mild restrictive impairment of lung function with a mean of 89% of predicted total lung capacity. One patient experienced extensive pleural calcification with a total lung capacity of 58% predicted associated with some lung fibrosis. The drainage only group had a response rate of 34/63 (63%) with a total lung capacity of 96% of predicted. The authors noted 3 cases of lung cancer in the talc arm and no cases of mesothelioma. Although the number of patients in both studies is small, the results do suggest that talc is safe for the treatment of patients with malignant pleural effusions, a population with a relatively short life expectancy

**APPEARS THIS WAY
ON ORIGINAL**

12.0 INTEGRATED SUMMARY OF SAFETY DATA FROM CONTROLLED AND NONCOMPARATOR STUDIES

ADVERSE EXPERIENCE	TALC - 25 Studies (1417 patients)	
ADVERSE EXPERIENCES IN ≥ 5% OF PATIENTS		
Fever	324/1417	(22.9%)
Pain	293/1417	(20.7%)
ADVERSE EXPERIENCES IN < 5% OF PATIENTS		
INFECTIONS		
Empyema	20/1417	(1.4%)
Infection not otherwise specified	11/1417	(0.8%)
RESPIRATORY DISORDER		
Respiratory failure/pneumonia	7/1417	(0.5%)
Adult respiratory distress syndrome	4 (with 1 fatality)/1417 1 fatality = 0.07%	(0.3%)
Pulmonary embolism	4 (with 1 fatality)/1417 1 fatality = 0.07%	(0.3%)
Dyspnea	3/1417	(0.2%)
Bronchopleural fistula	2/1417	(0.14%)
Hemoptysis	1/1417	(0.07%)
Granulomatous pneumonia	1/1417	(0.07%)
SC/surgical Emphysema	13/1417	(0.92%)
CARDIAC DISORDER		
Tachycardia	3/1417	(0.2%)
Myocardial infarction	2/1417	(0.14%)
Hypotension	2/1417	(0.14%)
Asystolic arrest	2/1417	(0.14%)
NEUROLOGIC DISORDER		
Peroneal nerve palsy	1/1417	(0.07%)
Post-op grand mal seizure	1/1417	(0.07%)
OTHER		
"Cancerous nodules"	10/1417	(0.7%)
Bleeding	3/1417	(0.2%)

A total of 25 articles (8 controlled, 17 uncontrolled) addressed adverse experiences in their

studies. Fever (324 cases) and pain (293) were reported most often in both controlled and uncontrolled studies. There were no overt differences in the type and frequency of adverse experiences between controlled and uncontrolled trials.

Of the 293 cases that reported pain as an adverse effect, 196 cases (66.9%) had simultaneous biopsies. Similarly 305 of 324 cases (94.1%) that reported fever had biopsies taken at the time of pleurodesis. Other reported adverse experiences that occurred with biopsies include 13/20 (65%) empyema cases and 7/13 (53.9%) surgical emphysema cases. It is possible that obtaining biopsies prior to talc administration may have a role in adding or potentiating the complications that were observed.

Two fatalities were observed in a total of the 1417 patients (0.2%) from articles that reported adverse experiences: one secondary ARDS, one pulmonary embolus, one MI. Only one fatality appears to have been possibly related to talc (Rinaldo). The purity of talc was uncertain and the dose was high (10 Gm). Two patients experienced reversible asystolic arrest (Fentiman 1986) under general anesthesia with no neurological, cardiovascular, or renal sequelae. Two patients experienced MI (Todd et al) in a reported abstract with no further information provided. Four cases of pulmonary embolus (Daniel, Bouchama, and Todd) occurred with 1 fatality reported (Daniel). It should be pointed out that patients with cancer are at high risk for pulmonary embolus. Four patients experienced ARDS (Rinaldo, Bouchama) with 1 reported fatality (Rinaldo) occurring 1 month post-treatment. Seven patients were reported to experience respiratory failure and or pneumonia in Todd's abstract with no further information provided. Taken as a whole, talc administration for the pleurodesis of a malignant pleural effusion, appears relatively safe.

13.0 NON-US POST MARKETING EXPERIENCE

There is no approved formulation of talc for the treatment of malignant pleural effusion.

14.0 SUMMARY

The FDA accepts filing of literature-based NDAs based on the Federal Food, Drug and Cosmetic Act, Section 505(b)(2). However, even if the sponsor does not conduct its own clinical trials, there must be referenced trials that are considered adequate and well-controlled and that provide substantial evidence of efficacy and safety.

Nine controlled trials (6 articles, 3 abstracts) have been submitted by the sponsor in support of Scierosol[®]; however 1 abstract (Hartman 1992) was excluded because it was a preliminary report of the Hartman 1993 article also submitted by the sponsor. Three other studies (abstracts) were found in an additional search performed by the Agency. In these eleven reports, the patient population appears to be appropriate for the indication. The trials present a variety of comparators, e.g., concurrent treatment with chest tube drainage alone, tetracycline, mustine, bleomycin, doxycycline, oxytetracycline, rolitetracycline as well as historical controls. In at least half of the trials, response criteria were defined and appear to

have been based on chest x-rays. Yet each trial consists of small numbers of patients and important aspects of trial design may not be described, i.e., description of randomization, statistical analysis, and other measures to limit bias.

The criteria for well-controlled trials as defined in CFR 314.126 (see Appendix) leave room for interpretation, but the FDA believes that some of the eleven controlled trials (see table below) with sufficient information (i.e., articles rather than abstracts) do meet these criteria.

DESIGN OF STUDIES (ARTICLES) WITH CONCURRENT CONTROLS

AUTHOR # PTS / ARM	DESIGN	STRATIFICATION	Rx/DOSE	TUMOR
NO TREATMENT CONTROL				
Sorensen et al; 1984 n = 14 (CT+T) ----- n = 17 (CT)	Pros. Rand -----	?	10 Gm Slurry ----- CT drainage	Variety
ACTIVE CONCURRENT CONTROL				
Fentiman, et al; 1986 n = 18 (T) ----- n = 23 (Tetracycline)	Pros. Rand -----	± mets requiring chem.	Poudrage dose not given ----- 500 mg Slurry	Breast
Fentiman, et al; 1983 n = 20 (T) ----- n = 17 (Mustine)	Pros. Rand -----	?	Poudrage dose not given ----- 15 mg Soln	Breast
Hamed et al; 1989 n = 10 (T) ----- n = 13 (Bleomycin)	Pros. Rand -----	± mets requiring chem..	Poudrage, dose not given ----- 1 mg/kg Soln	Breast

It is noted that talc is consistently equal to or superior to the control arms, across studies, institutions, and over time.

All four studies were prospective and randomized. In 2 of the 4 articles, stratification according to the presence or absence of metastases requiring systemic chemotherapy was undertaken. The dose of talc was provided in only one study. (The supportive data for a safe and effective dose is based on the entirety of the literature, i.e., controlled and uncontrolled trials.) Tumor type in 3 articles was limited to breast cancer, which is one of the two cancers most frequently complicated by an MPE. One article enrolled a variety of tumors types (breast, mesothelioma, ovary, prostate, GI, and lung).

RESPONSE DATA OF STUDIES (ARTICLES) WITH CONCURRENT CONTROLS

AUTHOR # PTS / ARM	#EVAL/ # ENT	DEF OF EVAL PTS	DEF of "SUCCESS"	METHOD EVAL "SUCCESS"	"SUCCESS" in EVAL PTS	INTENT TO TREAT ANALYSIS	RESPONSE DURATION	SX RELIEF
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NO TREATMENT CONTROL

Sorensen et al; 1984 n = 14 (CT+T) ----- n = 17 (CT)	9/14	Lung re-expansion by 72 hrs	No fluid reaccum for 3 mos.	CXR at 1 mo, then q 3 mos	9/9 100%	9/14 64%	until death 10 mo median; range 3-24 mos	9/9 (dyspnea)
	12/17				7/12 58%	-- 7/17 41%		

ACTIVE CONCURRENT CONTROL

Fentiman, et al; 1986 n = 18 (T) ----- n = 23 (TCN)	12/18	Survival ≥ 1mo & CXR	No fluid reaccum for 12 mos. min.	CXR at 1 mo	11/12 92%	11/18 61%	12 mos min	?
	21/23				10/21 48%	-- 10/23 43%		
Fentiman, et al; 1983 (T) ----- n = 17 (M)	20/23	Survival ≥ 1mo & CXR	No fluid reaccum for 6 mos. min.	CXR at 1mo, then q 3 mo	18/20 90%	18/23 78%	mos min or until death	?
	17/23				9/17 53%	-- 9/23 39%		
Hamed et al; 1989 n = 10 (T) ----- n = 13 (Bleo)	10/13	Survival ≥ 1mo & CXR	No fluid reaccum on all flus	By CXR	10/10 100% (procedures)	?	?	?
	13/16				(procedures) 5/15 33%			

Number of evaluable patients, definition of "success", method of evaluating "success", and "success" rates were defined in all 4 studies. An intent-to-treat analysis was performed by the agency for 3 of the 4 articles; Hamed 1989 reported their "success" rates in number of procedures making this type of analysis not possible. Although the response rates fell when an intent-to-treat analysis was performed, talc was still seen to be superior to the control arm in the 3 articles.

15.0 ONCOLOGY DRUGS ADVISORY COMMITTEE SUMMARY

ODAC, chaired by Paul Bunn, M.D., met on December 14, 1995. The primary reviewers were Dr. Paul Bunn and Dr. James Krook, who led the discussion of the questions posed by the FDA. The committee was in agreement that articles by Sorensen 1984, Fentiman 1986, Fentiman 1983, and Hamed 1989 were the best representation of "adequate and well controlled trials" in the literature. The safety profile of a single administration of 4 to 8 Gm of talc was considered acceptable by all ODAC members based on the entirety of the medical literature, i.e., comparator and noncomparator studies. All were in agreement that Sclerosol® was approvable for the palliative treatment of malignant

pleural effusions. ODAC suggested that the acceptability of literature-based NDAs for cancer populations and therapeutics was based on whether there is sufficient data in the literature to substantiate efficacy and safety. Cytotoxic, hormonal, and supportive care products could all be potential candidates for a literature-based NDA.

16.0 RECOMMENDED REGULATORY ACTION

The application is approvable.

Lydia V. Larson, Pharm.D.

7/11/96. ISI

son Martin, M.D.

7/12/96 ISI

Robert Justice, M.D.

7/18/96 ISI

CC: ORIGINAL NDA 20-587
HFD-150 / DIVISION FILE
HFD-150 / LKIEFFER
HFD-150 / AMARTIN
HFD-150 / DCATTERSON

APPENDIX

CFR 314.126

Published Controlled Clinical Trials

(b) When a petition described in paragraph (a) of this section is submitted, the agency shall consider the evidence in the petition and any other evidence before the agency, and determine whether the listed drug is withdrawn from sale for safety or effectiveness reasons, in accordance with the procedures in §314.161.

(c) An abbreviated new drug application described in paragraph (a) of this section will be disapproved, under §314.127(a)(11), and a 505(j)(2)(C) petition described in paragraph (a) of this section will be disapproved, under §314.93(e)(1)(iv), unless the agency determines that the withdrawal of the listed drug was not for safety or effectiveness reasons.

(d) Certain drug products approved for safety and effectiveness that were no longer marketed on September 24, 1984, are not included in the list. Any person who wishes to obtain marketing approval for such a drug product under an abbreviated new drug application must petition FDA for a determination whether the drug product was withdrawn from the market for safety or effectiveness reasons and request that the list be amended to include the drug product. A person seeking such a determination shall use the petition procedures established in §10.30 of this chapter. The petitioner shall include in the petition information to show that the drug product was approved for safety and effectiveness and all evidence available to the petitioner concerning the reason that marketing of the drug product ceased.

[57 FR 17990, Apr. 28, 1992; 57 FR 29353, July 1, 1992]

§ 314.125 Refusal to approve an application or abbreviated antibiotic application.

(a) The Food and Drug Administration will refuse to approve the application or abbreviated antibiotic application and for a new drug give the applicant written notice of an opportunity for a hearing under §314.200 on the question of whether there are grounds for denying approval of the application under section 505(d) of the act, or for an antibiotic publish a proposed regulation based on an acceptable petition under §314.300, if:

(1) FDA sends the applicant an approvable or a not approvable letter under §314.110 or §314.120;

(2) The applicant requests an opportunity for hearing for a new drug or the question of whether the application is approvable or files a petition for an antibiotic proposing the issuance, amendment, or repeal of a regulation; and

(3) FDA finds that any of the reasons given in paragraph (b) of this section apply.

(b) FDA may refuse to approve an application or abbreviated antibiotic application for any of the following reasons:

(1) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.

(2) The investigations required under section 505(b) or 507 of the act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(3) The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.

(4) There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(5) There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in §314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

(6) The proposed labeling is false or misleading in any particular.

(7) The application or abbreviated antibiotic application contains an untrue statement of a material fact.

(8) The drug product's proposed labeling does not comply with the require-

ments for labels and labeling in part

The application or abbreviated antibiotic application does not contain bioavailability or bioequivalence data required under part 320 of this chapter.

(10) A reason given in a letter refusing to file the application or abbreviated antibiotic application under §314.101(d), if the deficiency is not corrected.

(11) The drug will be manufactured or processed in whole or in part in an establishment that is not registered and not exempt from registration under section 510 of the act and part 207.

(12) The applicant does not permit a properly authorized officer or employee of the Department of Health and Human Services an adequate opportunity to inspect the facilities, controls, and any records relevant to the application or abbreviated antibiotic application.

(13) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211

(14) The application or abbreviated antibiotic application does not contain an explanation of the omission of a report of any investigation of the drug product sponsored by the applicant, or an explanation of the omission of other information about the drug pertinent to an evaluation of the application or abbreviated antibiotic application that is received or otherwise obtained by the applicant from any source.

(15) A nonclinical laboratory study that is described in the application or abbreviated antibiotic application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(16) Any clinical investigation involving human subjects described in

the application or abbreviated antibiotic application, subject to institutional review board regulations in part 58 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

(17) The applicant or contract research organization that conducted a bioavailability or bioequivalence study described in §320.38 or §320.63 of this chapter that is contained in the application or abbreviated antibiotic application refuses to permit an inspection of facilities or records relevant to the study by a properly authorized officer or employee of the Department of Health and Human Services or refuses to submit reserve samples of the drug products used in the study when requested by FDA.

(18) For a new drug, the application failed to contain the patent information required by section 505(b)(1) of the act.

(c) For drugs intended to treat life-threatening or severely-debilitating illnesses that are developed in accordance with §§312.80 through 312.88 of this chapter, the criteria contained in paragraphs (b) (3), (4), and (5) of this section shall be applied according to the considerations contained in §312.84 of this chapter.

[50 FR 7493, Feb. 22, 1985, as amended at 53 FR 41524, Oct. 21, 1988; 57 FR 17991, Apr. 28, 1992; 58 FR 25928, Apr. 28, 1993]

§ 314.126 Adequate and well-controlled studies.

(a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. The characteristics described in paragraph (b) of this section have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation. The Food and Drug Administration considers these characteristics in determining whether an investigation is adequate and well-controlled for purposes of sections 505 and 507 of the act. Reports of

Treatment of malignant pleural effusion with drainage, with and without instillation of talc

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Abstract: In order to determine whether pleural drainage with talc instillation was better than pleural drainage alone, in the treatment of malignant effusion, the present trial was initiated. Thirty-one patients with malignant pleural effusion and progressive disease, resistant to conventional therapy, were included. All patients had pleural drainage applied. After re-expansion of the lung, half of the patients had talc instilled through the chest tube. Twenty-one of the 31 treated patients were evaluable. After pleural drainage with talc instillation, all of 9 treated patients obtained complete resolution of the effusion and subjective improvement. After pleural drainage alone, 7 of 12 patients obtained complete resolution of the malignant effusion. If it is possible to re-expand the lung during pleural drainage in patients with a malignant pleural effusion, pleurodesis can be obtained in 60% of the treated patients with pleural drainage alone. This study showed a statistically significant improvement in the treatment associated with instillation of talc into the pleural cavity and this was achieved without causing increased discomfort to the patient.

Traitement des épanchements pleuraux malins par un drainage avec ou sans instillation de talc.

Résumé: L'objet du présent essai a été de déterminer si un drainage pleural, accompagné d'une instillation de talc, était supérieur au drainage pleural isolé dans le traitement des épanchements malins de la plèvre. Ont été inclus dans l'essai, trente et un patients atteints d'un épanchement pleural malin et d'une maladie progressive, résistant à la thérapeutique conventionnelle. Le drainage pleural a été appliqué chez tous les patients. Après réexpansion du poumon, du talc a été instillé par le tube de drainage chez la moitié d'entre eux. L'évaluation a été possible chez vingt et un des trente et un patients traités. Une résolution complète de l'épanchement et une amélioration subjective ont été observées chez les 9 patients traités par drainage pleural avec instillation de talc. Une résolution complète de l'épanchement pleural a été observée chez 7 des 12 patients soumis à un drainage pleural isolé. Lorsque la réexpansion pulmonaire peut être obtenue au cours du drainage pleural chez des patients atteints d'épanchement pleural malin, une symphyse peut être obtenue chez 60% des sujets traités par le simple drainage pleural. Cette étude montre une amélioration significative des résultats du traitement associé, comportant l'instillation de talc dans la cavité pleurale. Ce résultat a été acquis sans augmenter l'inconfort subi par le patient.

Key Words: malignant neoplasms - drainage - talc - pleural effusion.

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Previous investigations (1, 4, 7, 9) have shown that malignant pleural effusions can be treated with pleural drainage and talc instillation with a good palliative effect. In these investigations, however, it is not possible to distinguish between the effect of

Fourteen patients were treated by pleural drainage and talc instillation, and 17 patients by pleural drainage alone. Twenty-one of these patients were evaluable. Seven patients (2 in the talc and 5 in the control group) died from their malignant disease within 3 months. In 2 patients it was impossible to re-expand the lung after application of pleural drainage and one patient, who had had talc instilled, developed an empyema.

All 9 patients who were treated by pleural drainage plus talc instillation obtained pleurodesis with resolution of the malignant effusion. Chest radiographs showed evidence of pleural thickening and diaphragmatic adhesion only. In all 9 patients, the complete response continued until the patients' death, a median response duration of 10 months (range 3-24 months). They all obtained subjective improvement with partial or complete resolution of dyspnoea. No patient complained of continuous chest pain after the intervention.

A positive result was obtained in 7 of 12 patients in the group that had pleural drainage applied without talc instillation. Chest X-rays showed pleural thickening with no recurrence of the effusion prior to the patients' death, median 10 months (range 4-17 months). Subjective improvement was seen in 6 of the 7 patients whose effusion did not recur.

As with those patients receiving talc, prolonged pain, attributable to the procedure, was not seen in those treated by pleural drainage alone. There was one case of staphylococcal septicaemia. All patients from both treatment groups suffered pain, requiring treatment for 2-3 days after insertion of the chest drain.

adenocarcinoma with unknown primary tumour).

DISCUSSION

Patients with the most commonly occurring solid tumours, such as breast cancer, ovarian cancer and lung cancer, frequently develop a pleural effusion in the end stage of their disease. As symptoms are often severe and the end stage of the disease often protracted, an effective palliative treatment is needed.

Anderson et al. (3) have described the treatment of malignant pleural effusion by thoracocentesis alone. Forty-nine patients had thoracocentesis performed with maximum removal of the effusion. The effusions recurred in all but one of the 49 patients. In half of the patients effusions recurred within 96 h of thoracocentesis and in the remaining patients within one month of the procedure being performed.

In principle, a chemical pleuritis with resulting pleurodesis may depend upon 2 effects of an anti-neoplastic drug instilled in the pleural cavity: a cytostatic effect on the pleural tumour, or an irritative effect on the surface of the pleura.

Instillation of such cytostatic drugs as nitrogen mustard, thiotepe and 5-fluorouracil, (8, 11, 16), into the pleural cavity after thoracocentesis, has been tried in order to prevent the recurrence of malignant pleural effusions. But the results have been poor, with response rates from 0 to 30%. These results probably are related to the fact that thoracocentesis alone will not allow complete removal of the effusion and, therefore, fails to create contact between the visceral and parietal pleura. In other studies, pleural drainage has been used to obtain maximum evacuation of a pleural effusion. After re-expansion of the lung, a cytostatic drug is instilled through the chest tube, and the tube then clamped. After some hours, suction on the chest tube is again applied for 48 h. By this procedure pleurodesis with resolution of the effusion can be obtained in

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A Comparison of Intracavitary Talc and Tetracycline for the Control of Pleural Effusions Secondary to Breast Cancer

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Abstract—Forty-one patients with malignant pleural effusions secondary to breast cancer were randomly allocated to treatment with either intracavitary talc or intracavitary tetracycline. Of 33 evaluable patients, radiological control was achieved in 11/12 (92%) of the talc group compared with 10/21 (48%) of the tetracycline group ($P = 0.022$). Intracavitary talc provides effective palliation of metastatic pleural effusions secondary to breast cancer.

INTRODUCTION

PATIENTS with metastatic breast cancer often develop symptomatic pleural effusions, either as a first manifestation of recurrence, or during the course of advanced disease. For patients without other detectable metastatic disease a local treatment may be preferable to systemic therapy. Furthermore, even those with evidence of metastases at other sites may better be palliated with intracavitary therapy in addition to systemic treatment. In a review of patients treated in this Unit it was found that control of effusions was achieved only in approximately one third of patients treated systemically [1]. Most patients with pleural effusions secondary to breast cancer are not in a preterminal state and the median survival is 13 months [1]. Therefore effective palliation of the effusion can relieve months of potential dyspnoea. Many agents have been recommended for instillation into the pleural cavity in order to produce pleurodesis, and include radioactive phosphorus [2], gold [3], thio-tepa [4], mustine [5], quinacrine [6], tetracycline [7] and talc [8]. In a recent controlled trial, in which patients were randomly treated by either intracavitary talc or intracavitary mustine the former treatment was found to be superior [9]. Because talc produced the best control of effusions with no recurrence in 90% of patients, this method of treatment was adopted as the routine management on this unit. However, intra-cavitary tetracycline was becoming more widely used elsewhere as an intrapleural sclerosant and had the

potential advantage over talc that it can be instilled without the need for a general anaesthetic. For these reasons the present controlled trial has been conducted, in which patients with symptomatic pleural effusions secondary to breast cancer have been randomly allocated to treatment with either intracavitary talc or intracavitary tetracycline.

PATIENTS AND METHODS

Forty-one patients were entered into the trial. To be eligible, each had histologically confirmed breast cancer, together with a symptomatic pleural effusion which had been verified radiologically. None had received any previous treatment other than simple needle aspiration without indwelling tube drainage. Furthermore, none had evidence of non-malignant causes for the pleural effusion. All patients had to be suitable for general anaesthesia and either form of treatment, with no history of sensitivity to tetracycline. Patients were stratified according to the presence or absence of other metastatic lesions requiring treatment and were then randomly allocated to one of the two treatment arms.

Talc pleurodesis

The detailed technique of talc pleurodesis has been described previously [9]. In summary under a general anaesthetic, the pleural cavity was drained to dryness and inspected thoracoscopically. Simple talc was then insufflated, intercostal drains were inserted and remained in place for 5 days.

a problem. Patients were given opiate analgesics for the first 24 hr postoperatively and thereafter usually only required mild analgesics. In this series empyema did not occur but this had been a complication in one patient who was treated before this trial started. In that case the drains were left in for more than 5 days because of a persistent pneumothorax. It is therefore recommended that whenever possible the intercostal drains should be

removed after no more than 5 days. With these provisions intracavitary talc provides an effective method of achieving successful pleurodesis which is suitable for the majority of patients with this complication of metastatic breast carcinoma. What still has to be achieved is a more accurate identification of those patients with poor prognosis who will die within one month and therefore will not benefit from aggressive local therapy.

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Control of Pleural Effusions in Patients With Breast Cancer

A Randomized Trial

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In a controlled randomized trial, 46 patients with pleural effusions secondary to breast cancer were treated at first diagnosis with either intracavitary mustine or talc, to determine which agent produced the more effective pleurodesis. Of the 37 evaluable patients, control of the effusion was achieved in 9/17 (56%) of those treated with mustine and 18/20 (90%) of the talc group ($P < 0.025$). This suggests that early treatment with intracavitary talc can effectively palliate this complication of breast cancer. *Cancer* 52:737-739, 1983.

PLEURAL EFFUSIONS occur commonly in patients with breast cancer, and usually recur after simple aspiration.¹ To prevent re-accumulation, obliteration of the pleural space is of value, and several agents including thiotepa,² mustine,³ quinacrine,⁴ tetracycline,⁵ and talc, both simple⁶ and iodized,⁷ have been used. However, most of the reported series comprised heterogeneous patients suffering from a variety of primary malignancies. A recent sequential series of 105 patients treated in this unit showed that control of recurrent effusions complicating breast cancer was achieved in only 10% of cases in which pleurodesis was attempted.¹ Such disappointing results could have arisen partly from delay in attempting definitive treatment, so that lung compression or effusion loculation prevented effective pleurodesis. In addition, the sclerosant agents used to produce pleural fusion may have been ineffective.

With the aim of improving the results of palliative treatment of pleural effusions in patients with breast cancer, a controlled trial has been conducted in which pleurodesis has been attempted at first presentation of the effusion, with random allocation of patients to treatment with either intracavitary talc or mustine.

Patients and Methods

Forty-six patients with histologically confirmed breast cancer were included in the trial, and all had radiologically verified pleural effusions. No previous local treatment had been given, although 20 patients had had simple needle aspiration for the immediate relief of dyspnea; none had any evidence of nonmalignant causes for the effusion. Thirty-eight patients were receiving or eventually received concomitant systemic therapy for the treatment of other lesions. Cases were stratified by the presence or absence of other metastases requiring treatment, and then allocated by balanced randomisation to one of the treatment arms. To prevent vasovagal attacks, atropine 0.6 mg was included in the premedication. All patients were thorascoped under general anesthesia to detect the presence and assess the distribution of pleural metastases, and the results of this study have been reported separately.⁸

Talc Pleurodesis

Under general anesthesia, with a single-lumen cuffed endotracheal tube, patients were placed in the appropriate lateral position, and the effusion was drained to dryness through an intercostal cannula. After inspection of the pleural cavity had been completed, using a Storz Biopsy thoracoscope, a second intercostal cannula was inserted. Simple Talc British (Pharmacopeia grade) (Evans Medical) was then instilled, using a Stanford Cade insufflator, until talc was seen to discharge freely from the second cannula. Two intercostal drains were

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of 16 months. There have been 18 deaths in the mustine group, including 12 assessable patients with effusion control, to death in eight (50%), median survival being 14 months. There are five patients in the mustine group who are still alive, and three of five show no evidence of effusion recurrence, with a median survival of 15 months. Of the mustine failures, two required further local treatment for symptomatic relief, and a further two showed resolution of recurrent effusion in response to systemic cytotoxic chemotherapy.

During the period of this trial, it was the policy of this unit to treat advanced breast cancer with endocrine therapy as a first measure. This comprised ovarian ablation in premenopausal patients, and tamoxifen for postmenopausal patients, with random allocation to additional prednisolone. Patients who relapsed on this regimen were given chemotherapy, starting with Adriamycin (\pm vincristine) followed by cyclophosphamide, 5-fluorouracil, and methotrexate. There was a similar distribution of concomitant systemic treatments used in the two pleurodesis groups. Table 4 shows that when the response to systemic treatment was assessed using the UICC criteria,⁹ and compared with the response to pleurodesis, there was a systemic response, partial or complete, in 33% of the mustine successes and in 41% of the talc success group. This indicates that the difference in the control of the effusions between the talc and mustine groups resulted from local rather than systemic therapy.

Discussion

In this study, the overall rate of treatment control (78%) has improved when compared with that in a retrospective analysis (10%), which was similarly assessed and excluded deaths within one month. This suggests that an active approach to treatment at the outset is important, while a conservative "wait and see" policy may compromise subsequent attempts at definitive treatment, perhaps because of adhesion formation.

This trial has also shown that talc is superior to mustine in achieving an effective pleurodesis. One possible explanation of the failure of mustine may be the rapid transpleural flux, or its hydrolysis, thereby reducing the duration of its inflammatory effect.

While this trial was in progress, talc pleurodesis was performed electively on ten other breast cancer patients whose effusions had not responded to previous attempts at local control. Effusion control was achieved in eight cases, but there were two early deaths, one from disease progression and the other from a probable pulmonary embolus.

In order to ensure that pleurodesis was complete, a widespread contact between parietal and visceral surfaces was essential. This necessitated total pleural fluid drainage, which in one patient totalled 3.2 litres. It

TABLE 3. Outcome of Treatment in the Two Groups

	Mustine	Talc
Total	23	23
Not assessable	6	3
Success	9/17 (56%)	18/20 (90%)
Failure	8/17 (44%)	2/20 (10%)
Total deaths	18	13
Median survival (months)	13.5	14.5
Patients still alive	5	10
Median survival (months)	16	17
Effusion control	3/5 (60%)	10/10 (100%)

TABLE 4. Response to Systemic Therapy and Comparison with Results of Attempted Pleurodesis

Systemic therapy	Mustine group		Talc group	
	Success (n = 9)	Fail (n = 8)	Success (n = 17)	Fail (n = 2)
Response (CR + PR)	3	2	7	0
No response	6	6	10	2

CR: complete response; PR: partial response.

should be stressed that all of these patients had their effusions drained under general anesthesia, with endotracheal intubation, and none showed any evidence of pulmonary edema as a consequence.

Provided that adequate precautions are taken, early definitive palliative treatment, using talc pleurodesis in patients with pleural effusions secondary to breast cancer, can achieve satisfactory long-term symptomatic relief for the majority of patients with this problem.

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Comparison of intracavitary bleomycin and talc for control of pleural effusions secondary to carcinoma of the breast

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In a prospective randomized study, patients with pleural effusions secondary to breast carcinoma were randomly allocated to be treated by pleurodesis using either intracavitary talc or bleomycin. For 25 assessable treatments in 22 patients, recurrence of effusion was observed in 5 of 15 (33 per cent) of the bleomycin group compared with none in the talc group. It is concluded that talc is superior to bleomycin in controlling pleural effusions secondary to breast carcinoma, but bleomycin may have a role in patients unfit for general anaesthesia or with extensive disease elsewhere.

Keywords: Breast cancer, pleural effusion, chemotherapy, pleurodesis

Malignant pleural effusions are commonly seen as a result of metastatic carcinoma of the breast. The mean time between diagnosis of breast carcinoma and development of pleural effusion is more than 3 years, and the mean survival after presentation with effusion is 14 months¹. Thus effective symptomatic control can significantly improve patients' quality of life. More than half of these patients have other metastases for which they are receiving or will receive systemic therapy². Only rarely can pleural effusion be controlled by systemic treatment alone, and local management provides the most effective method of control. Many agents are in use for pleurodesis, some with cytotoxic properties (mustine, doxorubicin, bleomycin) and others which are sclerosants (talc, tetracycline), with a wide range of efficacy reported³. In this unit talc pleurodesis has been previously tested against mustine and tetracycline and found to be superior to both^{4,5}. Promising results have been reported using bleomycin, but it has not been directly compared with talc, and for this reason a prospective randomized trial has been conducted.

Patients and methods

Twenty-nine patients with breast carcinoma who had developed radiographically confirmed pleural effusion were entered into the trial. No previous local treatment had been given apart from simple aspiration for initial symptomatic relief. None had any evidence of non-malignant causes for the effusion. Patients were stratified by the presence or absence of other metastases requiring systemic treatment to enable balanced randomization. All the patients had the effusion drained to dryness under general anaesthetic and then were allocated randomly to have either a talc pleurodesis or a single intercostal drain inserted. The latter was followed by instillation of bleomycin 1 mg/kg in 50 ml normal saline after a chest radiograph had shown re-expansion of the lung and when the patient could be postured to facilitate distribution of the drug. This was usually performed within 48 h. Both the bleomycin and talc treated cases had only one intercostal drain.

Assessment of response

Patients were deemed assessable for response to pleurodesis provided they survived for > 1 month after the procedure, and they had a repeat chest radiograph at this time. The immediate postpleurodesis film was used as a baseline from which to assess subsequent radiographs. Success was defined as a continued absence of reaccumulation of pleural fluid on all follow-up radiographs; any reaccumulation was regarded as treatment failure.

Results

Twenty-nine patients entered into the study. One patient who was allocated to the bleomycin pleurodesis deteriorated rapidly,

the procedure was cancelled, and the patient died a few days later. Another patient who was assigned to talc was unable to have insufflation of the agent because of loculations. After apparently successful pleurodesis two patients in the bleomycin group and three in the talc group survived for < 1 month and so were excluded from the analysis. Thus there were 22 assessable patients of whom nine were treated with talc, 12 with bleomycin, and one had talc on one side and bleomycin on the other. Two patients had bilateral bleomycin pleurodeses. In total, ten talc and 15 bleomycin assessable procedures were performed.

Median follow-up was 24 months. During the period of the study 23 of the 29 patients died, and 16 of these survived for < 6 months. In these 16 patients, extrapleural disease was encountered in 23 sites compared with nine in the seven patients who survived for > 6 months (Table 1). Seven patients in the talc and six in the bleomycin group were receiving systemic treatment for disseminated disease. The two groups were similar with regard to age at diagnosis of breast carcinoma and menopausal status, but there were more patients with stage 3 disease in the talc group (Table 2). The mean time to development of effusion was shorter in the talc group than in the bleomycin group (4.6 versus 5.5 months). There was also a longer mean delay between diagnosis of effusion and treatment in the talc group (6.6 versus 4.8 months).

In the talc group none of the 10 patients developed evidence of relapse of the effusion compared with 5 of 15 (33 per cent) in the bleomycin group (Fisher exact test $P=0.057$) after a mean follow-up of 9 months. Two patients in the bleomycin group underwent subsequent talc pleurodesis with significant symptomatic improvement in one, but no benefit for the other

Table 1 Sites of extrapleural disease before pleurodesis in 23 patients who subsequently died

Site	Survival	
	< 6 months (n = 16)	> 6 months (n = 7)
Cutaneous	8	1
Skeletal	6	3
Lung	5	3
Liver	2	1
Abdomen	1	-
Choroidal	1	-
Central nervous system	-	1
None	3	1

Etude randomisée de l'efficacité du talcage thoracoscopique et de l'instillation de tétracycline dans le traitement des pleurésies cancéreuses récidivantes

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40 malades porteurs d'une pleurésie cancéreuse intarissable ont eu une thoracoscopie. Talcage ou tétracycline ont été tirés au sort avant la fin de la thoracoscopie. Les deux groupes après randomisation avaient les caractéristiques suivantes : groupe talqué = 16 cancers secondaires, 4 mésothéliomes; qualité moyenne de liquide ponctionné avant thoracoscopie = 5.1 ± 1.9 l par malade. Groupe « tétracycline » = 14 cancers secondaires, 6 mésothéliomes; 5.5 ± 3 l ponctionnés.

Les résultats obtenus ont été jugés après une période de 6 mois. Parmi les malades talqués, 6 étaient décédés. Les 14 autres malades n'avaient plus d'épanchement. Parmi les malades qui avaient reçu de la tétracycline, 5 étaient décédés, 8 étaient guéris de leur pleurésie, mais 6 avaient rechuté. Il apparaît donc qu'à 6 mois de recul le talcage pleural a une meilleure efficacité que la tétracycline dans le traitement des pleurésies cancéreuses.

Mésothéliome malin métastatique d'une tumeur adénomatoïde testiculaire

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Les auteurs rapportent l'observation d'un patient de 43 ans hospitalisé pour un épanchement pleural droit survenu trois ans après une castration unilatérale pour tumeur adénomatoïde de la vaginale testiculaire. L'anamnèse professionnelle ne retrouve pas d'exposition asbestosique.

L'évolution est marquée par la récurrence de l'épanchement pleural lymphocytaire, riche en acide hyaluronique, et par l'apparition d'un élargissement médiastinal polycyclique deux mois plus tard.

Les prélèvements histologiques obtenus par pleuroscopie, puis par médiastinoscopie sont confrontés à l'examen anatomopathologique de la pièce opératoire testiculaire et permettent de conclure à la nature métastatique de l'extension thoracique.

Malgré un traitement associant polychimiothérapie et radiothérapie, le décès survient 20 mois plus tard dans un tableau de dissémination métastatique à la plèvre contralatérale et au péritoine.

La tumeur adénomatoïde de la vaginale testiculaire, bénigne dans la grande majorité des cas, possède des potentialités malignes exceptionnelles que l'examen histologique initial ne permet pas toujours de déceler. Grâce aux études ultrastructurales, une histogenèse commune avec les autres séreuses est actuellement reconnue. Le pronostic des rares formes à évolution métastatique est aussi péjoratif que celui du mésothéliome pleural primitif.

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Aspergillome et tuberculose pulmonaire évolutive concomitante

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Monsieur G., 61 ans, consulte en janvier 1981 pour une altération de l'état général et une expectoration hémoptoïque. Le bilan radiotomographique du thorax révèle des opacités nodulo-infiltratives. A droite, existe une opacité ovalaire de 3 sur 4 centimètres, surmontée d'un croissant clair. Une radiographie du thorax pratiquée en 1969 est normale. La tuberculose est confirmée par la présence de bacilles acido-alcool-résistants à l'examen direct de l'expectoration avec aux cultures, l'identifica-

tion d'un bacille de Koch dont la sensibilité est conservée à tous les tuberculostatiques. Avant tout traitement le sérodiagnostic vis-à-vis d'*Aspergillus fumigatus* met en évidence l'arc en immunodiffusion et l'arc en immunoelectrophorèse. La recherche d'arcs spécifiques catalase et chymotrypsine est positive, l'immunofluorescence indirecte est positive à la dilution de 1/40°. Après 18 mois de traitement par triple association tuberculostatique, on note à la radiographie du thorax une nette régression des opacités

PLEURAL DRAINAGE WITH TALC VS DOXYCYCLINE IN THE CONTROL OF MALIGNANT PLEURAL EFFUSIONS. J.F. Muir, F. Cerisiel, C. Defouilloy, P.M. Broussier, A. Hermant, P. Aubry, S. Megerlince, N.J. Botto, S. Arlati. Service de Pneumologie et Réanimation Respiratoire, C.H.U. Amiens 80000, France.

In a controlled randomized trial, 30 patients with pleural effusions secondary to disseminated cancer were treated at first diagnosis with either intracavitary doxycycline (D group) or talc (T group), to determine which agent produced the more effective pleurodesis. All patients had a thoracoscopy followed by chest tube drainage of their effusion and insertion of a pleurocatheter. During the thoracoscopy, 5 ml of Luznac talc was insufflated over as much of the pleural space as possible for the T group; in the D group, after the thoracoscopy, the chest tube was clamped during 3 hours, and 20 mg/kg of doxycycline in 200 ml of saline was instilled through the pleurocatheter with the patient's position changed to insure adequate dispersal; the chest tube was then unclamped for an additional 24 hours and so on every day until the drainage was minimal. In order to be evaluable, the patient had to survive one month after instillation of the sclerosing agent. All patients were evaluable; 0/15 patients in the T group (follow-up: 4.8±/-4.2 months), and 2/15 patients had recurrence of pleural effusion in the D group (follow-up: 3.9±/-3.3 months). Chest tube drainage duration for the 13 patients of the D group without recurrence was 10.3±/-4.3, days. Both the talc and doxycycline were well tolerated. No pleurocutaneous fistula was observed. Intrapleural lavage-drainage with doxycycline is as effective as talc for control of malignant pleural effusions.

PLEURAL DRAINAGE WITH TALC VS ROLITETRACYCLINE
CONTROL OF MALIGNANT PLEURAL EFFUSIONS J-F
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In a controlled randomized trial, 24 patients (2F/12M) with pleural effusions secondary to disseminated cancer were treated at first diagnosis with either intracavitary rolitetracycline (R group) or talc (T group), to determine which agent produced the more effective pleurodesis. All patients had a thoracoscopy followed by chest tube drainage of their effusion until pleural flow was minimal. During the thoracoscopy, 5 ml of Luzenac talc were insufflated over as much of the pleural space as possible for the T group; in the R group 20 mg/kg of rolitetracycline were vaporized according to the same procedure as for the talc. In order to be evaluable, the patient had to survive one month after instillation of the sclerosing agent. 1/12 patients in the T group (follow-up: 5,7 ± 4,9 months; deaths: 10), and 2/12 patients had recurrence of pleural effusion in the R group (follow-up: 8,2 ± 5,1 months; deaths: 9). Chest tube drainage duration for the 12 patients of the (R) group without recurrence was 7,7 ± 2,1 days, and 7,8 ± 3,2 days for the T group [N.S.]. On a long term basis, non recurrence rates of pleural effusion were similar in the two groups (T group: 87,5% / R group: 83,3%). Both the talc and rolitetracycline were well tolerated. No pleurocutaneous fistula were observed. Pleurodesis with rolitetracycline is as effective as talc for control of malignant pleural effusions.

The value of a new prosthesis with sponge-layer covered funnel for the treatment of malignant esophago-respiratory fistula
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Results following a new, surgical, exclusive esophageal intubation with a tube having a sponge-layer covered funnel are discussed as regards mortality and benefit. 9 patients with malignant tracheo- or broncho-esophageal fistula were managed by this specially prepared tube at the Thorac. Surg. Clin. Budapest, in the last 5 years. The over-all mortality was 11,5%. All alive patients have resumed on oral soft diet, esophago-respiratory symptoms disappeared. Pull-through esophageal intubation with the new, composite, detachable prosthesis allows insertion of the tube only in the malignant narrowing. Simultaneously, the sponge-layer on the external surface of the funnel, provide a hermetically exclusion of the fistula. The end of the tube does not pass across the cardia, so the patient is free from gastro-esophageal reflux and its consequences. The authors suggests, that in this circumstance, the exclusive esophageal intubation with this new, specially prepared tube is safer than the conventional one, and is the less risk procedure with good results.

Adenosine deaminase activity in lung cancer.
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Adenosine deaminase (ADA) is an enzyme considered as a marker of cellular immunity. Its plasma activity is found to be elevated in those diseases in which there is a cell mediated immune response.

Deficiency of ADA is associated with defective cellular and humoral immunity.

In this preliminary study the ADA activity was assessed in bronchial washing and blood in 69 patients who were subdivided into the following three groups. 1) 14 patients with small cell lung carcinoma (SCLC), 2) 16 patients with non small cell lung carcinoma (NSCLC) and 3) 39 patients with benign disease.

The ADA activity was assessed with Guisti's colorimetric method.

	Bronchial washing	blood
SCLC	0.42 U/L	24 U/L
NSCLC	1.87 U/L	31 U/L
Benign diseases	2.52 U/L	35 U/L

The results show that ADA concentrations of bronchial washing achieved in SCLC are statistically lower than the other groups.

Specificity (0.85) and sensitivity (0.77) of the test in SCLC are high when a value of less than 1 U/L is considered. Comparing the ADA activity of blood in SCLC with all others the difference is significant only among the groups of SCLC and benign diseases.

In conclusion ADA assays in bronchial washing and blood may be considered as a tumor marker for SCLC. The study is continued.

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Lymphangioleiomyomatosis of the lungs. Isolated form and combination with tuberous sclerosis

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Two cases of lymphangioleiomyomatosis of lung are presented, one of them with clinically and radiologically diagnosed tuberous sclerosis and other soft tissue tumors, with slow disease progression, the other one representing an isolated lung involvement (form frust) without signs of tuberous sclerosis and other organ involvements, but with severe and progressive course.

Immunohistochemistry and electron microscopy can be helpful in defining the cells of origin, but are not essentially for establishing the diagnosis. Pulmonary involvement in this disease is very rare, therefore it is of importance to know this striking picture and to differentiate it from similar pathological entities.

BOMBESIN-LIKE PEPTIDE IN BRONCHOALVEOLAR LAVAGE FLUID AND SERUM IN NON-SMALL CELL LUNG CANCER. TH Lie*, CLV Anderson, MD Seeman FCCP, SJ Harwood, S Narain, J Rashkin, H Singh, G Emmanuel FCCP, Bay Pines VAMC, USF, Tampa, FL.

Bombesin is present in small cell lung cancer (SCLC) cell lines. Increased levels have been reported in SCLC with metastases. Bombesin was measured in serum and bronchoalveolar lavage fluid (BALF) in 9 patients with non-small cell lung cancer (NSCLC) (4 squamous cell, 1 adenocarcinoma, 3 poorly differentiated, 1 nontypable) and in 8 control patients without cancer. With a threshold sensitivity of 20pg/ml, bombesin was detected in the serum of 5/9 patients with NSCLC (mean 52.8, range 22-110) and 5/8 patients with no lung cancer (mean 30, range 20-50). Bombesin was detected in BALF in 3/17 patients; 2 with lung cancer and one control. The two cancer patients with detectable BALF bombesin also had increased serum levels; the control patient did not. We conclude that bombesin may be detected in serum and BALF of controls without lung cancer and in patients with NSCLC. Although patients with cancer may have higher levels, the data do not support bombesin levels of serum or BALF as useful in differentiating lung cancer patients from controls.

EVALUATION OF FOLLOW-UP MRI IN LUNG CANCER PATIENTS TREATED BY RADIATION AND CHEMOTHERAPY

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To evaluate therapeutic effect of lung cancer treated by conservative therapy including radiation and chemotherapy, MRI was performed in 46 patients with lung cancer. Tumor size and its signal intensity after treatment and the delineation of recurrent or remaining tumor and radiation pneumonitis were discussed. We divided MRI patterns of therapeutic effect into 3 types. In 28 of 46 cases, mild tumor reduction without change of signal intensity of the tumor after treatment was recognized (type I). In 10 of 46 cases, high intensity areas considered to be tumor necrosis were observed inside tumor on T2 weighted image (type II). In the remaining 8 cases, marked tumor reduction were observed (type III). It was suggested that there were some correlation between MRI patterns and histologic types. Concerning to delineation tumor from radiation pneumonitis, in 5 of 8 cases recurrent or remaining tumor was clearly delineated by T2 weighted image, therefore T2 weighted images were most helpful in these cases. In conclusion, MRI was considered to be useful to evaluate therapeutic effect and detect recurrent tumor.

SUCCESSFUL PULMONARY RESECTION FOR T₃ CARINAL LESIONS FOLLOWING 8,500-11,000 RADS OF³ COMBINED EXTERNAL AND ENDOBRONCHIAL RADIATION. George E. Cimochoowski*, FCCP, Lee Roy Joyner, FCCP, Larry Hauskins, John H. Smith. St. Francis Medical Center, Monroe, LA. Six patients with squamous cell carcinoma underwent consecutive therapy consisting of external radiation (5000-7500 rads) proceeded by 3500 rads of endobronchial Brachy therapy via an irridium wire placed by flexible bronchoscopy using a new hand loading technique developed by us. Obstructing lesions were resected by Nd:YAG laser photovaporization followed by Brachy therapy and external radiation. Five of 6 lesions were T₃ because of proximity to the carina or actual carinal implants. All 6 patients underwent successful pneumonectomy(5) or lobectomy(1). Adjuvant techniques consisted of bronchoscopy just prior to surgery to examine the potential endobronchial site of resection which in each case showed healthy appearing mucosa despite the amount of radiation given. All had pericardial(5) or pleural(1) flaps buttressing the suture line with high frequency jet ventilation to minimize Baro trauma intra and post operatively. Thirty day operative mortality was 0. Pulmonary complications were 1/6; 1 patient who presented with a bilobar lung abscess from an obstructing tumor developed empyema and bronchopleural fistula which caused his demise 6 mos. later. Five of 6 were alive and free of their primary tumor 18 mos. to 5 yrs. from the original diagnosis. Pathological specimens were sterilized in 5 of 6 patients. Successful resection can be carried out with a low morbidity and mortality in what would be considered prohibitive amounts of previous radiation.

TALC VS. TETRACYCLINE PLEURODESIS FOR MALIGNANT PLEURAL EFFUSIONS. D.P. Jones, M.D., F.C.C.P., Toronto Western Hospital, Toronto, Canada Frequently malignant pleural effusions do not respond well to systemic therapy, although other metastatic sites may be controlled. This study compared the previous "gold standard", Talc pouddrage, to Tetracycline pleurodesis. Fifty-four pts referred for treatment of symptomatic, malignant pleural effusions unresponsive to systemic therapy, were allocated as follows: 37 pts to the Talc gp and 17 to the Tetracycline gp (higher operative risk patients in the Tetracycline gp). Talc pouddrage was done under general anaesthesia; Tetracycline under local (1.5 gm Tetracycline + 40 mg xylocaine in 200 cc N/S infused via chest tube). If success is defined as relief of symptoms and satisfactory CXR, 94% of the Talc gp were successful vs. 95% of the Tetracycline gp. Because of these results, a further 190 consecutive pts were prospectively treated with Tetracycline; 96.7% being successful. Avg follow up for the Talc gp was 9.9 mo vs 8.7 mo for all Tetracycline pts. One Talc pt had significant bleeding from chest wall tumour and most Tetracycline pts had easily controllable discomfort. In conclusion, with proper pt selection, Tetracycline Pleurodesis by this method offers excellent, palliative, symptomatic relief of malignant pleural effusions.

Recurrent malignant pleural effusions and talc powder aerosol treatment

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Pleural effusion is a fairly common problem encountered by physicians managing patients with a variety of malignant lesions. A significant number of such patients develop large recurrent malignant pleural effusions that cause progressive discomfort, inanition, dyspnea, and death from respiratory insufficiency. Of this group, a considerable number may live additional months or years in comfort when the recurrent effusions can be controlled.

The many methods that have been advocated for intracavitary treatment of malignant effusions attest to the practical interest in the subject and to the fact that no one method has been generally successful. A variety of agents including radioactive isotopes, cancericidal drugs, and pleural irritants have been used with only partial success.

It would appear that the fundamental factor underlying most successful results is satisfactory obliteration of the pleural space. No space, no fluid! This requires temporary drainage of further fluid accumulation following intrapleural introduction of the agent used to produce pleural symphysis. By the initial maintenance of an empty pleural space with full lung expansion by means of proper intercostal catheter drainage, effective fusion of visceral and parietal pleural surfaces can take place.

The purpose of this paper is to present a simple closed technique for treating symptomatic recurrent malignant pleural effusions

by the production of pleural symphysis with use of a newly developed talc powder aerosol unit. Also to be presented are relevant highlights from a recent 10 year review of patients with recurrent symptomatic malignant pleural effusions from the inpatient services of the Buffalo General Hospital and the Roswell Park Memorial Institute.

CLINICAL REVIEW

The charts of all inpatients from the Buffalo General Hospital and the Roswell Park Memorial Institute who had a diagnosis of malignant pleural effusion recorded during the 10 years period from July 1, 1956, through June 30, 1965, were reviewed. For the purpose of this presentation, attention is directed to 40 patients with large symptomatic recurrent pleural effusions. The criteria used for selecting this group of patients for closer analysis centered on the number of thoracenteses required and the total amount of fluid removed during hospitalization. Of the 40 patients, 31 required more than 5 thoracenteses and had more than 3 liters of fluid aspirated. The other 9 patients had 3 or 4 thoracenteses and over 2 liters of fluid removed. A number of other patients with large symptomatic malignant pleural effusions were not included because of unsatisfactory clinical records or incomplete follow-up data. Admittedly, others may have escaped our attention through failure to have pleural effusion specifically listed as a complication of the primary malignant growth.

The sites of origin of the primary malignant lesions in the 40 patients were: breast,

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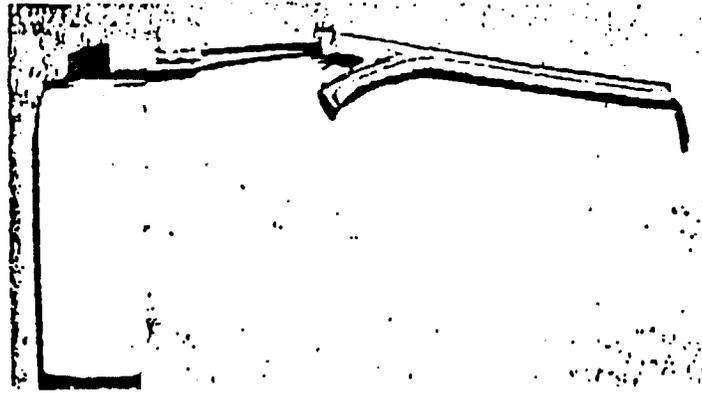


Fig. 1. Photograph of talc powder aerosol container with attached Teflon catheter. Catheter inserted through 5 inch long intercostal cannula sheath after removing the trocar. Length of the Teflon catheter has been shortened here for photograph. Note curved tip of catheter projecting just beyond distal end of cannula (see text).

talc as the primary active ingredient. A second powder, Microcel B (amorphous calcium silicate), is added in small amounts by the manufacturer to coat the talc particles; this "fluidizes" them so that they flow freely and do not clump. In addition, the Microcel B also absorbs the third element of the system, the fluorocarbon propellant. The powder has a huge surface area per unit weight which causes it to absorb fluid and stick to the pleural surface on contact.

When the aerosol unit is activated by the push button, a stream of powder escapes through the Teflon catheter and disperses evenly throughout the entire pleural space as a fine, dry, powder cloud. The rate of powder discharge from the unit is approximately 2 Gm. per second. The absorbed propellant instantly vaporizes when released from the container and escapes from the pleural space through the larger trocar (No. 20F) sheath through which the Teflon delivery catheter 2 mm. in diameter has been inserted. The entire talc aerosolization takes less than 30 seconds, and the technique is extremely simple.

Following insertion of the intercostal trocar, all fluid is aspirated from the pleural space by means of a soft rubber catheter introduced through the cannula sheath. In practice, thoracoscopy is not necessary unless there is a need to establish the etiology of

the effusion by direct vision forceps biopsy. After several full inflations, the anesthesiologist temporarily discontinues positive pressure; this creates a partial pneumothorax. The lung need be only partially collapsed. The small Teflon catheter is then inserted through the trocar sheath until its curved tip just projects into the pleural space. The proper length has been previously marked on the catheter. The talc aerosolization is now quickly performed and consists of 3 or 4 one second depressions of the aerosol can push button while the curved intrathoracic tip of the Teflon catheter is pointed in several directions. The rotations of the catheter tip may vary with the location of the trocar and the local anatomy. When the procedure is performed under local anesthesia, the talc powder is insufflated into the temporarily induced partial-pneumothorax space through the trocar sheath in the same way.

After the talc aerosolization, a large intercostal drainage catheter must be properly placed so as to keep the pleural space empty and the visceral and parietal pleural surfaces in contact. We have preferred to use a right-angle catheter tube with a short intrathoracic limb containing a side hole. The catheter is inserted through a stab wound by means of a curved hemostat, and it is immediately connected to a water-seal system with suction. The lung is promptly re-expanded.

CLINICAL EXPERIENCE—TALC POWDER AEROSOL

To date, 4 selected patients with massive recurrent malignant pleural effusions have been treated with the talc aerosol unit at the Buffalo General Hospital. Two were men, aged 57 and 66 years, one of whom had malignant mesothelioma and the other bronchogenic carcinoma. One of the 2 women was 67 years of age and had a bronchogenic carcinoma (Fig. 2). The other woman was 61 years of age and had carcinoma of the breast. Each patient had the diagnosis of malignant effusion confirmed either by tissue biopsy or by the presence of tumor cells in the pleural fluid.

The patients had been ambulatory until incapacitated by the dyspnea and distress associated with the large recurrent pleural effusions. All had had multiple thoracenteses. Two patients had previously received intrapleural quinacrine and nitrogen mustard in unsuccessful attempts to control the effusions. The man with the mesothelioma had been treated at another hospital with water-seal suction drainage of the effusion through a large, dependently placed intercostal catheter. Despite complete lung expansion during the period of catheter decompression of the pleural space, the fluid recurred within 2 weeks after the catheter had been removed.

Three patients had the talc aerosolization performed under general anesthesia and one under local anesthesia. The patients were placed in the lateral position with the involved side up. A trocar was inserted through approximately the seventh or eighth interspace in the lateral or posterior axillary line. All fluid was removed by means of a catheter inserted through the trocar. The amounts of fluid removed ranged between 2 and 3 liters. Although it was not necessary as a routine, the interior of the hemithorax was inspected with a Ruddock peritoneoscope modified for use as a thoracoscope. Thoracoscopic inspection of the hemithorax after talc aerosolization showed excellent distribution of the powder. Following talc aerosolization, the drainage tube was inserted through the

trocar site or through a stab wound placed in a more dependent area of the hemithorax.

Postoperatively, the patients had mild to moderate chest pain which was readily controlled by appropriate analgesic agents. The patient who had talc aerosolization performed under local anesthesia experienced relatively little discomfort during and after the procedure. Drainage through the thoracotomy tubes ranged from 100 to 600 ml. of fluid during the first 48 hours, the amount rapidly diminishing after the first day. Practically no talc was noted in the drainage fluid. Fluid drainage stopped by the end of the second or third day, and the chest tube was removed. As the tube was removed, a previously placed loose mattress suture was tied to close the skin opening.

No complications were associated with the talc aerosolizations other than temporary chest pain and a variable temperature elevation associated with the induced pleuritis. Systemic antibiotics were administered to 3 of the 4 patients during the time the tube was in place. No patient had a recurrence of the pleural effusion after aerosolization, although 3 patients later showed progressive growth of tumor on chest roentgenograms. At the time of death, which ranged from 5 to 10 months after talc aerosolization in 3 patients, postmortem examinations showed that the pleural space was obliterated and free of fluid. Some areas had tumor extension between lung and chest wall. There was no evidence of talc in the other organs examined. The patient with breast carcinoma is alive 17 months following talc aerosolization without need for thoracenteses, although her disease is progressing.

DISCUSSION

Our findings are in agreement with those generally present in the literature—namely, that carcinoma of the lung is the most common cause of malignant pleural effusion in men, and carcinoma of the breast ranks similarly in women. Ultman¹⁰ has stated that roughly one half of patients with metastatic carcinoma of the breast develop pleural

little discomfort, and it eliminates the need for repeated thoracenteses following local treatment.

The finely dispersed, thin layer of aerosolized talc powder produces an effective symphysis of visceral and parietal pleural layers without excessive fibrosis or granuloma formation; nor does it cause fibrous extension into the lung or chest wall.⁴ Based upon our experience to date, the talc powder aerosol technique appears to be most encouraging and merits further usage.

SUMMARY

The management of patients with recurrent large malignant pleural effusions continues to be a difficult problem for the medical profession. Unnecessarily premature disability and death from respiratory insufficiency may occur when the effusions cannot be controlled. A 10 year review of inpatients with recurrent malignant pleural effusions in 2 hospitals illustrates pertinent considerations in this clinical problem.

A recently developed talc powder aerosol unit used to control recurrent pleural effusions is presented. With this unit, pleural symphysis can be easily produced by aerosol insufflation of the talc powder preparation through a small intercostal trocar. The talc powder aerosol technique has been used in 4 patients with massive recurrent malignant pleural effusions. The procedure effectively prevented further recurrent effusions in the 4 patients.

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Comparison of insufflated talc under thoracoscopic guidance with standard tetracycline and bleomycin pleurodesis for control of malignant pleural effusions

The standard palliation of malignant pleural effusions involves tube thoracostomy drainage with chemical pleurodesis. The insufflation of intrapleural talc under thoracoscopic guidance ($n = 39$) was evaluated against documented controls that consisted of patients ($n = 85$) who participated in a randomized study with tube thoracostomy drainage followed by either bleomycin or tetracycline sclerosis. Under local anesthesia, which was supplemented by intravenous sedation, patients in the talc group underwent complete pleural fluid evacuation. The talc was then insufflated evenly on the entire pleural surface under thoracoscopic guidance. Of the patients in the talc group who survived their disease process, 97% had a successful pleurodesis at 30 days and 95% at 90 days. In comparison, the bleomycin group demonstrated a success rate of 64% at 30 days and 70% at 90 days ($p = 0.003$ and $p = 0.017$ versus the talc group). The tetracycline group had successful pleurodesis in only 33% at 30 days and 47% at 90 days ($p < 0.001$ and $p < 0.001$ versus the talc group). There were only two patients in the talc group in whom pleurodesis was not successful, and both were subsequently found to have extraluminal compression of the right lower lobe bronchus, which prevented lung reexpansion. These data demonstrate that the insufflation of talc into the pleural cavity under thoracoscopic guidance is a safe and efficacious procedure in the control of malignant pleural effusions. (*J THORAC CARDIOVASC SURG* 1993;105:743-8)

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Symptomatic malignant pleural effusions are caused by a variety of frequently incurable tumors that involve the pleural surfaces. As many as 50% of patients with breast and lung cancer will have a pleural effusion during the course of their disease.¹ Numerous methods² have been advocated to induce pleurodesis, but no therapy has been consistently demonstrated to be superior.

In North America, the most widely accepted treatment of malignant pleural effusions includes initial tube thoracostomy drainage for a variable period of time, followed by instillation of tetracycline to achieve a chemical pleurodesis.^{1,3} This form of therapy, however, has a significant prevalence of morbidity, which includes pain^{4,4} and, not infrequently, treatment failures that require additional therapy.⁵ Talc has been applied directly to the pleural surfaces after open thoracotomy^{6,7} to achieve successful pleurodesis. However, this technique has never become popular because a prolonged recovery is necessary in patients with limited life expectancies. Boutin, Viallat, and Cargnino⁸ have demonstrated that insufflated talc may be introduced into the pleural space by modern thoracoscopic techniques with minimal morbidity. We performed this study to evaluate talc insufflation under thoracoscopic guidance as a potentially more effective treatment of symptomatic malignant pleural effusions with a lower morbidity rate.

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keley, Calif.) on a Macintosh II FX computer (Apple Inc., Cupertino, Calif.).

Results

Talc group. Eighteen patients died of their underlying disease before the 90-day evaluation, and six of these patients died within 30 days of the procedure. No deaths were attributable to the procedure or to recurrent effusions. All but two patients had successful pleurodesis. In both cases, extrinsic tumor compression of the right lower lobe bronchus prevented complete lobar reexpansion, which allowed reaccumulation of fluid. After 30 and 90 days, the objective success rate as determined by roentgenograms of the chest in evaluable patients was 97% and 95%, respectively, which was significantly better than in either control group (Table II).

We perceived only minimal discomfort in patients during thoracoscopy and talc insufflation. We attribute this to the amnestic effects of midazolam and to parenteral narcotic analgesia. The mean duration of chest tube drainage was 4.0 ± 1.2 days, which was significantly less ($p < 0.001$) than the duration for those patients randomly selected for treatment with either bleomycin (mean 6.6 ± 1.6 days, $n = 11$) or tetracycline (mean 6.5 ± 2.1 days, $n = 10$). The number of days of hospitalization before and after pleurodesis was dependent on factors unrelated to the sclerosis procedure; therefore, the length of hospitalization for the treatment groups was not statistically compared.

Immediately after thoracoscopy and talc pleurodesis, one patient had severe chest pain; 12-lead electrocardiography demonstrated diffuse, nonspecific ST-T wave changes. The patient was admitted to the intensive care unit, and a myocardial infarction was ruled out. Fever (37.5° to 39.0° C) occurred in seven patients (17%) and lasted approximately 24 hours (range 12 to 72 hours). Six patients (15%) had minor subcutaneous emphysema that required no intervention.

Control group. At 30 days, 55 patients were evaluable, 28 and 27 in the bleomycin and tetracycline groups, respectively. Eighteen patients (64%) in the bleomycin group and 9 (33%) in the tetracycline group showed no evidence of pleural fluid reaccumulation ($p = 0.022$). After 90 days, 73 patients were evaluable; 26 of 37 patients (70%) in the bleomycin group, and 17 of 36 patients (47%) in the tetracycline group had no radiographic evidence of recurrent effusion ($p = 0.045$).

Discussion

An understanding of the various direct and indirect pathophysiologic processes that result in pleural fluid accumulation is essential in the treatment of patients with

Table II. Success rates of pleurodesis at 30 and 90 days after therapy.

Agent/technique	30 days	p Value	90 days	p Value
Talc/thoracoscopy	97% (32/33)		95% (20/21)	
Bleomycin/tube	64% (18/28)	0.002	70% (26/37)	0.04
Tetracycline/tube	33% (9/27)	<0.001	47% (17/36)	<0.001

Number of patients with successful pleurodesis expressed as a percentage and fraction (in parentheses) of the total number of evaluable patients within treatment groups. P values generated by χ^2 versus talc.

malignant pleural effusions. Although direct invasion of the pleura is the most common mechanism, other etiologic factors may require therapeutic approaches other than pleurodesis.¹

Various forms of local therapy have been advocated for the treatment of malignant pleural effusions. Thoracentesis is valuable for relieving dyspnea. However, this has not been shown to be an effective long-term palliative measure. Anderson and associates¹¹ report that the mean time for an effusion to recur after thoracentesis is 4.2 days and that there is a 97% recurrence rate within 30 days. Tube thoracostomy alone for the control of malignant pleural effusions has also been shown to be ineffective.¹² Another approach involves surgical placement of a pleuroperitoneal shunt.¹³ However, controlled studies have yet to compare the advantages with those of chemical sclerosis.

Our findings in this prospective phase II study demonstrate that the combined use of the thoracoscope for primary drainage and subsequent visual application of insufflated talc is efficacious in achieving pleurodesis for the control of malignant pleural effusions. These data are similar to those found in previous reports.¹⁴⁻¹⁸ In various randomized clinical trials that compared thoroscopically guided talc insufflation with the use of other sclerosing agents, including mustine,¹⁸ tetracycline,¹⁵ doxycycline,¹⁹ and bleomycin,¹⁷ talc has an overall success rate that exceeds 90%. Tetracycline and bleomycin are the most commonly used sclerosing agents. Both are soluble and are therefore more easily administered through a tube thoracostomy than is talc slurry.^{1,2,9} Tetracycline has been considered to be the agent of choice in many institutions because of lower cost and availability. However, long-term success rates have been variable,^{8,20} and within our control group this agent was inferior to bleomycin. The variability that is found among studies is, in part, due to a lack of uniform criteria for classification of a complete response and, possibly, to suboptimal dosing (less than 1000 mg). Uneven distribution of sclerosing

clinical trial that compares standard chemical sclerosis with thoracoscopically guided talc insufflation should be considered.

We thank Lawrence H. Einhorn, MD, Indiana University Division of Hematology and Oncology, and Bristol-Myers Pharmaceutical Group (Evansville, Ind.) for providing control group data. We acknowledge the technical assistance of Cherry Smith of the Indiana University Pulmonary Endoscopy Suite.

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Discussion

Dr. Watts R. Webb (New Orleans, La.). I would like to strongly support Dr. Hartman's use of talc. We have used it in a slightly different way, instilling it into the body through the chest tube. We have used 5 gm of talc and have also added 3 gm of thymol iodide. I am not sure that this adds very much to the effectiveness, but it does give a very nice picture of the areas of lung that are completely reexpanded. The slurry, which looks like Mississippi River mud, is injected with an Aseptu syringe through the tube. The tube is then clamped and the patient is turned rapidly in all directions for a couple of hours. The tube is then unclamped and left in place for an additional 4 or 5 days until the fluid is expelled and the lung is well reexpanded.

In our initial series of approximately 33 patients, six were treated for benign disease and the rest for malignant disease

Our experience proves the importance of laser treatment of inoperable endotracheobronchial lesions for improving the quality and prolonging the life of the patients. Recanalization of airways is a) prevention against b) ability of treating unreachable bronchopneumonia. It is the bronchotherapeutic treatment options for the patients who suffer from lung cancer.

Care of the appliance is easy. Careful tending of the appliance is important, during the performance especially of the cap of the optical fibre.

507/CHEMICAL PLEURODESIS WITH OXYTETRACYCLIN, DOXYCYCLIN OR TALC IN MALIGNANT PLEURAL EFFUSIONS

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69 patients with malignant pleural effusions were treated with chest tube drainage and intrapleural instillation of tetracyclin derivatives or talc. In 24 cases 20mg/kg oxytetracyclin, in 25 cases 10mg/kg doxycyclin, in 25 cases 3-10 g talc (suspended in saline) was instilled.

The treatment was successful in 21/24 cases with oxytetracyclin, in 23/25 cases with doxycyclin, and in 24/25 cases with talc inside 3 month. As opposed to tetracyclins, there were no pain and fewer after talc instillation, however pleural thickenings and clinically insignificant loculated fluids were much frequent (10/25), then in the tetracyclin group.

Talc pleurodesis with instillation is an inexpensive, effective and comfortable method, but it needs a proper thorax drainage with large and well positioned chest tubes.

508 THE RESULT OF LONG-TERM STUDY OF THE NONSELECTIVE SET OF PATIENTS WITH LUNG CANCER IN ONE DISTRICT IN THE CZECH REPUBLIC

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During an epidemiological study the authors evaluated the incidence of lung cancer in one district in the central Bohemia region in 1981-1985 with a catchment area with a population of 44,000. The group of patients comprised 157 subjects, the male:female ratio being 10:1, 91% were smokers. 78% of patients were detected because of their complaints, 17% at preventive examination and 5% on necropsy. The calculated incidence for men was 129/100,000, for women 13/100,000. Morphologically were confirmed 79% of this set, mostly only by cytological examination 15% of the patients, i.e. 23 patients were operated on.

In October 1993 the authors reviewed the whole set of patients and evaluated survival in different groups according to their morphological types, TNM stages, therapy and type of detection. The results were compared statistically and curves of survival were constructed. 37% of all patients having the resection for lung cancer done survived 5 years. In 13 patients who died after successful resection causes of death were analysed. The authors assessed the real situation in diagnostic, therapy and survival of patients with lung cancer.

509 HOSPITAL MANAGEMENT OF LUNG CARCINOMA CASES IN TWO LUNG DEPARTMENTS OF EASTERN BOHEMIA, CZECH REPUBLIC

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Lung carcinoma inpatients represent a great part (1) of all the patients hospitalized in lung departments. Some of them need rehospitalisation, once or more times (2), in course of their disease.

The purpose of hospital admission usually is the therapeutic intervention, radical or preventive, by means of cytostatics (3) and/or irradiation (4), rarely in combination with surgical operation (5) or by operation alone (6).

An important portion of inpatients are those who need and can obtain a supportive or symptomatic therapy only (7), which is necessary because of neoplasma itself (8), concomitant disease (9), sometimes also with participation of social factors.

All these characteristics (1-9) were analysed in two different groups of patients: one (A) hospitalised in 1988 in lung department of a district hospital, the other (B) were treated in 1993 in lung department of the teaching hospital. Both institutions were headed by the same person, i.e. the author.

Detailed results confirm the commonly known bad prognosis of tumours too lately recognised, the origin being the absence of early symptoms and lack of some case-finding programme. As a logic consequence there is the necessity of large supportive and specialised hospital care of these cases, performed actually in lung departments.

510 ACCURACY OF EVALUATION OF TREATMENT EFFECT IN BRONCHOGENIC CARCINOMA

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In patients with bronchogenic carcinoma, the bronchoscopic assessment of the effect of cytostatic therapy is recommended for adding precision to the information obtained by roentgenological examination. The aim of our study was to determine factors responsible for the differences between roentgenological and bronchoscopic evaluation. 318 patients with bronchogenic carcinoma treated with cytostatics in cisplatin-based regimes were included. According to the roentgenological evaluation, 46 patients out of 78 with SCLC and 97 out of 240 with NSCLC were responders. More favourable results were obtained if bronchoscopic evaluation was used: the numbers of responders increased to 60 and 125, respectively. Differences according to the bronchoscopic signs of tumour were found in this case, however. Only 56 patients in the SCLC group and 144 in the NSCLC group were assessed alike if both evaluating methods were used simultaneously; 22 patients in the SCLC group and 96 in the NSCLC group were classified as responders by one of the methods, but as nonresponders by the other. The differences were affected neither by histological type, size and localization of the tumor nor by the therapy regimen used.

USUHS/FDA FELLOW MEDICAL OFFICER REVIEW OF NDA#20-587

I. General Information

Submission date: 8/11/95
Drug name: hydrated magnesium silicate
Proposed trade name: Sterile Aerosol Talc
Sponsor: Bryan Corporation
Pharmacologic category: Sclerosing agent
Dose/route of administration: A single 4 to 8 g dose intrapleurally through a spray canister (1-2 cans) at a rate of 0.4 g per second

II. Proposed Indication

"For the treatment of malignant pleural effusions secondary to malignancies having spread to the pleural space".

III. NDA Submission 7 volumes.

Summary of the Literature Search:

1. Medline and Biosis databases for 1966-1994. Search parameters used were "malignant pleural effusions" and "talc pleurodesis" resulting in 32 references.
2. Embase database for 1966-1994 utilizing same search parameters as in #1 above resulting in 13 references.
3. Medline database for 1966-1992. Search parameters used were "malignant pleural effusions" and "chemical pleurodesis". A literature article was obtained by the sponsor that reviews malignant pleural effusions by Walker-Renar; some of the references listed in the review were utilized (12 in total).
4. The reference lists for all the papers retrieved above were reviewed and another list of 33 papers was compiled.
5. Duplicates, papers in foreign languages, and papers that did not mention the use of talc were omitted resulting in a total of 53 papers being submitted with this NDA covering the time span from 1958 until 1994.

Summary of the Literature:

1. There are 9 controlled clinical studies consisting of 3 in the U.S. and 6 foreign.
 - A) 1 study reported on the treatment of patients by pleural drainage with and without talc.
 - B) 5 papers compared talc to other agents (tetracycline, bleomycin, doxycycline, and mustine hydrochloride)
 - C) 3 papers compared talc to historical controls.
2. A total of 26 uncontrolled clinical studies were obtained from the literature searches consisting of 12 in the U.S. and 14 foreign.
3. A bibliography of other studies and general information was provided consisting of 18 additional papers.

Integrated summaries of effectiveness, safety, and benefits & risks of the drug were submitted with the NDA.

NOTE: No original clinical data was submitted by the sponsor for this NDA. The FDA will be compiling data that has been obtained from Sterile Aerosol Talc Compassionate INDs.

IV. **Impression:** The NDA appears to meet criteria for filing.

Lydia V. Larson, Pharm.D.

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Alison Martin, M.D.

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