old was defined at the concentration at which the subjects coughed at least five times, provided they also coughed at subsequent higher concentrations. The threshold concentration of citric acid did not differ significantly among six aged decades (p>0,20, one way-analysis of variance) (Fig 1).

The present study shows that cough reflex, an important protective reflex in the airway, did not decrease with the advance of age. Therefore, a pronounced decrease in cough reflex observed in patients suffering from aspiration pneumonia may not be explained by aging effects on this reflex.

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Corynebacterium parvum Pleurodesis

To the Editor:

We read with great interest the article by Sanchez-Armengol and Rodriguez-Panadero in the November 1993 issue of Chest, in which the relationship between glucose and pH levels of the pleural fluid and either survival and outcome of talc pleurodesis was evaluated. The authors studied a large group of patients with metastatic pleural effusions who underwent thoracoscopy and talc pleurodesis, and they found that pleurodesis failed in 43% (6 of 14) of the patients with a pleural fluid pH level lower than 7.20 (low pH), in comparison to 9% (8 of 92) of patients with a pH ≥7.20 (normal pH) (p<0,01). Moreover, patients with a low pleural fluid pH plus a low-glucose level (<60 mg/dL) had significantly shorter survival than patients with normal pleural fluid pH plus a normal glucose level (≥60 mg/dL) (1.9 vs 5.7 months, p<0,005). As the authors remarked, these results contrast those we reported in a small group of 12 patients treated intrapleurally with Corynebacterium parvum. Therefore, we wish to report our results relating to a larger series of patients.

We treated with C parvum 26 consecutive patients with malignant pleural effusions. Ten patients had lung cancer, nine breast cancer, four mesothelioma, two lymphoma, and one gastric carcinoma. Twenty-two of 26 patients were examined for response. Four patients, who died a few days after the treatment, were not evaluable. Two patients are still alive, with a follow-up of 4.8 and 3.4 months, respectively. Five of 22 patients (23%) were receiving systemic therapy at the time of pleurodesis, most commonly cisplatin, etoposide, or tamoxifen citrate. We obtained complete response (total resolution of pleural effusion after three injections of C parvum at the most) in 20 of 22 patients (91%), after a single dose of C parvum in 12 cases (60%), after two doses in 6 cases (30%), and after three doses in 2 cases (10%) (mean follow-up 7.5±7.8 months, ranging from 1.9 to 36.5). Two patients (9%) had a partial response (forming of asymptomatic loculated effusion) after one dose and after two doses of C parvum respectively, with a follow-up of 1.9 months in both. Nine of 21 patients (43%) had a pH lower than 7.30, and 5 of 21 patients (24%) had a pH lower than 7.20. All the patients had favorable responses. The remaining patients with pH ≥7.20 had favorable responses. The four patients not evaluable had a pleural fluid pH higher than 7.20. Thus, in our study, an effective pleurodesis was obtained in all the patients either with normal or low pleural fluid pH. Four patients with low glucose level and low pH had favorable responses. The mean survival in the group with low pH was 6.1±4.0 months (range 3.3 to 13.1), whereas the mean survival in the group with normal pH was 8±9.9 months (range 1.9 to 36.5) (p not significant). The survival was longer in patients with breast cancer (11.8±12.6; range 3.5 to 36.5) compared with patients with lung cancer (6.1±5.3; range 1.9 to 18.2) and with patients with mesothelioma (7.2±5.1; range 1.9 to 14), but not significantly. The survival in 4 patients with low pH plus a low glucose level was less than in 15 patients with normal glucose and normal pH levels (4.3±1.1 months, range 3.3 to 5.4, vs 8.6±9.0 months, range 1.9 to 36.5), but not significantly. Autopsies were done for only four patients, three with normal and one with low pH. In the patient with low pH malignant pleural effusion and with pulmonary adenocarcinoma, the pleura was extensively invaded by the tumor. Two of the three patients with normal pH pleural effusion had breast cancer; in one of these, the pleural lesions were widespread, and in the other, focal lesions on the visceral pleural surface were found. The third patient with mesothelioma had massive neoplastic lesions involving the parietal pleura. The two patients with normal pH and breast cancer were not evaluable for response due to early death. Pleurodesis was successful in the other two patients, one with normal and one with low pH.

Elevated levels of carcinoembryonic antigen (CEA) have been felt to reflect tumor burden. Since our autopsy findings are limited, we evaluated the relationship between the survival and CEA pleural fluid levels in patients with breast and lung cancer. The mean survival was longer in patients with CEA levels ≥10 ng/mL (10.6±10.4 months, range 1.9 to 36.5) than in patients with CEA levels <10 ng/mL (3 patients) (4.6±1.1 months, range 3.3 to 5.4), but not significantly. Moreover, a significant correlation between survival and CEA levels were not found.

Our data on a larger number of patients confirm our previous results: the survival and the success of pleurodesis in patients treated intrapleurally with C parvum are the same in patients with low pH malignant effusions as those in patients with normal pH malignant effusions. Our patients, compared with those studied by Sanchez-Armengol and Rodriguez-Panadero, present

Figure 1. The mean values of the lowest citric acid concentrations producing five or more coughs are presented and are expressed as mean ± SEM. The age points are the mean values for each decade of age and are expressed as mean ± SEM.
a higher frequency of successful pleurodesis and a more prolonged survival. Although the group of our patients is smaller and it is difficult to compare different series of patients, we think that our results show that *C. parvum* is effective in both normal pH pleural effusion and in low pH pleural effusion, which is different from tetracycline\(^1\) and talc.\(^3\) Longer survival observed in our patients, as emphasized by other authors\(^5,6\) suggests that *C. parvum* may be acting not only as a sclerosant, but also as an immunostimulant. Therefore, we think that *C. parvum* deserves wider use.

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**To the Editor:**

The letter from Foresti and Villa regarding *Corynebacterium parvum* pleurodesis is interesting in several respects, as they report their experience with this agent in a series of 26 patients with malignant pleural effusions, regarding both survival and outcome of pleurodesis. Though they do not specify at what time of the follow-up they evaluated the results of the procedure, it could be assumed that they rated the pleurodesis as successful only when the pleural effusion did not recur at any time during the entire follow-up of the patients. We think that this point must be stressed, since outcome of pleurodesis has been evaluated only 1 month after the procedure in many series, and we believe that this would be insufficient.

In their letter, Foresti and Villa report a successful *C parvum* pleurodesis in 20 out of 22 patients who could be evaluated (91%), which seems to be a high success rate in comparison with our 72% rate of complete success with talc pleurodesis. They emphasize that outcome of *C parvum* pleurodesis was equally good both in cases with high and low pleural fluid pH. However, there are some points that should be discussed in their series.

First, when we closely examine their results, they obtained only a 60% of complete success after the first application of *C parvum* into the pleural cavity, and they reached their 91% of success only after three applications in some patients. Our series referred only to results of pleurodesis after a single application of talc, so we think that our series could be comparable only when the first application of the sclerosing agent is considered. Thus, we had a 72% rate of complete success with a single application of talc (see Table 1 in Chest 1993;104:1482-85), while the comparable results in the series of Foresti and Villa would be 60%.

Second, regarding outcome of pleurodesis as related to pleural pH, the rate of response after the first application of *C parvum* pleurodesis in patients with pH lower than 7.20 is not reported in the series of Foresti and Villa. Therefore, we could not establish any comparison in this respect with our own series.

Regarding survival, these authors report an average of 6.1 ± 4.0 months in patients with low pH (supposedly below 7.20, which is the cut-off that we used in our series), vs 8 ± 8.9 months in those patients with higher values of pleural pH. They did not find any significant differences and overstate, to our view, that survival is the same in patients with low pH malignant effusions as in those with normal pH. Their study could have some biases in this respect. First, they presumably used a statistical test, not specified in their report, to compare means between groups, or perhaps medians, if they used a nonparametric test, which would be required in small groups. Survival data, however, is not suitable for this type of analysis, and the Kaplan-Meier method for comparison between groups should be used. On the other hand, they do not specify whether they are expressing their data with SD or SEM, so we can only figure out about the scatter in their groups. Presumably, the specification of the median values would be of more help to understand differences, as this is the key parameter used by nonparametric tests to compare small groups. Second, when pleural fluid pH and glucose are considered together, these authors found an average of 4.3 months vs 8.6 in the low and high-values groups, respectively, which would presumably make some difference if their groups were larger. Though levels of glucose are closely related to pH in malignant effusions, the association of both parameters below or above the chosen cut-off reinforces their role in predicting both survival and outcome of pleurodesis in our series. The apparently wider difference in means when both variables are considered in the series of Foresti and Villa makes us presume that they will find significant differences in the future, when their series grows enough.

Regarding carcinoembryonic antigen (CEA), pleural tumor burden, and survival, we would like to make some comments. We studied CEA in pleural fluid of 100 patients with malignant pleural effusions and found neither significant relationship of CEA with tumor burden in the pleural space as observed by thoracoscopic examination nor with survival (unpublished data, F. Rodriguez-Panadero, MD, and MA. Gonzalez Captop, MD, 1990). Thus, we think that this marker is not useful to make predictions in malignant pleural effusions. Moreover, the inclusion of four patients with mesothelioma, which usually shows no significant expression of CEA, in the series of Valeriano and Antonio would introduce an important bias when comparing survival between groups.

Although Foresti and Villa suggest in their letter that it is difficult to compare our series, they make the conclusion that the survival and the success of pleurodesis in patients treated intra-pleurally with *C parvum* pleurodesis are the same, regardless of levels of pH and that their patients have a longer survival after instillation of *C parvum* pleurodesis. In support of their (overstated to our view) conclusion, they invoke an hypothetic immunostimulant role of *C parvum* pleurodesis in the pleural space, but there was a study published by Rossi and colleagues\(^7\) in which there was no enhancement of local cellular immunity found, and further support is not provided in the letter by Foresti and Villa.

We think that survival in patients with malignant pleural effusions not only is mainly related to the stage of the tumor, both in the pleural cavity and in other organs, but also to the aggressiveness of the tumor cells themselves, since we found a long-term survival rate (see Table 2, Chest 1983; 104:1482-85) in patients with metastatic breast carcinoma despite pleural tumor burden being larger than in other groups. In our view, pleural fluid glucose and pH are very good markers of the pleural tumor staging.