Tumor Markers in Patients with Lung Cancer*

Mogens Hansen, M.D.; and Anders Gersel Pedersen, M.D.

The most examined tumor markers in lung cancer patients are CEA, hormonal peptides, and some neurogenic enzymes in small cell carcinoma. Calcitonin, ACTH, ADH, CEA, neurophysin, oxytocin, β-endorphin, neuron-specific enolase, and CK BB are elevated in serum specimens in 25-75% of cases of small cell carcinoma. The level of these markers is related to the stage of the disease in groups of patients; elevated pretreatment levels decrease with tumor regression. Marker levels are not valid in defining the tumor load and the presence of disease in the individual patient. It has not yet been documented that the markers can be used for clinical decisions on antineoplastic therapy. A recent development is the finding that measurement of CSF and plasma concentrations of ADH, calcitonin, CK BB, bombesin, and neuron-specific enolase may contribute in the diagnosis of CNS metastases including meningeal carcinomatosis.

Neoplastic cells produce and release several substances corresponding to their normal counterparts. In some cases the occurrence of such substances have not been documented in the normal cells, leading to the term "ectopic production." In addition, peptides similar but not necessarily identical to the genuine hormonal counterpart may be released. When the substances are characteristic of the fetal development, they are referred to as "oncofetal antigens."

Within the past 15 years some tumors were found to produce substances with such consistency that they became of importance in the management of these tumors, i.e., hCG in choriocarcinoma and some testicular cancers, calcitonin in medullary carcinoma of the thyroid, and α-fetoprotein in hepatomas and some testicular cancers, as well as some gastrointestinal (GI) peptide hormones in islet-cell tumors.

Lung tumors have been reported for decades to produce hormonal substances. Many studies have now been performed to elucidate the occurrence of tumor markers in patients with lung cancer. With the advances of radioimmunoassays specific for different parts of the polypeptides in question, comparisons may be complicated by differences between the assays. In this review only clinical studies will be considered. Substances investigated included: hormones, glycoproteins, immunoglobulins, enzymes, and oncofetal antigens. Hitherto, no study has documented specific biologic products in lung cancer, and neoplastic cells are apparently variants of normal cells. It may be that more specific substances will appear with the development in molecular biochemistry, such as growth factors or other oncogenic products.

**IMPLICATIONS IN LUNG CANCER**

It is reasonable to suggest that all lung cancers produce at least a few substances. The vast majority of all known substances are, however, far from being significantly or diagnostically elevated in a substantial number of patients. Accordingly, a substance for use in screening of asymptomatic patients has not yet been found. This fact does not detract from the possible use of known markers in the evaluation of treatment of patients diagnosed as having lung cancer. At present, only surgery is of major prognostic importance in the treatment of non-small cell lung cancer. Accordingly, the main interest of markers in these patients would be to distinguish between operable and inoperable patients or to detect residual disease postoperatively. On the contrary, patients with small cell lung cancer primarily are treated with chemotherapy. In these patients, it would be of considerable interest to have markers indicating the tumor load and the response to treatment, and predicting relapses as well as residual subclinical disease.

Carcinoembryonic antigen (CEA) was one of the first markers described in lung cancer. This and other substances were examined in the 1970s by several investigators. Apparently CEA remained the only marker of continued interest in non-small cell lung cancer, while in small cell carcinoma attention has been paid to hormonal peptides and recently also to some enzymes. Since this is also the background for our experience, this review will focus on the potential use of markers in small cell carcinoma.

**ENDOCRINE SYNDROMES**

An association between an endocrine syndrome and SCC was suggested in 1928, a few years before Cushing described the syndrome related to his name. About 20 years ago it was documented that ACTH as well as ADH could be produced by SCC tumors. Although the ACTH-syndrome and the SIADH are particularly related to SCC, the frequency of the syndromes in consecutive series of patients has been found to be low** (Table 1).

**INCIDENCE**

Several hormonal peptides have been measured in serum of untreated patients with SCC and non-SCC. The frequency of elevated concentrations have been found to be significantly higher in patients with SCC than in patients with the other histologic types. Only results based on sufficiently large numbers of patients are included in this review.
The pretreatment frequency of elevated serum calcitonin has been determined in several studies (Table 2). On the average the concentration of serum calcitonin was found to be elevated in 59% of 425 patients. The incidence varies from 25 to 76%, which may be explained by random error, patient selection, and the assays used. Elevated concentrations of serum calcitonin are rare in other types of lung cancer.

Immunoreactive ACTH concentrations are elevated in a lower number of patients with SCC (Table 3). The average being 27% in 252 patients with a range of 24-30%. The concentrations are only slightly elevated in the majority of cases, but in other histologic types of lung cancer even marginal elevations were rare. These findings do not correspond to the results of 2 studies measuring "big" ACTH. These studies included all types of lung cancer, but the incidence was found to be 55% in 83 patients and 72% in 74 patients, i.e., significantly higher than in studies with ACTH including only patients with SCC (Table 3). Although the 2 studies were published 6 and 11 years ago, it is not yet known, how the discrepancy is to be explained.

Table 2—Incidence of Elevated Serum Calcitonin in Untreated Patients with SCC

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKenzie et al 1977</td>
<td>28</td>
<td>75</td>
</tr>
<tr>
<td>Hansen et al 1980</td>
<td>74</td>
<td>64</td>
</tr>
<tr>
<td>Greco et al 1981</td>
<td>54</td>
<td>51</td>
</tr>
<tr>
<td>Sappino et al 1981</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Wallach et al 1981</td>
<td>24</td>
<td>76</td>
</tr>
<tr>
<td>Bierbaum et al 1982</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Luster et al 1982</td>
<td>135</td>
<td>56</td>
</tr>
<tr>
<td>Total 425</td>
<td>59</td>
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Table 3—Incidence of Elevated Plasma Concentrations of ACTH in Untreated Patients with SCC

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gropp et al 1980</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Hansen et al 1980</td>
<td>75</td>
<td>29</td>
</tr>
<tr>
<td>Ratcliffe et al 1982</td>
<td>63</td>
<td>24</td>
</tr>
<tr>
<td>Spaulding et al 1983</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Bork et al 1985</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Total 252</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

on the methods used for identification of the syndrome. Taking into account plasma osmolality, the concentration of ADH was inappropriately elevated in 35% of 279 patients (Table 4). The interpretation of the results in the individual patients is difficult, and it should be mentioned that SIADH may occur in several nonmalignant disorders, some of which may be secondary to the malignant disease.

Several other peptides have been investigated (Table 5). None of these appears to contribute significantly to the clinical value of hormones in patients with SCC.

Recently bombesin or the mammalian counterpart, gastrin-releasing peptide (GRP), was found commonly to be produced by SCC cell lines. However, preliminary results with serum specimens from patients with SCC disclosed elevated concentrations of GRP in only 2/25 untreated patients. The different results between cell lines and serum from patients may be explained by a fast degradation in plasma of secreted GRP.

Some enzymes have within the past been found to be related to SCC, e.g., neuron-specific enolase (NSE) and the creatine kinase BB (CK BB). These enzymes were also first found in cell lines derived from SCC tumors, and both have been detected in sera from SCC patients.

Table 4—Incidence of Inappropriately Elevated Plasma ADH in Untreated Patients with SCC

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
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</tr>
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<tbody>
<tr>
<td>Haefliger et al 1977</td>
<td>23</td>
<td>65</td>
</tr>
<tr>
<td>Hansen et al 1980</td>
<td>75</td>
<td>33</td>
</tr>
<tr>
<td>North et al 1980</td>
<td>61</td>
<td>48</td>
</tr>
<tr>
<td>Greco et al 1981</td>
<td>54</td>
<td>17</td>
</tr>
<tr>
<td>Gropp et al 1981</td>
<td>66</td>
<td>30</td>
</tr>
<tr>
<td>Total 279</td>
<td>35</td>
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Table 5—Other Peptide Hormones in Untreated Patients with SCC

<table>
<thead>
<tr>
<th>Peptide Hormone</th>
<th>No. of Patients</th>
<th>%</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>α—MSH</td>
<td>43</td>
<td>19</td>
<td>Gropp et al</td>
</tr>
<tr>
<td>β—Endorphin</td>
<td>58</td>
<td>45</td>
<td>Gropp et al</td>
</tr>
<tr>
<td>LPH</td>
<td>24</td>
<td>54</td>
<td>Odell et al</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>61</td>
<td>30</td>
<td>North et al</td>
</tr>
<tr>
<td>ADH-neurophysin</td>
<td>103</td>
<td>65</td>
<td>Maurer et al</td>
</tr>
<tr>
<td>Parathormone</td>
<td>43</td>
<td>27</td>
<td>Gropp et al</td>
</tr>
<tr>
<td>Inulin</td>
<td>65</td>
<td>5</td>
<td>Hansen et al</td>
</tr>
<tr>
<td>Gastrin</td>
<td>69</td>
<td>20</td>
<td>Hansen et al</td>
</tr>
<tr>
<td>Glucagon</td>
<td>46</td>
<td>11</td>
<td>Hansen et al</td>
</tr>
<tr>
<td>Secretin</td>
<td>46</td>
<td>0</td>
<td>Hansen et al</td>
</tr>
<tr>
<td>VIP</td>
<td>46</td>
<td>0</td>
<td>Hansen et al</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>46</td>
<td>9</td>
<td>Hansen et al</td>
</tr>
<tr>
<td>GRP (bombesin)</td>
<td>28</td>
<td>7</td>
<td>Bork et al</td>
</tr>
</tbody>
</table>

been evaluated clinically with promising results. Serum CK BB was elevated (>10 μg/ml) in 26% of 63 patients in 1 published study and in 64% of 25 untreated patients in our unpublished study. Similarly, in 6 studies NSE has been found to be elevated on an average of 65% of 397 SCC patients (Table 6). On the contrary, NSE was elevated in only 14% of 190 patients with non-SCC. These enzymes are of interest for further evaluation in patients with SCC.

**Marker Panels**

Since no single marker is significantly elevated in the majority of patients with SCC, it has been evaluated if the incidence might increase by combining two or more markers (Table 7). In this way, the incidence of elevated markers is about 20% higher than with calcitonin alone.

The clinical value of a marker has been examined in a large multicenter study. Havemann et al measured calcitonin, ACTH, and CEA monthly before and during treatment in 250 patients with SCC. They found as their best result a correlation between calcitonin plus CEA and x-ray films in 80% of the patients. The examinations were disappointing with regard to detection of early relapses. In the same study, serum calcitonin concentrations alone were related to monitoring with x-rays in 78% of the patients. Thus, among the hormonal peptides, calcitonin is of further interest for evaluation in marker panels including other peptides, eg, neurophysins. In addition, inclusion of the enzymes may be of importance.

**Table 7—Incidence of at Least One Elevated Marker in Marker Panels in SCC**

<table>
<thead>
<tr>
<th>Study</th>
<th>Markers</th>
<th>No. of Patients</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gropp et al</td>
<td>ACTH</td>
<td>50</td>
<td>0.78</td>
</tr>
<tr>
<td>1980</td>
<td>Calcitonin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hansen et al</td>
<td>ACTH</td>
<td>75</td>
<td>0.64</td>
</tr>
<tr>
<td>1980</td>
<td>ADH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hansen et al</td>
<td>CEA</td>
<td>40</td>
<td>0.50</td>
</tr>
</tbody>
</table>

**Relation to Stage**

It is also noteworthy that the concentrations of NSE as well as of CK BB were related to the disease stage. CK BB was elevated in only 1% of 41 patients with limited disease but in 41% of 63 patients with extensive disease. As seen in Table 6 the frequency of elevated NSE is also higher in patients with extensive disease (89%) compared with patients having limited disease (55%). With regard to hormonal peptides, a corresponding trend has been detected. Calculated from studies publishing the figures, plasma ACTH is elevated in 31% of 72 patients with extensive disease and in 24% of 54 patients with limited disease. For calcitonin, the respective figures are 80% in 81 extensive disease patients and 56% in 75 patients having limited disease. Even with regard to ADH, a relation between SIADH and tumor load has been registered. Therefore, the concentrations of currently known markers are related to stage and thereby presumably to the tumor load. This is substantiated by the usual finding that elevated pretreatment levels of the markers decrease with response to therapy. However, in the individual patient the level of the marker does not predict the tumor load, as the occurrence of the elevated markers vary from patient to patient, and even for different markers in the same patient. Furthermore, initially elevated markers do not in all instances increase again with relapse.

In accordance with these problems, a well-defined role of the markers for decisions on therapy has not yet been presented.

**Metastatic Sites**

While Aroney et al found a relation to disease status for CEA in all types of lung cancer and also for neuron-specific enolase and ACTH in SCC, no relation was found for these markers to specific metastatic sites. For CK BB a significant association between the number of metastatic sites and the elevated serum CK BB has been detected. In addition, particular markers might indicate spread to a particular region. Nyström et al studied 141 patients with either malignant or benign effusions, and found an association between malignant effusion and elevated concentrations of CEA in the fluid. Findings in accordance with this were subsequently published by others. The main conclusion of
these investigations was that CEA might contribute to the
diagnostic evaluation only when combined with other clinical
findings and cytologic examination. It is our impression that
measurements of CEA for diagnosing malignant effusions
have not come into a routine use.

Within recent years measurements of peptides in the
cerebrospinal fluid (CSF) have been studied to evaluate whether
markers might be of help in the detection of spread to the
CNS. The results of these investigations have been interesting
with regard to SCC.

Markers in the Diagnosis of CNS Metastases

CSF has been analyzed for several unspecific biochemical
compounds in patients suffering from a variety of malignant
diseases. In recent investigations and reviews only β-glucoridase, CEA, and lactic dehydrogenase isoenzymes were found to be of some interest in the detection of meningeal carcinomatosis. None has so far been of value in detecting parenchymal CNS metastases.

CNS metastases are frequent in SCC and often difficult to
diagnose. Metastatic seedings to the leptomeninges are particularly difficult to diagnose.

It has been proposed that SCC patients with ectopic hormone production were more inclined to develop CNS metastases. This hypothesis was evaluated in 104 consecutive patients in whom we measured plasma ACTH and in 86 patients evaluated for SIADH at the time of diagnosis. The results are shown in Table 8. After a minimum observation of five years, no significant difference in the propensity to develop CNS metastases has been detected between patients with and without increased plasma levels of the hormones.

The markers were measured in the CSF and plasma of patients suspected of CNS metastases. Table 9 shows the number of patients examined and the frequency of elevated CSF concentrations. In a preliminary study ACTH appeared to be significantly elevated in patients with CNS metastases, but this could not be supported in a more extensive study. In this study the ratio between CSF and plasma ACTH concentrations was significantly increased in patients with CNS metastases. The difference seemed, however, to be related to a high plasma ACTH in patients without CNS metastases rather than to a high CSF concentration of patients with CNS metastases.

In the study evaluating ADH, only patients with meningal carcinomatosis were found to have significantly increased concentrations of arginine vasopressin (ADH). The ratio between CSF ADH, and plasma ADH was significantly higher in patients with CNS metastases than in patients without CNS metastases. This significance persisted if patients with SIADH were excluded. Of 51 patients with CNS metastases, 21 had CSF/plasma ratios of ADH exceeding the upper range limit for patients without CNS metastases.

In 2 investigations CSF calcitonin was measured. Calcitonin was found to be of no value in the one study, but with a different assay it was found to be significantly increased in patients with CNS metastases. Any patient with a CSF calcitonin concentration above 24 fmol/ml had CNS metastases.

The frequency of elevated CSF calcitonin is the same for patients with parenchymal metastases and with meningal carcinomatosis (Table 9). On the contrary, patients with meningal metastases seemed selectively to have elevated CK BB and bombesin. These 2 biomarkers are both present in normal brain tissue. It is unknown if the increased concentration in the CSF originates from SCC tumor cells in the meninges or from necrotic brain tissue adjacent to the CSF. The very high specificity seem promising for these two mark-

Table 8—Plasma ADH and ACTH as Tumor Markers of CNS Metastases in SCC

<table>
<thead>
<tr>
<th>Tumor Marker</th>
<th>Status at Time of Diagnosis, No. (%)</th>
<th>No. with CNS Metastases, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Elevated* 23 (22) 6 (26) NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal 81 (78) 16 (19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated† 29 (34) 6 (21) NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal 57 (66) 12 (21)</td>
<td></td>
</tr>
</tbody>
</table>

*Plasma ACTH >76 mg/L.
†Vasopressin elevated relative to osmolality.
‡Determined as arginine vasopressin.

Table 9—Frequency of Elevated Biomarkers in the CSF of SCC Patients Suspected of CNS Metastases

<table>
<thead>
<tr>
<th>Tumor Markers</th>
<th>Metastases, No. (%)</th>
<th>Any CNS Metastases, No. (%)</th>
<th>Parenchymal Metastases, No. (%)</th>
<th>Meningal Carcinomatosis, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>0/8 (0)</td>
<td>11/13 (85)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0/25 (0)</td>
<td>9/32 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/24 (13)</td>
<td>12/51 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0/8 (0)</td>
<td>1/14 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcintron</td>
<td>2/27 (7)</td>
<td>21/42 (50)†</td>
<td>13/27 (48)†</td>
<td>8/15 (53)†</td>
</tr>
<tr>
<td></td>
<td>3/30 (0)</td>
<td>14/51 (27)†</td>
<td>1/33 (3)†</td>
<td>13/18 (72)†</td>
</tr>
<tr>
<td></td>
<td>0/22 (0)</td>
<td>20/43 (47)†</td>
<td>5/26 (19)</td>
<td>15/17 (88)†</td>
</tr>
<tr>
<td></td>
<td>6/23 (26)</td>
<td>35/49 (71)†</td>
<td>15/28 (54)†</td>
<td>30/21 (95)†</td>
</tr>
<tr>
<td></td>
<td>3/25 (12)</td>
<td>11/48 (23)</td>
<td>5/30 (17)</td>
<td>6/18 (33)</td>
</tr>
</tbody>
</table>

*p<.05 when compared to patients without CNS metastases (Mann-Whitney).
†Upper limit of controls 2 pg/ml.
‡Upper limit 18 fmol/ml.
§Upper limit 10 ng/ml.
#Upper limit 170 nmol/L.
ers, being also characteristic findings from SCC cell lines.

Neuron-specific enolase seems to be related both to the
presence of parenchymal metastases and meningeal metastas-
es. Plasma NSE has in 1 series been found to be related to
CNS metastases in patients also suffering from other types of
lung cancer. This could point to the possible use of NSE in
the management of intracranial metastases in patients with
other histologic types than SCC. In non-SCC the tumor does
not produce NSE, and an elevated plasma NSE concentra-
tion must be caused by NSE coming from the brain tissue. In
SCC patients it could, however, come from the tumor tissue
elsewhere in the body.

Biomarkers thus seem to be of value in isolated clinical
settings. In particular the analysis for bombesin and CK BB
seems interesting in the diagnosis of meningeal carcinoma-
tosis. More series and larger experience is necessary before
the true value of these markers can be judged.

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