Elevated Plasma Calcitonin as a Marker for Bronchogenic Carcinoma

The observation of ectopic synthesis and secretion of polypeptide hormones by nonendocrine tumors has been reported with increasing frequency in the past decade. Carcinomas of the lung have been particularly versatile in this regard. Reports have included corticotropin (adrenocorticotropic hormone) and vasopressin found in some oat-cell carcinomas, gonadotropins predominantly in large-cell carcinomas, growth hormone in anaplastic carcinomas and adenocarcinomas, and parathyroid hormone predominantly in squamous-cell carcinomas of the lung; however, the observed incidence of hormone production by any of these tumors has been small.

In 1974, Silva et al. described two patients with ectopic secretion of calcitonin by oat-cell carcinomas of the lung. Several reports of calcitonin production by various neoplasms have subsequently been published. Milhaud et al. consider the frequency of ectopic production of calcitonin by neoplasms to exceed that of parathyroid hormone, and they suggest that calcitonin may be the most common polypeptide hormone produced by tumor cells which embryologically originate from the neural crest. Therefore, elevated plasma calcitonin levels may indicate the presence of tumors of this origin.

The paper by Silva et al. in this issue of Chest (see page 495) sheds further light on this subject. These investigators found that 62 percent (16) of 26 patients with bronchogenic carcinoma had elevated plasma levels of calcitonin, as determined by radioimmunoassay. The incidence of increased calcitonin levels was much greater in small-cell carcinoma and adenocarcinoma than in the epidermoid type. In several patients, the calcitonin levels varied directly with exacerbation and regression of the neoplastic disease.

These data suggest the interesting possibility that hypercalcitoninemia may be an important "marker" in discovering early bronchogenic carcinoma and in drawing inferences as to the histologic type of the tumor. Serial calcitonin determinations could have prognostic value in evaluating exacerbations and regressions, especially in response to therapy. Further studies are necessary by multiple investigators to fully clarify and evaluate the validity of these suggestions. Silva et al. emphasize the importance of additional observations and have a long-term study underway.

Hopefully, the endocrinologists' interest in the hormone calcitonin, and their rather recently developed radioimmunoassay for human calcitonin can also serve the oncologist and chest physician in their diagnosis and treatment of pulmonary neoplasms.

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References

Pulmonary Hypertension and Oral Contraceptive Usage

In the February, 1976 issue of Chest, Kleiger and co-workers reported on a study of six patients with pulmonary hypertension (three secondary and three primary) who had used oral contraceptives for varying intervals before the onset of clinical manifestations of their disease. Three of their patients died (two secondary and one primary), and the survivors have shown stable or increasing symptoms. Whether or not the frequency of their cases first observed during an eight-month period and the few other previously reported cases which they cited...
may be greater than a chance occurrence is presently unknown. Nevertheless, these clinical observations warrant suspicion that the use of oral contraceptives may induce or enhance pulmonary hypertension in a subgroup of the population and justify further surveillance of this possible association. Although this condition is admittedly rare, it affects younger women primarily, has a poor prognosis, and is unlikely to regress once established, thereby urging attention to its early recognition or possible prevention.

A considerable amount of literature has accumulated on the vascular effects of oral contraceptives since their marketing in 1960. Studies have been published since the late 1960s, including controlled data on ambulatory, hospitalized, or deceased women, which supported clinical observations made early in the decade suggesting that the use of oral contraceptives contributed to the occurrence of pulmonary embolism, venous thrombosis, cerebrovascular occlusive syndromes, hypertension, and myocardial infarction; however, the mechanisms of such incriminated effects are essentially unknown, and no double-blind experimental trials have been conducted to prove that oral contraceptives can cause these vascular disorders (and such studies seem out of the question). Instead, the available estimates of increased risk attributable to oral contraceptive use are derived mainly from controlled observational retrospective or prospective studies.

An impressive degree of agreement has been found among studies of similar design in different populations, and several have implicated the estrogen component of the oral contraceptives as the responsible agent in thromboembolic disease, however, it has been stated that “relative estrogen potency” of a particular oral contraceptive drug is more meaningful than simply the type and amount of estrogen, since the progestogen component, which may have either an additive (agonistic) or antagonistic effect, must also be considered. Accordingly, the following tabulation shows the ratios of the comparative number of cases of idiopathic thromboembolism to the number of symptom-free matched controls who used various types of oral contraceptives, regrouped according to relative estrogen potencies of the products:

<table>
<thead>
<tr>
<th>Total Sequentials</th>
<th>15:0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combinational</td>
<td></td>
</tr>
<tr>
<td>Higher-dose estrogen (75+μg) plus agonistic progestogen</td>
<td>19:3</td>
</tr>
<tr>
<td>Higher-dose estrogen (100μg) plus antagonistic progestogen</td>
<td>18:12</td>
</tr>
<tr>
<td>Lower-dose estrogen (50μg) plus antagonistic progestogen</td>
<td>6:6</td>
</tr>
</tbody>
</table>

With the sequentials, estrogen alone is taken for 14 to 16 days, and then a combination of estrogen and progestogen is taken for the remainder of the cycle. Both estrogen and progestogen are included in each combinational pill taken for 21 days. The sequentials and those combinations with an additive progestogen effect were used significantly more frequently by patients with thromboembolism than by matched controls. More accurate information is needed on the relative estrogen potency of various oral contraceptive drugs, since the present methods are difficult to quantitate and are based either on clinical observations or the mouse uterine bioassay method.

It should be emphasized that estimates of risk are averages derived from studies of populations or patient groups and consequently are not strictly applicable to individuals. Even accepting this point, the physician and patient must consider additional medical and personal factors in deciding whether to use oral contraceptives or other methods of contraception. Age, health status, family history, and certain exposures influence the natural occurrences of many vascular disorders whose risks are believed increased by oral contraceptive use. A several-fold increase of an extremely low natural risk may be acceptable to a healthy young patient under close medical supervision but may not be to an older patient with a higher natural risk of morbidity or mortality. Furthermore, potentially increased risks should be considered in regard to personal factors related to using oral contraceptives, e.g., physiologic tolerance, convenience, available alternatives, relative contraceptive effectiveness, and consequences of pregnancy.

Regarding pulmonary hypertension, no risk estimate is presently available, and clinical judgment must prevail until results of further surveillance or controlled studies become available; however, generally speaking, the possible added risk in a young healthy woman under close medical surveillance would not be expected to outweigh all other considerations. A personal preference has been to use oral contraceptive drugs of lowest effective estrogen potency and not to use oral contraceptives as substitutes for estrogen-replacement products in older women, since oral contraceptives are several times more potent.

The evidence suggesting that oral contraceptives induce pulmonary hypertension as a result of increased pulmonary arteriolar resistance from intimal proliferation, rather than from the more generally implicated process of thromboembolism, deserves comment. Autopsy in the three cases of Kleiger et al and in the few other cited cases with oral contraceptive usage did not reveal thromboembolism but
impressive arteriolar intimal proliferative changes. In one large autopsy series of cases of idiopathic pulmonary hypertension, arteriolar intimal proliferation was observed in every patient and constituted the most striking histologic manifestation.\(^6\) It could not be determined if these changes contributed to or resulted from the hypertension or what relationship they may have had to other suggested mechanisms in this disease.

The age and sex predisposition of idiopathic pulmonary hypertension, occurring mainly in younger women, suggests a role of hormonal factors. Perhaps, in susceptible women, oral contraceptives can induce or aggravate the necessary predisposing conditions. Irey and Norris\(^6\) reported intimal vascular lesions in several organs (including the lungs) which were associated with reproductive steroids either produced endogenously in pregnancy or taken exogenously as contraceptives. Intimal proliferative changes found in cerebrovascular occlusive diseases associated with the use of oral contraceptives were suggested as contributing to the pathogenesis.\(^7\) Intimal proliferation may be a tissue reaction to excess or unopposed estrogens or other sex steroid imbalances. Scant information is available on the vascular effects of sex steroids in relation to morphologic, physiologic, or pathologic findings. Such studies may contribute to a better understanding of idiopathic pulmonary hypertension, as well as other diseases which display intimal proliferative changes more diffusely, eg, systemic lupus erythematosus, which also predominates in young women.

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REFERENCES


Dead or Alive?
The Preservation of Myocardium

The preservation of ischemic myocardium has emerged as a leading endeavor in the treatment of coronary arterial disease. During the past two years, a number of studies have appeared regarding evaluation of the viability of abnormally contracting myocardium.\(^1,4\) Our knowledge in this area has been pioneered by the authors of the report entitled "Reversible Asynergy and its Determinants," which appeared in the January 1976 issue of *Chest.*\(^7\) Their most recent studies indicate that hypokinetic and akinetic areas show a substantially greater chance of potential improvement if collaterals exist in the presence of severe coronary arterial narrowing.\(^1,2\)

Several interventions have been utilized to evaluate potential reversibility of asynergic areas, including the administration of nitroglycerin\(^4,4\) or epinephrine\(^5\) and postextrasystolic potentiation.\(^6\)

Following a control left ventricular angiogram, either nitroglycerin or epinephrine is administered, after which a repeat left ventricular angiogram is obtained. Segmental areas are then compared to determine the potential reversibility of abnormally contracting areas. Studies have shown that approximately 75 percent of hypokinetic areas and 50 percent of akinetic areas improve following these interventions, whereas dyskinetic areas remain unchanged. Postextrasystolic potentiation, which may be performed using one angiogram, has shown similar results. These observations were obtained by noting function before and after a random premature ventricular contraction occurring during the left ventricular angiogram or by means of inducing a premature ventricular contraction during the angiogram. It has been suggested that improved segmental wall motion following these interventions indicates a better prognosis.

Another clue that has been helpful in evaluating potential improvement in wall motion is the electrocardiogram. A normal ECG usually is associated with potential improvement in abnormal segmental motion, whereas a Q wave usually indicates an akinetic area,\(^8\) which may or may not improve following an intervention.\(^1\)

In our experience the *clinical presentation* has been an important determinant of reversibility in asynergic areas. Thus, in subjects with *preinfarction