PROTOCOL

TITLE: A Retrospective Clinical and Pathologic Analysis of Over Five Hundred Patients with Thyroid Carcinoma

PURPOSE: This study will have three major objectives:

1. To analyze the clinical features of a large series of patients with thyroid carcinoma.
2. To make a detailed study of the histopathologic features of thyroid carcinoma and to correlate this with the clinical features.
3. To study long-term survival with respect to the clinical, pathologic and therapeutic data.

BACKGROUND:

Although many retrospective studies of thyroid carcinoma are available,[1-15] relatively large series with long-term survival data are not abundant.[12,20] Moreover, many such reports contain data which have been accumulated for a specific therapeutic modality,[1] or the experience of an individual investigator with a specific surgical procedure[4] The study by Woolner and associates,[20] probably the most comprehensive clinical and pathologic review, lacks extensive follow-up data for a number of patients. Accordingly, there are divergent opinions regarding the interaction of survival with the clinical, pathologic and therapeutic aspects of thyroid carcinoma.

There are over 500 cases of thyroid carcinoma registered with the USAF Central Tumor Registry (CTR). Approximately 120 of these cases are from Wilford Hall USAF Medical Center and the remainder originate from Air Force Hospitals throughout the world. Each case record, maintained on microfilm by the CTR, contains a detailed narrative summary, pathology report(s), surgical operative note(s) and current follow-up data. Dr. Conrad, Director of the CTR, has made these microfilmed records available to us for extensive review. This group of patients offers a unique opportunity to study many cases of thyroid carcinoma in detail with special reference to the clinical, pathologic and therepeutic features. The analysis of long-term survival data which is available on many patients will be particularly meaningful when considered in light of these features. We, therefore, propose to study a large, heterogeneously treated group of patients on whom extensive clinical and follow-up information is available which should lend itself well to a careful analysis of survival data.

Study of the histopathologic features of each case will be done by Dr. James E. Oertel, Chief of the Endocrine Pathology Branch of the Armed Forces Institute of Pathology. We believe that many if not most of the tissues will be availabe in the AFIP archives or at Wilford Hall.

TECHNICAL APPROACH:

The following clinical information will be collected from the microfilmed records on each patient;

CLINICAL: 1. Name, age, sex, race

2. Parity

3. Presenting symptoms--character and duration

4. Significant past medical history--history of irradiation to the head or neck, history of Graves' disease or thyroididtis etc.

5. Presence of other disorders--other carcinomas, other endocrine disorders, pregnancy

6. Size and character of thyroid and nodule and the presence or abscence of neck nodes on physical exam.

7. Metabolic status of the patient-- thyroid function tests.

8. The character of the ^{131}I thyroidal scan

SURGICAL: 9. Amount of tissue removed--partial lobectomy, lobectomy, and isthmus removal, bilateral lobectomy, radical neck dissection, modiefied radical neck dissection, limited local node resection.

10. Intra-operative and post-operative complications--hemorrhage, laryngeal nerve damage, hypoparathyroidism.

11. Long-term complications--as above, also neurologic sequellae of radical neck dissection etc.

PATHOLOGIC: 12. Extent of involvement of the specimen.

13. General appearance of parenchyma of the thyroid in which the cancer arises. Papillary carcinoma tends to occur in normal glands or sometimes in

in association with lymphocytic thyroiditis or thyrotoxicosis. Follicular carcinoma more often arises in association with adenomas or nodular glands. Therefore, the following will be noted:

a. Presence of normal parenchyma, adenomas or nodules
b. Lymphocytic thyroiditis
c. Thyrotoxicosis
d. Physical relationship in space of the cancer to any other type of localized lesion in the gland.

14. Other characteristic of the tumor--cystic or solid, encapsulated

In addition to this general information which will be obtained on each patient, special features will be studied in the various types of thyroid carcinoma.

PAPILLARY CARCINOMA

Papillary carcinomas vary from mostly papillary patterns to almost entirely follicular patterns and have characteristic cytologic features[16,18,19,20] that allow them to be rather easily recognised regardless of their architecture. The follicular variants have histologic characteristics (in addition to their typical cell types) that also aid in recognition. Hazard[17] and Woolner[20] have touched on this point, and Dr. Oertel has developed his own ideas. Accordingly, we will note those tumors in which the overall histologic pattern is typical of papillary

carcinoma, but which lack the characteristic cytologic features.

Special features include:

1. Mostly papillary pattern.[20]
2. Mostly follicular pattern.[20]
3. Extent of solid component.[20]
4. Infiltration of tumor with lymphocytes.[20]
5. Substantial mononuclear infiltration around tumor.
6. Substantial encapsulation of tumor.[16]
7. Presence or absence of extensive fibrosis in or around tumor.
8. Psammoma bodies.[18,20]
9. Foci of undifferentiated carcimona (probably these tumors belong with the anaplastic group) (16,20)
10. Presence of tall cell carcinoma.[16]
11. Presence of oxyphilic cells.

These special features will be evaluated in terms of

patient age
lymph node metastases
distant metastases
survival

FOLLICULAR CARCINOMA

Types

Well circumscribed or slightly invasive (usually encapsulated).

Moderately or markedly invasive.

Well differentiated follicular carcinoma can only be distinguished from an adenoma by finding invasion of vessels or penetration of the capsule. Less well differentiated examples usually are definitely aggressive and thus present no problem so far as recognition of their malignant nature is concerned.

patients in the first 2 categories were [illegible]. It seems apparent that the two groups were similar. He also seems to have [illegible] in the first group.

1. Predominantly follicular.
2. Predominantly trabecular.
3. Predominantly solid.
4. Oxyphilic cells regardless of pattern.

We will evaluate whether the important feature is oxyphilia, histologic pattern, or aggressiveness. We suspect that the last is most important.

Special features to be noted include:

1. Extensive fibrosis.
2. Infiltration of tumor with lymphocytes.
3. Substantial mononuclear infiltrates around tumor.
4. Mitotic activity.
5. Psammoma bodies.
6. Papillary foci.

In Dr. Oertel's experience, none of these items is likely to be a conspicuous or major feature of the tumors, except possibly mitotic activity. In occasional follicular cancers numerous mitotic figures are visible.

MEDULLARY CARCINOMA

Points of special interest

1. Definite capsule around tumor
2. Presence of a second carcinoma in the thyroid.
3. Follicular or papillary elements in tumor.(19)
4. Extent of amyloid.
5. Appearance of parathyroids.
6. Adrenal tumor or other endocrine abnormality.

The Mayo Clinic group has indicated that it is important whether the tumor is confined to the gland at the initial operatio or is associated with lymph node metastases.(21) Prognosis differ substantially. We whould not only keep their results in mind, but should see whether encapsulation is ever a notable feature.

Encapsulation also brings up the point that some medullary carcinomas and so-called atypical adenomas(17) have considerable resemblance to one another. We will consider is any cases were first diagnosed as atypical adenomas.

ANAPLASTIC CARCINOMA

We are not likely to have more than a handful of these. We can record the principal cellular types (spindle cell, giant cell, small cell, etc.) and note whether or not a differentiated tumor is also present.

SURVIVAL DATA:

Since, in general, thyroid carcinoma is of relatively low grade malignancy in terms of survival, it will be most critical to consider only long-term survival (i.e. 5 years or more) as significant. Survival data will be considered in light of:

1. Quality of follow-up--information letter from patient, physician examination, thyroid scan etc.
2. Survival in numbers of years.
3. Evidence of recurrent neoplasia--locally or at distant sites.
4. Morbidity will be considered, both from the neoplasm and that resulting from surgery
5. Clinical and histopathologic features as they reflect upon survival.

SUPPLIES AND EQUIPMENT: No special supplies or equipment will be required for this study.

FUNDING: Approximately $500 will be required to cover the cost of TDY for Dr. Mazzaferri and Dr. Mullins to meet with Dr. Oertel at the end of the study. At this time the clinical and pathologic correlations will be made. These funds will also cover the cost of publication, and statistical evaluation of data.

SCHEDULE: We anticipate that this study will be completed within six months

MANPOWER: The review of charts, correlation of informatin etc. will be accomplished during off duty hours by Drs. Mazzaferri, Kemmerer and Kocher. The histopathology will be performed by Drs. Oertel and Mullins.

Personnel Data:

1. Medical Facility Commander: P.W. Myers, Col., USAF, MC
   Commander

2. Principle Investigators: Ernest L. Mazzaferri, Lt. Col. USAF, MC, Div. Endocrinology & Metabolism

   James E. Oertel, M.D., Chief, Endocrine Pathology Branch, AFIP

2. Associate Investigators: William T. Kemmerer, Col. USAF, MC
   Chief General Surgery Service

   James D. Mullins, Maj., USAF, MC
   Resident in Pathology

   David B. Kocher, Maj, USAF, MC
   Fellow in Endocrinology