INTRODUCTION

It is the purpose of this paper to estimate the radiosensitivity of the various types of carcinoma of the thyroid. Such a study is suggested by the increasing use of radiation in the treatment of these tumors.

In 1885 Braun collected 34 cases in which extirpation had been done in malignant disease of the thyroid, and found that the operative mortality was 64 per cent and that an additional 22 per cent died of recurrence within a year. He attributed these disastrous results to the fact that by the time a clinical diagnosis of cancer of the thyroid is possible the tumor has almost always infiltrated vital structures of the neck or metastasized, rather than to any deficiency in surgical technic. Ehrhardt, writing in 1900, was able to collect reports of 249 malignant thyroid tumors. He reported a lower operative mortality, which he attributed to the introduction of local anesthesia and the more careful selection of cases. He deplored a lack of follow-up data which prevented an accurate determination of the proportion of cures. From occasional reports of cases with survival for from three to five years after operation, however, he believed that surgical removal was justified. In 1918 Balfour reviewed 103 cases seen at the Mayo Clinic, and presented the most complete study of surgical end-results which had appeared up to that time. He concluded that when clinical evidences of cancer were present the results of surgical treatment were discouraging. Bérard and Dunet in their monograph on thyroid cancer (1924) concluded that the surgeon is reduced to palliative operation only, and cannot think of radical attempts to cure.

As a result of these unsatisfactory results of surgery alone (Table I), more recent writers, expert in the treatment of thyroid disease, recommend the combination of surgery with radiation. Pool has stated that "cancer not limited to an adenoma is rarely cured by surgery. . . . When the clinical diagnosis is definite,
irradiation is in general preferable to bold attempts at radical extirpation.” Tinker believes that “extensive operations do not seem justified when the favorable results of radium following partial removal are considered.” Pemberton finds that the results of surgery are more encouraging than is popularly believed. He advocates operative removal. If the local growth cannot be removed completely, radium needles should be buried in the tumor and external irradiation given subsequently. “Probably in no other malignant disease are radium and roentgen ray so valuable as in the treatment of malignant tumors of the thyroid.” Lahey has stated that “when malignant degeneration of a thyroid adenoma is diagnosable, it is hopeless surgically. It is here that we have seen some of our very best results in a palliative way from x-ray treatment.” Craver advises that “when a clinical diagnosis

**Table I**

*Reported Results in Carcinoma of the Thyroid Treated by Surgery Alone*

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of cases</th>
<th>Operative mortality</th>
<th>Well after one year</th>
<th>Well after five years</th>
<th>Lost track of fatal termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braun</td>
<td>1885</td>
<td>34</td>
<td>64%</td>
<td>3%</td>
<td>11%</td>
<td>86%</td>
</tr>
<tr>
<td>Ehrhardt</td>
<td>1902</td>
<td>16</td>
<td>31%</td>
<td>44%</td>
<td>43%</td>
<td>43%</td>
</tr>
<tr>
<td>Müller and Speese</td>
<td>1906</td>
<td>11</td>
<td>18%</td>
<td>27%</td>
<td>27%</td>
<td>66%</td>
</tr>
<tr>
<td>Balfour</td>
<td>1918</td>
<td>63</td>
<td>6%</td>
<td>6%</td>
<td>2%</td>
<td>54%</td>
</tr>
<tr>
<td>Bérard and Dunet</td>
<td>1924</td>
<td>29</td>
<td>10%</td>
<td>10%</td>
<td>20%</td>
<td>65%</td>
</tr>
<tr>
<td>Breitner and Just</td>
<td>1925</td>
<td>72</td>
<td>10%</td>
<td>21%</td>
<td>54%</td>
<td>69%</td>
</tr>
<tr>
<td>Pool</td>
<td>1927</td>
<td>16</td>
<td>6%</td>
<td>19%</td>
<td>13%</td>
<td>67%</td>
</tr>
<tr>
<td>Portmann</td>
<td>1929</td>
<td>52</td>
<td>23%</td>
<td>20%</td>
<td>11%</td>
<td>67%</td>
</tr>
</tbody>
</table>

of cancer of the thyroid can be made, operation should be avoided, and thorough radiation . . . should be carried out.” To judge from these opinions, radiation has won for itself a definite place in the treatment of cancer of the thyroid—if not alone, at least in conjunction with surgery.

When the first reports of the use of radiation in this disease became available about ten years ago, there was considerable emphasis on the radiosensitivity of thyroid carcinoma. As the cases have accumulated, marked variations in radiosensitivity, according to the morphology of the tumor, have come to light. The earlier enthusiasm has been tempered by the fact that some types of carcinoma of the thyroid apparently do not respond at all to radiation, and it has been recognized that even in those cases which do regress, permanent cure in the strict sense of the
word can rarely, if ever, be hoped for. As a guide to therapy it would seem that an attempt should be made to estimate more exactly the radiosensitivity of malignant neoplasms of the thyroid. It is the purpose of this study to classify these tumors morphologically, to analyze the natural history of the various types, and to determine which are resistant and which are sensitive to radiation.

**General Laws of Radiosensitivity**

In approaching the study of the radiosensitivity of any one tumor, it is of interest to review the general laws governing this phenomenon which have been deduced by various writers. In 1903, as a result of his observations on the treatment of rodent ulcer and skin metastases of mammary carcinoma, Perthes suggested that, since carcinoma cells differ from the epithelial cells from which they spring chiefly in their increased growth activity and their accelerated cell division, this function of cell division might be the very one which is injured by radiation. This hypothesis was supported by the results of experiments in which he radiated granulation tissue and the wings of young chicks. Perthes was, therefore, the first to associate the radiosensitivity of a tissue with its reproductive activity.

Regaud and Blanc in 1906, in experiments with testicles, found that the spermatogones, the mother cells of spermatic cells and the most undifferentiated or embryonal cells of the spermatic epithelium, are the most sensitive to radiation. The extreme sensitivity of these spermatogones to x-rays accounts for the immediate and definitive sterilization of the seminal epithelium. Regaud and Blanc deduced that in the life of a cell the stage of karyokinesis is the time of least resistance to x-rays as well as to other disturbing factors.

Later in the same year Bergonié and Tribondeau, as a result of their observations of human tumors and from their experiments with rat testicles, derived the general law that "the greater the reproductive activity of cells, the more prolonged their process of karyokinesis, and the less definitively fixed their morphology and their functions, the more intense is the action of x-rays upon them."

Regaud and his associates objected that such a law exceeded the known facts. They have continued to study radiosensitivity through extensive experiments on the effects of roentgen rays and radium on the normal adult tissues of the higher animals, and in
the treatment of human cancer. From animal experiments they have found that there are differences in radiosensitivity not only between different organs, between different tissues of the same organ, between different cell types of the same tissue, but also between different physiological phases of the same cellular species. In treating human cancer they have found great differences in the radiosensitivity of different types of tumors. They have been conservative, however, in the matter of deducing general laws regarding the phenomena. Regaud has limited himself to the statement that “radiosensitivity goes hand in hand with activity of cell reproduction, at least if we consider examples of the same species of tissue.” He qualifies this general rule by stating that cells are scarcely, if at all, radiosensitive when they are in a condition of good secretory activity, this being a factor in the radioresistance of adenocarcinomas of the rectum and the uterus, and in cancers in glandular tissues in general. He also finds that in epidermoid carcinomas in which there is a clear distinction between a germinative layer, where the cell divisions are localized, and outer layers, where keratinization takes place, the radiosensitivity is good and the definitive sterilization of the tissue is relatively easy. The varieties of epidermoid epitheliomata in which there is no distinct reproductive layer are less favorable to radiotherapy. Regaud recognizes that the radiosensitivity of a tumor is diminished by previous radiation, by secondary infection, and by a decreased blood supply.

Many other workers, however, have been more free in drawing up laws of radiosensitivity. Thus we find Widmann and Weatherwax stating that “highly cellular cancers are extremely malignant and also very radiosensitive.” In the opinion of Schmitz, “very rapidly growing cells are most affected of any by radiations.” Souttar believes that “tumors of any sort in which rapid division of the cells occurs tend to be sensitive, while those of slow growth . . . show no reaction at all to therapeutic doses.” Berven states that “the more frequently karyokinesis occurs, the greater the growth or reproductive activity of a tissue, the more radiosensitive it must be.” Voltz finds that “the less mature forms of carcinoma are apparently more favorably influenced by radiation than other forms.” Statements such as these are frequently encountered.

When we attempt to apply these laws of radiosensitivity clinically, however, they are not at all satisfactory. In the first place, a definition of radiosensitivity is necessary. Two distinct
phenomena are involved, the primary regression of the tumor following radiation, and the definitive cure of the tumor. These two phenomena do not parallel each other. Primary regression, for example, is almost always obtained in lymphosarcoma with but small amounts of radiation, but definitive cure apparently seldom results. In a highly differentiated type of squamous carcinoma situated on the lip, however, primary regression is obtained only after the use of a large dose of radiation, and definitive cure results in a considerable proportion of cases. For purposes of clear thinking, therefore, it would seem desirable to consider the primary regression of a tumor and its definitive cure quite separately.

1. The Application of Laws of Radiosensitivity to Primary Regression: By primary regression is meant the decrease in size or disappearance of a tumor within a period of a few months following treatment by radiation.

If we take the two most frequently quoted indices of radiosensitivity—namely rapidity of growth and anaplastic character—and attempt to apply them to tumors in general as a measure of their primary regression under radiation, we at once encounter many paradoxes and contradictions. Some varieties of tumors which are among the most rapidly growing, the most cellular, the richest in mitoses, the most malignant, and the most anaplastic, are thoroughly resistant to radiation. Melanomas, osteogenic sarcomas, and the more anaplastic neurogenic (spindle-cell) sarcomas are examples. Adenocarcinomas of the gastro-intestinal tract are usually refractory to irradiation, irrespective of the grade of the tumor. Knox finds that the more differentiated carcinomas of the breast are more easily influenced by radiation and gives examples of slowly growing breast carcinomas with a regular alveolar structure which regressed with small doses of roentgen rays.

These types of cancer are in obvious contrast to those rapidly growing tumors, such as lymphosarcoma, lymphogranuloma malig-

\[1\] Hansemann, in 1893, first advanced the idea that a scale might be drawn up to indicate the degree of anaplasia, that is the degree to which tumor cells have deviated in form from the mother cells from which they arose. These morphologic changes include irregular mitotic figures, hyperchromatism, variation in size and shape of cells and nuclei. Such anaplastic cells are said to have lost their differentiation. The degree or grade of anaplasia is frequently identical with the grade of malignancy.

At the Memorial Hospital certain types of tumors, i.e. skin, uterine, and rectal carcinoma, have been found to be gradable into grades I, II, and III on this basis. Thyroid carcinomas readily fall into such a classification. As indicated in Table III, the malignancy increases with the anaplastic character of the tumor.
num, embryonal carcinoma of the testis, lympho-epithelioma, transitional-cell carcinoma, and myeloma, in which primary regression is obtained with small doses of radiation. It is questionable, however, whether these constitute a large enough proportion of all malignant tumors to justify the deduction of general rules of radiosensitivity.

2. The Application of Laws of Radiosensitivity to Definitive Cure: By a definitive cure is usually meant one that has lasted for at least five years. Indeed, for certain organs, such as the rectum and the thyroid, in which very slowly growing types of carcinoma appear, for some tumors of the parotid gland, and for the low-grade types of neurogenic (spindle-cell) sarcoma, definitive cure should mean no less than ten years of freedom from evidence of disease.

The published statistics of radiation treatment in which five-year cures are related to tumor morphology are few. Healy's results for carcinoma of the cervix would seem to indicate that definitive curability increases with the degree of anaplasia. Lacassagne, however, in reviewing his end-results, finds that the chances of cure of carcinoma of the cervix are practically the same whatever the histologic grade of the carcinoma. Similarly, Döderlein reports that the end-results for the different Reifegrade of epidermoid carcinoma of the cervix are approximately equal.

It can only be said, in regard to the application of laws of radiosensitivity to definitive cure, that there are not as yet sufficient statistical data available. Despite this scarcity of published end-results, however, it is a well defined clinical impression that, although life is prolonged by radiation, there are exceedingly few definitive cures of some of the most radiosensitive tumors—lymphosarcoma, lymphogranuloma malignum, and myeloma.

Even when we attempt to limit the application of these laws of radiosensitivity to tumors arising from one species of tissue in a particular anatomical location—the mucosa of the oropharynx, for instance—we find confusing contradictions. Although the grade III, rapidly growing, cellular, anaplastic lympho-epitheliomas and transitional-cell carcinomas which arise in this region quite uniformly regress primarily with moderate doses of radiation, we not infrequently encounter in the same anatomical region typical, rather adult grade II epidermoid carcinomas which are very radiosensitive. The same grade II carcinoma situated in the anterior buccal mucosa is usually a great deal more radioresistant. Unpublished data as to the definitive cure of these different types of
carcinoma in the tonsillar area have been found by Duffy to indicate that the percentage of five-year cures for grade I and grade II epidermoid carcinoma is substantially the same as for grade III carcinoma (including transitional-cell carcinoma and lymphoepithelioma), the figures being 22 and 20 per cent respectively.

These proposed laws governing radiosensitivity fail because the phenomenon is a great deal too complex to be envisaged by a simple statement of one or two factors. Ewing has emphasized that the general condition of the patient, as well as the local conditions about the tumor, must be considered in an estimation of radiosensitivity. We would suggest the following factors:

1. CONSTITUTIONAL FACTORS
   a. Age: Young persons tolerate radiation much better, and some tumors seem to respond more readily in the young than in the old.
   b. Development: A robust constitution may have some influence.
   c. Nutrition: In cachectic individuals tumor radiosensitivity appears to be lessened.
   d. Hemic status: Anemia diminishes tumor radiosensitivity.
   e. Systemic disease: The effect, if any, of concomitant systemic disease, such as syphilis or tuberculosis, is not clear.

2. LOCAL FACTORS
   a. Infection: Marked infection in and about the tumor apparently lessens radiosensitivity.
   b. Blood supply: The experiments of Jolly, as well as clinical observation, suggest that measures which produce a diminution in the blood supply to a tumor lessen its sensitivity to radiation.

3. FACTORS INHERENT IN THE TUMOR
   a. Its natural history: Rate of growth.
   b. Its morphological characteristics: Cellularity, embryonal quality, anaplastic character, etc.
   c. The anatomical situation: This is certainly of great significance. It would seem that the cell stocks from which tumors arise in different regions vary markedly in radiosensitivity.

It is apparent that our knowledge of these many factors which seem to condition radiosensitivity is vague, generalized, and incomplete. There are probably many other factors of which we have as yet no inkling. Further knowledge must come through pains-taking analysis of the reaction of particular groups of tumors to radiation. It is with this purpose that we have approached the question of the radiosensitivity of thyroid carcinoma.
<table>
<thead>
<tr>
<th>Type</th>
<th>Per cent of total</th>
<th>Average age</th>
<th>Per cent males</th>
<th>Pre-existing goiter</th>
<th>Months average duration pre-existing goiter</th>
<th>Known metastasis</th>
<th>Dead</th>
<th>Total duration of disease in dead, in years</th>
<th>Per cent Living</th>
<th>*Total duration of disease in living, in years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Papillary cystadenocarcinoma</td>
<td>30%</td>
<td>47.8</td>
<td>44%</td>
<td>56%</td>
<td>11%</td>
<td>30</td>
<td>0</td>
<td>33%</td>
<td>4.5</td>
<td>67%</td>
</tr>
<tr>
<td>2. Small alveolar, large-cell (Hürthle-cell) carcinoma</td>
<td>6.6%</td>
<td>47.5</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>50%</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>3. Adenocarcinoma</td>
<td>46.7%</td>
<td>45.1</td>
<td>28.6%</td>
<td>71.4%</td>
<td>57%</td>
<td>21.1</td>
<td>14.3</td>
<td>57%</td>
<td>5.9</td>
<td>43%</td>
</tr>
<tr>
<td>4. Giant-cell carcinoma</td>
<td>10%</td>
<td>55.3</td>
<td>66.6%</td>
<td>33.3%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100%</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>5. Small round-cell carcinoma</td>
<td>6.6%</td>
<td>57</td>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100%</td>
<td>2.5</td>
<td>0</td>
</tr>
</tbody>
</table>

* The total duration of the disease may seem unduly long. When, however, the patient gives a history of having had a goiter for some years which grew slowly and steadily until operation disclosed carcinoma, and denies that at any particular period acceleration of growth took place, it can only be supposed that the carcinoma dates from the time the goiter appeared. This was occasionally the case in our series.
CLASSIFICATION OF CANCER OF THE THYROID

As a basis for comparison of the different types of cancer of the thyroid, a classification is necessary. This is particularly difficult in the case of thyroid cancer, for it is well known that its morphological variations are extreme. They embrace varieties as different as the relatively benign appearing but malignant papillary adenoma and the extremely anaplastic giant-cell carcinoma (so-called sarcoma). The result of this complexity has been a bewildering array of classifications.

One of the confusing factors has been the difficulty of determining which tumors are malignant. Cohnheim reported the first apparently “benign” metastasizing thyroid tumor. The structure of the primary and the secondary tumors in his case was that of simple colloid goiter. So frequently have metastases been reported as having originated from adenomatous thyroid tissue that the statement has been made that 10 per cent of thyroid adenomas metastasize. Simpson, however, has pointed out that all such cases arise from an undetected area in the thyroid which, when found by multiple sections, has all the usual histologic characteristics of a malignant tumor. In different portions of the same goiter the structure of simple adenoma, adenocarcinoma, and carcinoma solidum may be found. “There is no such entity as the benign metastasizing goiter.”

Most pathologists, however, point out the great difficulty of differentiating between benign and malignant thyroid growths. Wilson admits that of a series of 97 clinically malignant tumors of the thyroid 23 were passed by the pathologist as benign. Graham, on the other hand, believes that he himself erred in the other direction, calling many benign tumors malignant. Using invasion of blood vessels as a criterion of malignancy, he found that 43 per cent of the adenomas which he had formerly classed as malignant were benign. All these patients whom he could trace were alive. He therefore concluded that “the morphological character of the cells and tissue is an unreliable basis for the determination of malignancy of thyroid epithelial tumors,” and that “the most constant single indication of thyroid epithelial malignancy is invasion of blood vessels.” In 1902 Ehrhardt stated that in his opinion “the infiltration of a blood vessel is of compelling importance as proof of the malignant character of the neoplasm.” Langhans described fully such invasion of blood vessels, and regarded the phenomenon as only one of the signs of malignancy.
In this group of cases from the Memorial Hospital which were diagnosed histologically as carcinomas of the thyroid, it has happened that in every instance the histologic diagnosis of malignancy has been confirmed by the finding of infiltrative growth into adjacent organs at operation, or by the recurrence or metastasis of the tumor. The need of multiple sections of the primary tumor in finding the malignant area is recognized. It is also clear that the type of the primary tumor cannot be determined from the histology of its metastases. Many observers have confirmed the tendency of metastases from thyroid carcinoma to revert toward the structure of the normal gland.

Wöllfer's classification was the first comprehensive one, and advanced the concept of thyroid tumors, both adenomas and carcinomas, developing from embryonal epithelial masses in the cortex of the gland. Ehrhardt's classification was more detailed. In excellent photomicrographs he showed the early neoplastic proliferation of the adult alveolar epithelium, thus contesting Wöllfer's hypothesis as to histogenesis. With Langhans' important study in 1907, the enumeration of the different types of thyroid cancer may be said to have been completed. He described seven varieties, most of which are still accepted.

Recent classifications have been more elaborate. That of Bérard and Dunet, based on very detailed presumptive histogenesis, includes no less than seventeen types originating from epithelium, connective tissue, and mixed tissue. Wilson, also attempting to outline the histogenesis of these tumors, describes fifteen different types.

We have tried to classify these tumors as simply as possible (Table II), realizing at the same time that the identity of definite morphological types should be preserved and their natural history and radiosensitivity determined. Following Ewing, we have considered them all to be of epithelial origin and have, therefore, included them all under the term carcinoma. In the very anaplastic types we have noted the presence of thyroid alveoli and all stages of their transition into the spindle-cell and giant-cell structures which the earlier writers called sarcoma. Although in reducing our classification to only five varieties we have been forced to combine under one type several closely related forms which might be considered separately, we have secured thereby a workable plan. In it each type has a fairly characteristic natural history—the malignancy increasing in the order named—and each
FIGS. 1 AND 2. PAPILLARY CYSTADENOCARCINOMA OF THYROID (CASE 2: F.N.). × 45 AND 105
type appears to have a rather constant and characteristic reaction to radiation.

This proposed classification, being purely a morphological one, takes no account of the fact that a very large proportion of thyroid cancers develop on the basis of pre-existing adenomas. Wölfler and others have pointed out that the geographic goiter regions are those in which thyroid cancer is most frequent. It would seem, however, that our knowledge of the etiology of these tumors is as yet too meager to allow their classification according to whether they develop from adult thyroid follicles, from fetal adenomas, or otherwise.

1. Papillary Cystadenocarcinoma

This type has been designated by various names (maligne papillären Cyst-adenome, Wölfler; Cystocarcinoma papilliferum, Ehrhardt; Papillome, Langhans). Its natural history and structure are, however, characteristic. It arises on the basis of a benign cystadenoma which has been present usually for many years. At some indefinite point, which is most difficult to detect clinically, malignant transformation occurs, and the tumor begins to grow more rapidly, and may break through its capsule and infiltrate surrounding structures. If removed, it recurs in about half the cases (Wölfler), often growing so slowly that it regains an appreciable size only after two to three years. Several such recurrences may take place. In our series of cases the total duration of the disease in those dead averaged 4.5 years, and in those still living 10.2 years. Death results from pressure on or infiltration of vital structures of the neck. Regional lymph nodes may become involved by direct extension, but metastases to bones and distant viscera almost never occur. Many writers (Ehrhardt, Müller and Speese, Graham) have stated that this is the least malignant type of thyroid carcinoma. This type constituted 30 per cent of our series of cases of thyroid carcinoma.

The structure (Figs. 1 and 2) is that of a network of branching papillae, projecting into cystic cavities which may be large and contain a gelatinous and sometimes blood-stained substance. The papillae are lined by single or multiple layers of epithelial cells which may be cuboidal or cylindrical. Ehrhardt and Langhans have emphasized the high cylindrical character of the epithelium at the apices of the papillae in certain of these tumors. In most cases the multiple layers of irregular, cylindrical, hyperchromatic
Figs. 3 and 4. Small alveolar, large-cell (Hurthle-cell) carcinoma of thyroid (Case 10: E.F.). × 45 and 120
cells, the loss of polarity, and the infiltrative growth through capsule into muscle clearly indicate the malignant nature of the tumor.

2. Small Alveolar, Large-Cell (Hürthle-cell) Carcinoma

This rather infrequent but well defined type of tumor has been particularly emphasized by Langhans and Ewing. The latter suggests that it originates from hypertrophic Hürthle cells of the thyroid alveoli. The tumor is distinctly malignant. In 80 per cent of Langhans' cases it grew rapidly, and in 20 per cent metastasized. In one of our two cases the tumor recurred, and in the other it metastasized. In both, however, the disease has been of long duration (average nineteen years).

The structure (Figs. 3 and 4) is that of small, irregular alveoli, lined by one or two layers of large, irregularly cuboidal cells. The protoplasm is homogeneous or finely granular, and eosinophile, and is proportionately large in amount. The nuclei are small and regular.

3. Adenocarcinoma

The greatest number of cases fall in the adenocarcinoma group. This division is also the most heterogeneous, including such varying forms as the less malignant "wuchernde Struma" of Langhans and the same author's more malignant group of "karzinomatöse Struma." These forms, nevertheless, occupy the middle ground of malignancy among thyroid tumors. Not only do most of them recur locally with considerable rapidity, but a considerable percentage metastasize, by way of both blood and lymph channels, to distant organs. The average duration of this type of tumor is stated by Ewing to be two years. Our data would indicate that it is somewhat longer, its total duration in our series averaging 5.9 years in those dead, and 5.1 years in those still living. A high proportion of these tumors likewise arise from a pre-existing benign goiter. This type of tumor constituted 46.7 per cent of our cases of thyroid carcinoma.

The structural feature common to this group is an alveolar arrangement. The "wuchernde Struma" type (Figs. 5 and 6) shows compact masses or cords of cells with ill-formed or occasional lumina in the periphery of each tumor lobule. Toward the center more adult alveoli containing colloid are seen. The cells, although regular and small, are in general atypical enough to distinguish this
Figs. 5 and 6. Adenocarcinoma of Thyroid (Case 24: S.S.). × 45 and 90
tumor from a benign adenoma (Ewing). Their cytoplasm, which is generally slight in amount, is opaque and granular, and stains heavily with eosin (Langhans).

In the more anaplastic forms of adenocarcinoma (Figs. 7 and 8) the malignant nature becomes very apparent. Hyperchromatic cells, varying in size and shape, form irregular alveoli or grow in cords or masses. Polarity is lost and a membrana propria is lacking. Solid masses of spindle-shaped cells growing in epidermoid fashion are seen in some tumors, other portions of which show typical alveolar carcinoma (Figs. 9 and 10).

4. Giant-cell Carcinoma

This tumor, described as a giant-cell sarcoma by Wölfler and others, and recently the subject of special consideration by Smith, is probably an anaplastic type of adenocarcinoma. The course of the disease is rapid and fatal, its total duration averaging seven months in our cases and four and eight-tenths months in Smith's large series. The malignancy is high, metastasis and death apparently being the rule. This type constituted 10 per cent of our series of thyroid carcinomas.

The structure (Figs. 11 and 12) is that of irregularly growing sheets and strands of very anaplastic cells, which are hyperchromatic and of varying size and shape, although tending to be fusiform. The largest of these form the so-called giant cells, and are sometimes multinucleated. Many atypical mitoses are seen. Areas can usually be found where the cells assume an alveolar arrangement, indicating the epithelial origin of these tumors. The morphological character of this tumor is reproduced in its metastases, which would tend to prove that the giant cells are not the result of degenerative changes in the primary tumor but are rather an integral feature of its anaplastic character.

5. Small Round-cell Carcinoma

Seven per cent of cancers of the thyroid, as tabulated by Müller and Speese, fall into this group. These authors classified them as sarcomas. Other writers, following Ewing, have classified them as carcinomas. Certainly they form a definite group with a characteristic natural history. They are probably the most malignant of thyroid tumors. In the cases reported by Müller and Speese the average age was fifty-six. Half of the patients had had a pre-existing goiter of an average duration of twelve years.
Figs. 7 and 8. Adenocarcinoma of thyroid, showing invasion of a vein (Case 13: J.L.). × 45 and 135
FIGS. 9 AND 10. ADENOCARCINOMA OF THYROID WITH MASSES OF SPINDLE-SHAPED CELLS (CASE 21: M.H.). \( \times 45 \) AND 90

Other areas of this tumor showed alveolar carcinoma.

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The course was very rapid, averaging only seven and four-tenths months. Death resulted in every case, almost always with widespread visceral metastases.

In the cases belonging to this group which we have studied histologically the structure suggested carcinoma of a type *sui generis* (Figs. 13 and 14). The tumors were composed of rather loosely arranged, small, round cells, growing diffusely and infiltrating capsule and surrounding structures. The nuclei were comparatively large, irregular, and hyperchromatic. The cells possessed a slight but distinct, finely granular, amphophilic cytoplasm. Occasional larger cells were seen. In some areas the cells formed irregular acini, strongly suggesting an epithelial origin.

It is true that this type of tumor is a frequent source of disagreement among histologists. Lymphosarcoma and Hashimoto's benign granuloma of the thyroid (Riedel's *eisenharte Struma*, ligneous thyroiditis) usually enter into the differential diagnosis. The former is identified not only by its morphology but by its marked radiosensitivity. The latter has the histological character of a granuloma and its clinical course is benign, spontaneous regression often occurring.

**Results of Treatment at the Memorial Hospital**

Over 100 cases of presumable carcinoma of the thyroid have been treated. We have used only those cases, however, in which a satisfactory biopsy and a follow-up report are available. We have also excluded, as having no bearing on the question of radiosensitivity, those cases which, following operative removal of the tumor, were referred for radiation, and in which no palpable tumor was found at the time of radiation. Thirty cases remain. The results of treatment in these cases are shown in Table III. The factors involved are so complex that a brief summary of each case seems indicated.

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2 It is apparent that since the natural history of the different types of thyroid cancer varies greatly, a knowledge of the histology is necessary as a guide to treatment and prognosis. In those cases in which resection is considered inadvisable, we have seen no harm from biopsy. The enucleation of a nodule of the tumor is best performed under local anesthesia and with an endotherm knife, which would seem to minimize the danger of metastasis.

3 For the privilege of reporting these cases we are chiefly indebted to Dr. Lloyd F. Craver, in whose thyroid clinic most of them have been treated. Dr. Douglas Quick has kindly permitted the use of several cases from his clinic. Dr. William Crawford White has generously contributed case No. 30 from his service at the Roosevelt Hospital.
× 45 AND 105
### Table III

Results of Treatment of Thyroid Carcinoma, Memorial Hospital Data

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Operation</th>
<th>Radiation</th>
<th>Primary regression</th>
<th>Living with disease</th>
<th>Living without evidence of disease</th>
<th>Length of follow-up after radiation (in years)</th>
<th>Dead</th>
<th>Length of life after radiation in those dead (in years)</th>
<th>Grade of malignancy</th>
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<tr>
<td>1</td>
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<td>Complete</td>
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<td></td>
<td>Totals</td>
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<td></td>
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<td>44%</td>
<td>22%</td>
<td>2 (average)</td>
<td>33%</td>
<td>1.9 (average)</td>
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<p>| | | | | | | | | | |
|          | | | | | | | | | |
|          | Small Alveolar, Large-cell (Hurthle-cell) Carcinoma | | | | | | | | |
| 10       | Complete resection | Interstitial and high voltage | Partial             | +                  | 4.3                             |                                            |      |                                                         | II                  |
| 11       | Incomplete resection | Low voltage | Slight                        | +                  | 6                                |                                            |      |                                                         | II                  |
|          | Totals              | | | 100%                           | 100%                | 100%                          | 5.1 (average)                       |                                              |</p>
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<th>Case No.</th>
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<th>Radiation</th>
<th>Primary regression</th>
<th>Living with disease</th>
<th>Living without evidence of disease</th>
<th>Length of follow-up after radiation in living (in years)</th>
<th>Dead</th>
<th>Length of life after radiation in those dead (in years)</th>
<th>Grade of malignancy</th>
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<td>0.3</td>
<td>III</td>
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<td>0</td>
<td>100%</td>
<td>0.9 (average)</td>
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CANCER OF THE THYROID

CASE 1. S.D., aged thirty, housewife: In 1917 she noted a lump in the left thyroid region, which gradually increased in size without causing symptoms. In April 1923 operation was done. The tumor infiltrated surrounding structures and could be only partly removed. The patient was referred to the Memorial Hospital in May 1923. A tumor mass beneath the operative scar and a node over the carotid bulb were observed. Six half-erythema doses of low-voltage roentgen rays and 8,000 millicurie hours with the emanation pack were given during the following six months. The tumor slowly regressed until in June 1924 only a fibrous band remained beneath the scar. In July 1930 there were a few hard subcutaneous nodules in the left supraclavicular space.

Pathology: Thyroid papillary cystadenocarcinoma, Grade I. Irregular alveoli and papillary projections lined by atypical cuboidal cells. Polarity lost in places.

CASE 2. F.N., aged thirty-five, housewife: A goiter appeared in 1905. In June 1920 the entire right lobe and part of the left lobe were resected, the tumor being densely adherent to the trachea. Within the following month 3,876 milligram hours of radium treatment were given. In September 1920 the patient came to the Memorial Hospital, with an area of induration beneath the scar, and was given 3,893 millicurie hours with an emanation tray. In May 1929 she returned with a small recurrent nodule along the trachea. Exploration was done, a biopsy specimen taken, and 10.4 millicuries in gold tubes inserted into the nodule. Complete regression ensued, and there was no evidence of disease in May 1931.

Pathology: Thyroid papillary cystadenocarcinoma, Grade I. The sections of the primary tumor differed distinctly from those of the recurrent nodule. Both were papillary in type, but in the former the epithelium was high cylindrical, and polarity was lost in areas, while in the latter the cells were cuboidal, small, and more regular.

CASE 3. M.F., aged fifty-six, housewife: In 1917 she noted a small lump in the right thyroid region, which gradually enlarged, causing tightening in the throat and deafness. Partial thyroidectomy was done in June 1922, and the patient was referred to the Memorial Hospital, where she was found to have a firm diffuse tumor at the base of the neck. During the following six months she was given six half-erythema low-voltage roentgen-ray treatments. There was no apparent effect on the tumor. Death occurred in June 1926.

Pathology: Thyroid papillary cystadenocarcinoma, Grade I. Cuboidal hyperchromatic, irregular cells line papillary projections into cysts and in areas infiltrate the stroma.

CASE 4. J.B., aged seventy, housewife: She began to have dyspnea and cough in 1920 and her doctor told her she had a growth in the thyroid region. This slowly increased in size and in December 1922 she came to the Memorial Hospital, where a hard mass 8 x 5 x 3 cm. was found in the right thyroid region. She was at once given 16,905 millicurie hours with the emanation pack. There being no appreciable effect on
the tumor, in January 1923 a tracheotomy was done, a biopsy specimen obtained, and 14 millicuries in bare tubes inserted in the tumor. There was no distinct regression. Death occurred in March 1924.

Pathology: Thyroid papillary cystadenocarcinoma, Grade I.

CASE 5. R.J.B., aged fifty-two, sailor. Since about 1895 he had had a right-sided goiter. In 1925 it began to grow actively and dysphagia and hoarseness developed. On examination at the Memorial Hospital a large hard mass in the right thyroid region was found, with enlarged hard nodes on both sides of the neck along the sternomastoids. Biopsy was done and the patient was given 20,000 millicurie hours with the emanation pack and two full erythema doses of high-voltage roentgen rays within a month's time. There was no apparent regression of the tumor and death ensued one month after radiation had been completed.

Pathology: Thyroid papillary cystadenocarcinoma, Grade II. Atypical, cylindrical cells line papillary projections and infiltrate stroma and capsule. Polarity lost.

CASE 6. B.J.P., aged forty-three, printer: In 1924 he noted a tumor in the right thyroid region. Within a year it attained considerable size and was resected. The pathologist reported it to be "a cystic adenoma." After two years a recurrence appeared. The patient came to the Memorial Hospital in November 1930, with a semi-cystic, nodular tumor in the right thyroid region, 10 cm. in diameter (Fig. 15). During the first days of November 80,000 milligram hours of element pack treatment were given. In the succeeding three months there was no appreciable regression of tumor. In January 1931 as much of the tumor as possible was resected. A portion about the carotid sheath could not be removed.

Pathology: Thyroid papillary cystadenocarcinoma, Grade I. Atypical high cylindrical cells line irregular papillae. Polarity lost in places.

CASE 7. W.G., aged fifty-three, workman in a rubber factory: In 1918 he first noted a goiter, which slowly enlarged without causing symptoms. In 1927 he began to have pain in the neck. On examination at the Memorial Hospital in 1928, there was a firm, movable tumor in the right thyroid region, 6 cm. in diameter, with several small nodes above it. Over a period of four months the patient received four erythema doses of intermediate-voltage roentgen-ray treatment, but no regression resulted. He was, therefore, referred to his surgeon, who completely excised an encapsulated cystic tumor in December 1928, and at a second operation, in April 1929, removed the adjacent nodes. In December 1930 a large nodule appeared in the lower right neck. With one full erythema dose of high-voltage roentgen rays this disappeared. In June 1931 there was no evidence of disease.

Pathology: Thyroid papillary cystadenocarcinoma, Grade I. The nodes dissected out at the second operation, however, showed small alveolar adenocarcinoma.

CASE 8. T.S.F., aged sixty-four, housewife: A small tumor appeared in the right thyroid region in 1927. It produced no symptoms, but in the fall of 1929 it began to increase in size. Examination in September 1929 disclosed a firm, irregular mass in the region of the right lobe of
the thyroid, measuring 3 cm. in diameter. There were several nodes lateral to it. The tumor was explored and found to be inoperable because of substernal extension. A biopsy was done, and 30.6 millicuries in gold tubes inserted into the growth. During the following three months the tumor regressed appreciably. When the patient was last seen, in January 1931, an area of induration remained beneath the scar but there was no further growth.

Pathology: Thyroid papillary cystadenocarcinoma, Grade I. Atypical high cylindrical epithelium.

Case 9. N.C., aged twenty-seven, clerk: In 1922 he noticed a goiter, which slowly enlarged to the size of an apple. In February 1927 operation was done. The tumor contained multilocular cysts, infiltrated surrounding structures, and could be only partially removed. Referred to the Memorial Hospital in December 1929, he was found to have a hard, fixed tumor 10 x 4 x 4 cm. at the base of the neck anteriorly. Roentgenograms showed a large substernal tumor. During December 1929 and January 1930 the patient received three suberythema doses of high-voltage roentgen rays over the tumor in the neck. In April 1930 he was given two, and in January 1931 an additional two fractional high-voltage exposures over the substernal portion of the tumor. None of the treatments produced an appreciable effect. In March 1931 the condition remained much the same as when treatment had begun.

Pathology: Thyroid papillary cystadenocarcinoma, Grade I.

Case 10. E.F., aged fifty-eight, housewife: In 1906, following childbirth, a goiter was noted. It enlarged slowly until it measured 11 x 8 x 5 cm. and in December 1915 was resected. The operator found it encapsulated and thought he removed it completely. In 1924 a small recurrence appeared at the site of the primary tumor. In July 1925, at another hospital, an unknown amount of radon was implanted in it. In January 1926 the patient began to have cough and hemoptysis and came to the Memorial Hospital. There was a hard, irregular mass 8 x 6 cm. at the base of the neck anteriorly. Typical circular metastases were noted in the lower third of each lung, and there was widening of the superior mediastinum. During the following two months four fractional high-voltage roentgen-ray treatments over the neck tumor and four full erythema exposures over the chest were given. Within a month cough and hemoptysis had ceased. The chest metastases, as judged by their roentgenographic appearance, seemed to have regressed. The neck tumor, however, did not decrease appreciably in size. During 1927 and 1928 four additional fractional high-voltage treatments were given over the neck tumor, and seven suberythema exposures over the chest. The condition remained unchanged. In July 1929 the cough reappeared and the mass in the thyroid region grew larger. Five suberythema high-voltage exposures were given over the chest and two over the neck tumor. The cough persisted. The tumor did not regress. In October 1929 the patient complained of back pain, and roentgenograms showed metastases in the body of the eighth dorsal vertebra. The back pain persisted, despite two fractional high-voltage treatments over the
vertebra. It was partially relieved by a spinal brace. During 1930 the patient was given two additional high-voltage suberythema exposures to the neck tumor, and two to the chest. In March 1931 she had weakened considerably. Cough persisted. The thyroid tumor remained about the same size, and the chest metastases appeared much the same as when radiation had begun four years previously. The area of destruction in the vertebra had increased in extent.

Pathology: Thyroid small alveolar, large-cell (Hürthle-cell) carcinoma, Grade II. Large cuboidal cells with an acidophile cytoplasm and small nuclei form compact, small, irregular alveoli.

Case 11. G.S., aged thirty-seven, housewife: In 1918 enlargement of the thyroid accompanied by nervousness and menorrhagia were noted. By 1924 the tumor measured 8 x 5 cm. and operation was done. The tumor had perforated its capsule and was only partially removed. The patient was referred to the Memorial Hospital with considerable tumor remaining. Between October 1924 and January 1925 this was treated with three half-erythema low-voltage roentgen-ray exposures. A slight decrease in size resulted. In October 1930 the tumor remained in much the same condition.

Pathology: Thyroid small alveolar, large-cell (Hürthle-cell) carcinoma, Grade II.

Case 12. F.K., aged thirty-two, steamfitter: He had had a goiter since the age of eighteen (1913). In January 1927 he noticed dyspnea. In February resection was attempted. The tumor was found to be infiltrating and only a portion of the left lobe could be removed. The patient came to the Memorial Hospital in March 1927 with a discharging sinus from the operative scar, beneath which there was a firm irregular tumor mass. During 1927 he was given eight suberythema high-voltage roentgen-ray treatments. Regression was apparently complete. In June 1931 no palpable tumor remained, although the sinus persisted.

Pathology: Thyroid adenocarcinoma, Grade II. Atypical cells forming small alveoli. Many large cysts. Prominent hyaline stroma.

Case 13. J.L., aged forty-two, butler: In 1920 he became nervous, had profuse sweating, and noted a left-sided goiter. In 1922 subtotal thyroidectomy was done. There was a large recurrence in 1926, and in 1928 further resection was attempted, but only a portion of the recurrent growth could be removed. Two postoperative roentgen-ray treatments were given. In April 1929 the patient came to the Memorial Hospital with a hard nodular recurrence, 6 cm. in diameter, in the left thyroid region. He was given 12,000 millicurie hours with the emanation pack. The tumor regressed markedly and in June 1930 still maintained this quiescent state.

Pathology: Thyroid adenocarcinoma, Grade II. Atypical cells growing in masses in which there are secondary alveoli.

Case 14. M.V., aged thirty-eight, housewife: She had had a goiter all her life. In 1914, after childbirth, it began to increase rapidly in size. In July 1920 an incomplete resection was done, and in September the patient was referred to the Memorial Hospital, with a hard mass in
the thyroid region 10 cm. in diameter. During succeeding months seven half-erythema low-voltage roentgen-ray treatments were given. There was no apparent regression. Death occurred in May 1921.

Pathology: Thyroid adenocarcinoma, Grade II. Solid areas of atypical cells with secondary alveoli lying in portions of old fibrosed parenchymatous goiter.

Case 15. M.H., aged fifty-eight, housewife: In 1895 she noted a slight swelling in the thyroid region. It remained stationary until 1915, when it began to grow rapidly. It was excised in 1916 but recurred rapidly, and in 1918, 1919, and 1920 attempts were made to excise recurrences. The patient came to the Memorial Hospital in June 1920, with a very large nodular tumor involving both sides of the base of the neck (Fig. 16). During June she was given 29,688 millicurie hours with the emanation pack, and 24.3 millicuries in bare tubes were inserted into the tumor. No regression resulting, an additional 18.5 millicuries in bare tubes were inserted into the tumor in July. The only result was breaking down of the wound. When the condition was much worse, in March 1923, two half-erythema low-voltage roentgen-ray exposures were given. Again there was no regression. Death occurred in January 1924.

Pathology: Thyroid adenocarcinoma, Grade II. Compact and irregularly infiltrating masses of cells interspersed with small alveoli.

Case 16. P.G., housewife: A goiter appeared in 1908 and grew slowly. In November 1928 it began to grow rapidly and became firm and nodular. In October 1929 the patient noticed a separate node on the opposite side. Her only symptom was a drawing sensation over the vertex. She came to the Memorial Hospital in November 1929 with a symmetrical, nodular, hard, fixed tumor of the thyroid measuring 10 x 8 x 4 cm. A biopsy was done. During the following month 32,000 milligram hours with the element pack and two suberythema high-voltage roentgen-ray treatments were given, but no regression followed. Death occurred in January 1930.

Pathology: Thyroid adenocarcinoma, Grade III. Solid masses of atypical cells, varying greatly in size and shape but tending to be fusiform.

Case 17. E.W., aged forty-eight, housewife: In September 1922 she noted diffuse swelling in the thyroid region, accompanied by a choking sensation and pain. In November a partial resection of a tumor of the pyramidal lobe was done. The patient was referred to the Memorial Hospital, where a firm, nodular, fixed tumor, 2 x 5 cm. in diameter, was felt beneath the scar. During the succeeding two months five half-erythema low-voltage roentgen-ray treatments were given. The tumor regressed completely. In November 1925, however, a new node appeared above the inner end of the left clavicle and was treated with two half-erythema doses of low-voltage radiation. Only slight regression resulted. Symptoms of dyspnea and pain persisted, and the patient grew steadily worse during 1926, despite six additional half-erythema low-voltage treatments. An emergency tracheotomy was done and she died in November 1926.
Pathology: Thyroid adenocarcinoma, Grade II. Alveolar areas which suggest adenoma malignum, papillary areas, and areas in which the cells grow in sheets in epidermoid fashion.

Case 18. E.K., aged fifty-four, housewife: In January 1922 she noted a tumor in the right thyroid region, which grew rapidly and caused pain and dysphagia. When she came to the Memorial Hospital, in July, the large tumor extended from the angle of the mandible to the suprasternal notch on the right. There was a single node on the left side. During August the patient was treated with 12,320 millicurie hours with the emanation pack, tracheotomy and biopsy were done, and 15.4 millicuries in bare tubes were inserted in the tumor. For three months it decreased moderately, then began to grow rapidly, despite further treatment of 2,000 millicurie hours with the emanation tray. Death occurred in February 1923.

Pathology: Thyroid adenocarcinoma, Grade III. Diffusely infiltrating cells, varying in size and shape, tending to be fusiform, forming irregular alveoli.

Case 19. F.M., aged fifty-three, laborer: Since about 1896 he had had a left-sided goiter. In 1924 it began to grow rapidly and he became hoarse. Examined at the Memorial Hospital in October 1926, he had a hard, fixed mass, 10 cm. in diameter, in the left thyroid region, extending down over the sternum, and a chain of nodes above it. There were pulmonary metastases. Biopsy was done and during November the patient received 24,000 millicurie hours with the emanation pack and two full erythema doses of high-voltage roentgen rays over the tumor. During the following month there was an appreciable reduction in the size of the tumor and phonation improved. In January 1927, however, the tumor began to grow rapidly again and 56,000 millicurie hours with the emanation pack and three suberythema high-voltage exposures had no effect. Death occurred in August 1927.

Pathology: Thyroid adenocarcinoma, Grade II. Closely packed, small, atypical cells forming irregular alveoli.

Case 20. C.S., aged fifty-five, housewife: In 1918 she noted enlargement of the thyroid, accompanied by dyspnea and pain. On examination at the Memorial Hospital in November 1919, there was observed a firm, nodular tumor involving the entire thyroid, but largest on the left, where it measured 6 x 3 cm. In November 18.9 millicuries in bare tubes were inserted in the tumor and during the succeeding month it decreased appreciably in size. It then resumed its growth. In February 1920, 7.8 millicuries, in October, 10.5 millicuries, in February 1921, 9.4 millicuries, and in October, 16 millicuries, were inserted in the tumor with similar results. The tumor continued to grow, pulmonary metastases developed, and a biopsy was done, following which the patient died in August 1923.

Pathology: Thyroid adenocarcinoma, Grade II. Cells growing in solid masses sometimes forming alveoli in which polarity is lost.

Case 21. M.H., aged forty-eight, housewife: A tumor appeared in the left thyroid region in 1920 and grew rapidly. In 1921 a partial
thyroidectomy was done and the patient was referred to the Memorial Hospital. On examination, in August 1921, there was no tumor palpable. During 1921 three fractional low-voltage roentgen-ray treatments were given over the thyroid area. The patient continued to be free of evidence of disease until January 1927, when a small hard node appeared at the site of the primary tumor. This was treated with one high-voltage fraction and slowly disappeared. In March 1931 there was no evidence of disease.

Pathology: Thyroid adenocarcinoma, Grade II. Irregular, colloid-filled alveoli and areas of spindle-shaped cells growing in masses.

Case 22. J.P., aged forty-three, housewife: A goiter appeared in 1906 and remained unchanged and symptomless until January 1927, when the right lobe began to enlarge rapidly. Within five months it had attained the size of an orange, and a resection was attempted. The tumor was found to be infiltrating and could be removed only in part. The patient was referred to the Memorial Hospital in July 1927 with an indurated area beneath the operative scar. She was given four suberythema intermediate-voltage exposures, and by April 1928 the indurated area had disappeared. In February 1931 there was no evidence of disease.

Pathology: Thyroid adenocarcinoma, Grade II. Atypical cells arranged as alveoli and solid masses. Blood vessel invasion.

Case 23. F.R., aged twenty-one, electrician: In 1917, when he was eight years old, a goiter appeared. In 1927 it began to grow rapidly and in November 1929 his surgeon partially removed the bulky tumor. Following operation the remaining tumor continued to grow. The patient came to the Memorial Hospital in January 1930 with a hard, fixed recurrent mass in the right thyroid region, measuring 10 cm. in diameter. During January he was given 30,000 milligram hours with the element pack, and on January 29, 36.71 millicuries in gold tubes were inserted into the tumor. It regressed considerably during the following two months. When the patient was last seen, in February 1931, the tumor remained stationary.

Pathology: Thyroid adenocarcinoma, Grade II. Small cells with regular nuclei form small alveoli without colloid, and in some areas grow in solid masses. Invasion of vessels.

Case 24. S.S., aged forty, housewife: In 1912 a right-sided goiter appeared. In 1917 it was the size of an orange and was resected. The tumor recurred, and in 1925 a second operative removal was done. Nine months later there was a second recurrence which was also removed. Following this last operation the left hip became swollen and painful. A series of twenty roentgen-ray treatments to the hip alleviated the pain. In 1929 the patient began to have a persistent cough and lost weight. When she came to the Memorial Hospital in November 1929, there were extensive metastases throughout both lungs and a large substernal tumor (Fig. 17), a large multilocular area of metastasis in the right ileum (Fig. 18), and several areas of metastasis in the frontal and parietal bones. All these areas were treated with suberythema doses of high-voltage
roentgen rays to the limit of tolerance. Under treatment the pain in
the hip became less and the tumor appreciably diminished in size.
The response in the other areas was not definite. The general condition
became worse and early in March 1931 death occurred.

Pathology: Thyroid adenocarcinoma, Grade II. Rather large, fairly
regular cells grow irregularly to form alveoli of varying size without

Case 25. M.B., aged forty-seven, housewife: In 1912, during her
first pregnancy, a goiter appeared, which slowly increased in size. In
1928 it began to interfere with her breathing, and in February of that
year a radical thyroideectomy was done. In January 1929 the patient
began to cough and have dyspnea and was referred to the Memorial
Hospital. She was found to have a large, hard, irregular tumor extending
from the region of the right lobe of the thyroid up to the right sub­
maxillary region. In March 1929 the tumor was explored, 18 millicuries
in gold tubes were inserted into it, and a tracheotomy was performed.
The tumor, however, continued to increase in size. In May 1929 a
second exploration was done and an additional 25 millicuries in gold
tubes inserted. Within two months the tumor had diminished markedly
in size. The regression continued so that by September 1930 no definite
tumor remained. In February 1931 the patient was still free of disease.

Pathology: Thyroid adenocarcinoma, Grade II. Small atypical cells
arranged for the most part in solid masses. Some areas alveolar. Very
vascular.

Case 26. G.H., aged fifty-eight, clerk: In September 1920 a tumor
appeared in the right thyroid region. It grew rapidly, and resection
was attempted Oct. 25, 1920. The tumor measured 10 x 8 cm. It
infiltrated surrounding structures and could be only partially removed.
The patient was referred to the Memorial Hospital with an indu­
rated area beneath the operative scar. In November he was given
10,058 millicurie hours with the emanation pack, and during December
9,930 millicurie hours. Despite these treatments the tumor grew
rapidly and dysphagia became marked. On Jan. 21, 1921, 7 milli­
curies in bare tubes were buried in the tumor, with no apparent benefit.
Dysphagia and dyspnea rapidly increased, and death occurred Feb. 7,
1921.

Pathology: Thyroid giant-cell carcinoma, Grade III. Cells show
great variation in size and shape, although tending to be fusiform.
There are mono- and multinucleated giant cells. In several areas
alveoli with neoplastic features suggest the transition of alveolar epi­
thelium into anaplastic tumor cells.

Case 27. H.S., aged forty-four, housewife: She first noted a tumor
in the thyroid region in March 1930. She was given several roentgen-ray
treatments which did not affect the course of the disease. The tumor
continued to grow rapidly, dyspnea increased, and death occurred on
Oct. 20, 1930.

Autopsy: Thyroid giant-cell carcinoma, Grade III. Anaplastic
spindle and giant cells. There was also a primary infiltrating comedo­
carcinoma of the left breast.
CASE 28. C.F.D., aged sixty-four, civil engineer: In July 1930 he first noted a tumor in the left thyroid region. It grew rapidly, and in October resection was attempted. A mass 5 x 4 cm. was removed, representing only a part of the tumor. When the patient was referred to the Memorial Hospital shortly afterward, the tumor measured 9 cm. in diameter. During November and December 1930 three full erythema high-voltage roentgen-ray treatments were given over the mass. A slight temporary decrease resulted, but in a few weeks the tumor resumed its rapid growth. A chain of nodes developed on the opposite side of the neck, dyspnea increased, and death occurred, February 1931.

Pathology: Thyroid giant-cell carcinoma, Grade III. Masses of anaplastic fusiform cells varying greatly in size, with some very large giant cells with single or multiple nuclei. Blood vessels and capsule invaded.

CASE 29. F.K.C.K., aged forty, carpenter: In 1918 he noted difficulty in breathing, which he described as "asthma." The dyspnea increased and he came to the Memorial Hospital in December 1921. There was fullness in the suprasternal notch, and roentgenograms showed a substernal tumor. In December 1921, 17,925 millicurie hours with the emanation pack, and in January 1922 three fractional doses of low-voltage roentgen rays were given over the substernal tumor. No relief in symptoms or decrease in size of the tumor was noted during the subsequent two months. The patient was then lost track of until April 1923, when he returned with an aggravated dyspnea.

A nodular tumor mass was now present in the suprasternal region, and the substernal tumor had increased in size. The patient was given 12,000 millicurie hours with the emanation pack without appreciable result. Biopsy was done and a tracheotomy attempted. This failed, and death occurred in September 1923.

Pathology: Thyroid small round-cell carcinoma, Grade III. Small, diffusely growing cells with large hyperchromatic nuclei and a slight amount of cytoplasm. There is some variation in size, occasional large round cells being seen.

CASE 30. F.S., aged seventy-four, business man: In September 1925, he first noted swelling of the neck. This rapidly increased so that when the patient was examined on Nov. 20, there was diffuse swelling, which seemed to be lateral to the left lobe of the thyroid and outside the jugular chain. He had recently been treated for pulmonary tuberculosis, the signs of which were evident from chest roentgenograms. At operation, on Nov. 12, a cellular tumor of the left lobe of the thyroid was found. It was adherent to surrounding tissues, extended behind the trachea, measured about 5 x 3 x 3 cm., and could be only partially removed. During December the patient was given four fractional doses of high-voltage roentgen-rays. This treatment had no effect on the tumor, which continued to grow rapidly. Dysphagia and dyspnea increased, and death occurred on Jan. 11, 1931.

Pathology: Thyroid small round-cell carcinoma, Grade III. Diffusely growing small round cells, varying somewhat in size, with hyperchromatic nuclei and a slight amount of cytoplasm. Distinct alveolar areas.
The estimation of radiosensitivity in these cases should rest first upon analysis as to definitive cure. It is at once apparent, however, that the long duration of the less anaplastic forms of thyroid carcinoma makes such an estimate almost impossible. There is no statistical information available, even in the complete English mortality data, as to the natural duration of carcinoma of the thyroid. Isolated case reports indicate, however, that papillary cystadenocarcinoma, adenocarcinoma, and small alveolar large-cell (Hürthle-cell) carcinoma frequently run a very slow course. In our data the average total duration of these types of disease in those dead (5.5 years) and those still living (9.4 years) was 7.5 years. Cases No. 3, No. 10, No. 15, and No. 24 particularly illustrate this long natural duration of the disease. In two instances we observed recurrence as late as nine years after treatment. Under such circumstances definitive cure should imply freedom from disease for at least ten years following treatment. In our series of cases the six patients still living without evidence of disease have been followed for an average of only three years after radiation. Nor do any other hitherto published reports of the treatment of thyroid carcinoma present ten-year end-results. Thyroid carcinoma is such an unusual disease, and hospital conditions which enable a ten-year follow-up are so infrequent, that these data may be a long time forthcoming. In the meantime we cannot maintain that any particular method of treatment yields a superior number of definitive cures.

We are, therefore, limited in our estimation of the radiosensitivity of thyroid cancer to a determination of the frequency with which primary regression is obtained. Primary regression, as Forssell has pointed out, is the most accurate index of palliation with radiation. In our series of cases primary regression occurred in some degree in 56 per cent and was complete in 23 per cent.

The frequency with which primary regression was obtained varied greatly in the different histologic types, however. In papillary cystadenocarcinoma (9 cases) it occurred in 33 per cent; in small alveolar, large-cell (Hürthle-cell) carcinoma (2 cases) in 100 per cent, and in adenocarcinoma (14 cases) in 71.4 per cent, while in no instance did primary regression result in giant-cell carcinoma (3 cases) or small round-cell carcinoma (2 cases).

These data indicate a moderate radiosensitivity of the more slowly growing and less anaplastic types of thyroid carcinoma, which is most marked in the adenocarcinoma group. The most
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rapidly growing and most anaplastic types appear to be uniformly radioresistant. This finding is not in agreement with the so-called law of Bergonié and Tribondeau and similar laws.

We are unable to discover any reason for this apparent contradiction of the laws of radiosensitivity other than the biological nature of the tumor itself. A careful review of the cases of giant-cell and small round-cell carcinoma, which as a group failed to regress, indicates that the radiation given all except one of these cases must be accepted as adequate external radiation according to modern standards, and that it was quite comparable to the treatment given the other groups in which regression was observed. Of the various constitutional and local factors which we have pointed out as of probable significance in the conditioning of radiosensitivity, only that of age is available for analysis in this series of cases. Primary regression resulted in 57 per cent of the patients under forty years of age and in 43 per cent of those over forty. Our patients with giant-cell and small round-cell carcinoma averaged 10.2 years older than those of the other groups. In our small series of cases, however, this difference is probably without significance.

REPORTED RESULTS WITH RADIATION TREATMENT

Most of the reports of radiation treatment of cancer of the thyroid do not distinguish between the various types of the disease. Forssell, for instance, states: "In my experience cancer of the thyroid gland, next to cancer of the skin, lips, and uterine cervix, yields the most constant and valuable results." The

As regards the type and amount of radiation given to this series of cases, it may be said in a general way that they were given as much of the type of radiation in use at the time as was thought possible, and the inclination at the Memorial Hospital has been toward large doses.

Low-voltage roentgen rays were usually given with 5 milliamperes, 140 kilovolts, 3 to 5 mm. of aluminum filter, focal distance of 38 cm. Seven minutes exposure constituted a fractional dose, and fifteen minutes half an erythema dose.

The factors for intermediate-voltage treatments were 30 milliamperes, 175 kilovolts, 0.5 mm. of copper filter, focal distance of 30 cm., and 10 x 8 cm. field. The exposure time for a fractional dose was five minutes, and for a suberythema dose ten minutes.

High-voltage factors were: 30 milliamperes, 185 to 200 kilovolts, 0.5 mm. of copper filter, 50 cm. focal distance, 10 x 8 cm. field. Five minutes constituted a fractional, ten minutes a suberythema, and twelve minutes an erythema dose.

Emanation pack treatments were given with from 1500 to 2000 millicuries of radon at a distance of 6 cm. and a filtration equivalent to 2 mm. brass.

Emanation tray treatments were given with about 1000 millicuries of radon at 3 cm. distance with a filter of 0.5 mm. of silver.

Element pack treatment as given to these cases signifies exposure to the 4 gram radium element pack at a distance of 0 cm., with filtration of 0.35 mm. of platinum and 1.5 mm. of brass.
reports of Sudeck, Werner, and Holfelder—all of a decade ago—were similarly enthusiastic. Dautwitz, from a series of 25 cases, believes that life was lengthened by radiation.

Schreiner, on the other hand, in reviewing the results of radiation treatment in 14 cases, states: "The results obtained in these advanced cases have not been as encouraging as in other types of malignancy." Bérard and Dunet were not enthusiastic over radiation treatment.

Fortunately, however, some writers have detailed their results with radiation in the different pathologic types of the disease. Schaedel found thyroid "carcinoma" to be very radiosensitive, while the four cases of "sarcoma" which he treated did not respond appreciably, for all the patients died in six months. Barthels found that in "wuchernde Struma," of which he treated five cases, the course of the disease could be retarded by radiation. In six cases of "carcinoma solidum" radiation had no effect. In his opinion the results of radiating "sarcoma" are bad. In the four cases which he radiated the duration of life was no longer than in the 20 unirradiated cases, all the patients dying within six months. Breitner and Just report the results in the large series of cases from Eiselberg's clinic. Twenty cases were radiated, of which nine were "carcinoma" of various types, and five "sarcoma." Adenocarcinoma was found to respond the most favorably to radiation. The results with "sarcoma" were uniformly bad. Haas also found "carcinoma" more radiosensitive than "sarcoma." These German writers, adhering to the histogenetic concept of the mesoblastic origin of some thyroid tumors, have classified as "wuchernde Struma" and "carcinoma" those types which we include in our groups small alveolar large-cell (Hürthle cell) carcinoma, and adenocarcinoma. They class as "sarcoma" those tumors which we have called giant-cell carcinoma and small round-cell carcinoma.

In America Clute and Smith have reported their extensive experience with thyroid cancer. They conclude: "We have the strong impression that roentgen treatment retards the rate of growth and delays the appearance of recurrence in the malignant adenomas of the thyroid, but it is not of benefit in squamous cell, giant cell, and small cell carcinoma of the thyroid gland." Portmann, from a large series of cases, reports that the "malignant adenomas" are radiosensitive while "papillary carcinoma," "scirrhous carcinoma," and "carcino-sarcoma" are radioresistant.
He found that "sarcomas" gave the most unfavorable results of all, being remarkably radioresistant.

Thus we find from clinics in both Germany and America evidence in agreement with the findings from the Memorial Hospital data, namely that the less rapidly growing and less anaplastic thyroid tumors are moderately radiosensitive, while the rapidly fatal and highly anaplastic types are not affected by radiation.

**TREATMENT**

Since the various types of thyroid cancer respond so differently to radiation, it would seem that treatment should be determined by the histologic type as well as by the size and extent of the tumor. The finding that the less rapidly growing and less anaplastic types are but moderately radiosensitive—partial primary regression resulting in 36 per cent and complete primary regression in 24 per cent of our cases of papillary cystadenocarcinoma, small alveolar large-cell (Hürthle-cell) carcinoma, and adenocarcinoma—suggests that in these types of the disease interstitial radiation may be preferable to external radiation. It has been found that in types of carcinoma which possess but slight radiosensitivity, such as inoperable metastatic carcinoma of cervical nodes, interstitial radiation produces much better growth restraint than external radiation. Interstitial radiation enables the concentration within the tumor—and particularly about its base—of a much larger amount of radiation than can be given externally with either high-voltage roentgen rays or gamma rays. Since the less anaplastic types of thyroid cancer exhibit but a moderate degree of radio-sensitivity, it would appear that this greater intensity afforded by interstitial radiation might more frequently and more completely bring about primary regression of the tumor. The thyroid cancers of smaller size would seem to be best adapted to such treatment.

The insertion of such interstitial radiation is a major surgical procedure. Under local anesthesia the usual collar incision is made, a flap of skin and platysma is turned back, and the pretracheal muscles are separated to expose the tumor, the limits of which are determined. The radiation (in the form of radon-containing gold tubes 0.3 mm. in thickness, at the Memorial Hospital) is inserted throughout the tumor in such a manner as to girdle its circumference and seed its base. If the amount of radiation used is considerable, the resulting increased pressure on the trachea from the tumor, and the frequently occurring edema
FIG. 15. Thyroid Papillary Cystadenocarcinoma (Case 6: B.J.P.)

FIG. 16. Thyroid Adenocarcinoma (Case 15: M.H.)
of the larynx, will require a tracheotomy until the acute phase of the radiation reaction has subsided.

The size of the tumor has, of course, an important bearing on the type of treatment. If a thyroid carcinoma of the less anaplastic type is large and fixed, as was that in Case 6, shown in Fig. 15, which measured 10 cm. in diameter, neither surgical excision alone nor any form of radiation alone has much chance of

**Fig. 17. Pulmonary Metastases of Thyroid Adenocarcinoma (Case 24: S.S.)**

effecting a cure. We have seen that surgical excision almost always fails to remove such a tumor completely, because it has broken through its capsule and infiltrated surrounding structures. External radiation alone is even less effective for such a tumor. Its base is at such a depth that by external means a sufficient dose cannot be delivered to this vital frontier. In such a bulky tumor interstitial radiation alone also becomes less applicable, for a dose sufficient to control a mass of such size is a dangerous one. It
would seem that in this sort of tumor—large, fixed, and of the less anaplastic type—the ideal treatment would consist in surgical excision of the bulk of the tumor without any attempt at radical complete dissection, merely for the purpose of removing its superficial mass, combined with thorough interstitial radiation of its base and surrounding suspicious areas.

When a tumor has attained such size and diffuseness as that shown in Fig. 16, it is, of course, unjustifiable to attempt either surgical excision or interstitial radiation. External radiation may afford some palliation in such tumors when they are of the less anaplastic type.

In the anaplastic, rapidly fatal, giant-cell and small round-cell types of the disease, surgical excision is, of course, contraindicated. External radiation may be tried, but it should be remembered that no one has as yet reported beneficial results. This being the case,
it should not be given to the point of making the patient uncomfortable.

Metastatic lesions, even when very extensive, have frequently yielded a worth-while degree of palliation with external radiation. (Figs. 17 and 18.)

**Summary**

1. The various forms of cancer of the thyroid have been grouped into five types. Each type has been shown to have a fairly characteristic natural history and morphologic structure. The malignancy and anaplastic character increase in the order of classification.

2. Thirty cases with complete data have been classified on this basis, and their reaction to radiation studied from the point of view of primary regression and of definitive cure. These data indicate a moderate radiosensitivity of the less anaplastic types of thyroid cancer, most marked in the adenocarcinoma group. The most rapidly growing and anaplastic types appear to be uniformly radioresistant. This finding is not in agreement with hitherto proposed laws of radiosensitivity, such as the law of Bergonie and Tribondeau.

3. In determining the type of treatment, emphasis is placed on the histologic type of the tumor, as well as its size and extent.

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