Identification of Cold Thyroid Lesions at Operation and Its Place in the Surgical Management of Carcinoma of the Thyroid

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FOR THE PAST 22 years, autoradiographs have been prepared with radioiodine (^{131}I) from most thyroid neoplasms removed at operation. During the course of studies on more than a thousand thyroid neoplasms, a large number of carcinomas of the thyroid have been encountered. In the early part of these studies, it was shown that carcinomas took up very little ^{131}I; in fact, many of them took up none at all.[1] A method for estimation of ^{131}I content of masses from the outside of the neck was developed and became an important diagnostic tool to identify cold nodules and to estimate the probability of encountering carcinoma.[2] Although this has helped to identify many neoplasms with poor uptakes, the method is nevertheless imprecise, owing to the presence of ^{131}I in the normal thyroid tissue lying in front of and behind the neoplasm, to the presence of superimposed masses, and to the presence of necrosis in neoplasms that might otherwise take up consideable ^{131}I.

Some basis was needed to permit a comparison of the uptake among neoplasms in different individuals. Thus a ratio was used to relate the uptake by a given weight of neoplasm to the uptake of an equal weight of the normal or paranodular thyroid tissue in the same individual. Using such ratios, a comparison of function of tumors among individuals can be made. Those neoplasms whose uptake was more than two times the paranodular tisssue were classified as "hot." Those for which the ratio was less than 0.5 were "cold." Those between 0.5 and 2.0 were considered intermediate. Approximately one third of the neoplasms fell into each of these three categories. All carcinomas were found in the cold group, although the majority of the lesions in the cold group were benign. Our experience, reported in 1949 [3] and based on 119 carcinomas of the thyroid, revealed no uptake at all in the highly malignant lesions. Even the most functional follicular carcinoma took up far less ^{131}I than the paranodular tissue.

For practical purposes it is useful for the surgeon to know what the upper limit of uptake might be among a large number of carcinomas of the thyroid and to be able to estimate precisely the uptake of neoplasms at the time of their removal. Furthermore, since the distinction between between benign and malignant thyroid lesions is sometimes difficult, especially on frozen sections, the information on the uptake of some of these debatably malignant neoplasms is also useful to the surgeon. Thus, an estimation of the uptake of neoplasms at the time of operation has become an important adjunct to the microscopic interpretation of frozen sections.

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Methods

All patients with nodular goiter are routinely given a tracer dose of ^{131}I the day before operation. At operation the entire thyroid is exposed. A careful search for possible metastases to lymph nodes is made in areas above and below the isthmus and posteriorly and inferiorly to both lobes. If none are found, the mass under consideration is excised meticulously, avoiding violation of the capsule by leaving a margin of normal thyroid tissue around it, but preserving as much normal tissue of that lobe as possible. The excised surgical specimen is immediately cut in such a way that the overlying extranodular thyroid tissue is separated down to the capsule of the neoplasm. The capsule is then cut with a fresh instrument which carries no contaminating radioactivity. Approximately 100 milligrams of the neoplasm is removed from just within the capsule, where the viability of an encapsulated lesion is most certain, or removed from the center of the neoplasm if it appears to be an infiltrating lesion with no capsule. The neoplastic tissue is placed in a test tube. Using the original knife, a piece of extranodular tissue of the same size is cut and placed in a second test tube. The two samples are independently counted for their radioactivity. This can be done within 2 or 3 minutes while the frozen sections are being prepared. Assuming equal weights of the two samples, a precise ratio of uptake of the tissues may thus be expressed:

$$\frac{\text{counts per minute—neoplasms}}{\text{counts per minute—extranodular tissue}}$$

Results

A wide spectrum of neoplasms representing all degrees of ^{131}I uptake have been found. It should be kept in mind that all neoplasms whose values are greater than 1.0 have more uptake than the extranodular tissue and that these ratios range upward to approach infinity, where the accompanying extranodular tissue is almost completely suppressed. No carcinoma has been found in this group of hyperfunctioning neoplasms.*

Among 99 carcinomas of the thyroid studied in this manner or with autoradio-

* It should be acknowledged that hot neoplasms occasionally accompany a malignant neoplasm situated at another site in the same gland.

TABLE 1. *The Ratio of ^{131}I Uptake of Malignant Thyroid Neoplasms to the Accompanying Paranodular Thyroid Tissue**

Ratio: $\frac{\text{neoplasm}}{\text{normal tissue}}$	0 to .0009	.001–.009	.01–.09	.1–.4	Totals
Pure papillary	13	2	2	1	18
Mixed papillary & follicular	18	6	1	0	25
Follicular	16	1	2	1	20
Solid cellular	12	5	2	0	19
Anaplastic	12	1	1	—	14
Metastatic to thyroid	2	0	1	—	3
Total malignant neoplasms	73	15	9	2	99
Atypical (? malignant)	3	3	3	2	11

* The ratios presented here represent individual neoplasms studied. The data have been derived from either autoradiographs or from fresh tissue countings or by both methods. When data from both methods were available on the same neoplasm, the lesions, which displayed either spotty necrosis or infiltration with normal thyroid tissue trapped in it, were interpreted best by autoradiographs from which selected areas were measured by microdensitometry. On the other hand, direct tissue counting proved accurate when the uptake was very low, too low to cause effective blackening on the autoradiograph. Because small amounts of radioactivity were attributable to trapped normal follicles and not to the neoplasm per se, a few of the higher uptakes represent error. As these causes of error have been found and precautions in selection of tissue for direct counting have been made, the method of direct tissue counting has been quite reliable and can be done at the time of the operation. Since autoradiographs require several weeks for preparation they are not available at the time of surgery.

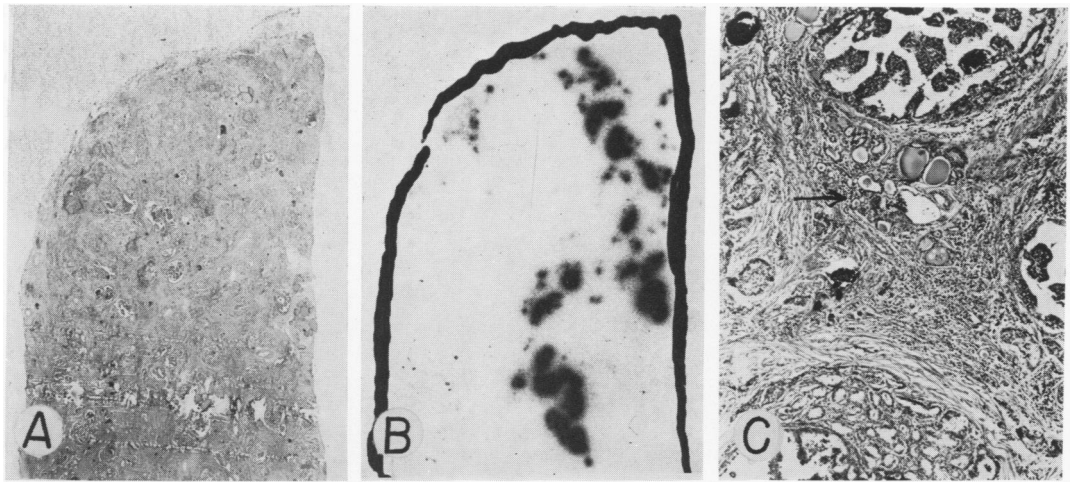

FIG. 1. A highly malignant infiltrating carcinoma of the thyroid.

A. Tissue section of carcinoma of the thyroid from an individual given ^{131}I before operation. Magnification from 6×.

B. Autoradiograph prepared from the same section of tissue.

C. A minute area of normal thyroid follicles trapped within the carcinoma. The area corresponds with an area of blackening in the autoradiograph. Magnification from 80×.

A few normal follicles of normal thyroid tissue have been trapped within the infiltrating carcinoma. Counting radioactivity in such a mass of tissue might reveal counts that were falsely attributable to the carcinoma, which in the autoradiograph is shown to pick up no ^{131}I. Errors such as this may be largely avoided by obtaining the small sample of tissue from as near the center of lesion as possible.

graphs, no significantly detectable uptake has been found in 73 (85%), i.e., the carcinoma contained less than 1/1000 of that of the paranodular tissue (Table 1). Of the remaining 26 malignant neoplasms which had some uptake, 15 were found to have taken up between 1/1000 and 1/100 of that of the normal tissue. Thus the uptake in approximately 90% of carcinomas of the thyroid had only 1/100 or less of the uptake of the accompanying normal tissue. Of the 11 carcinomas found to have more than 1/100, the histologic pattern might have been expected to be follicular

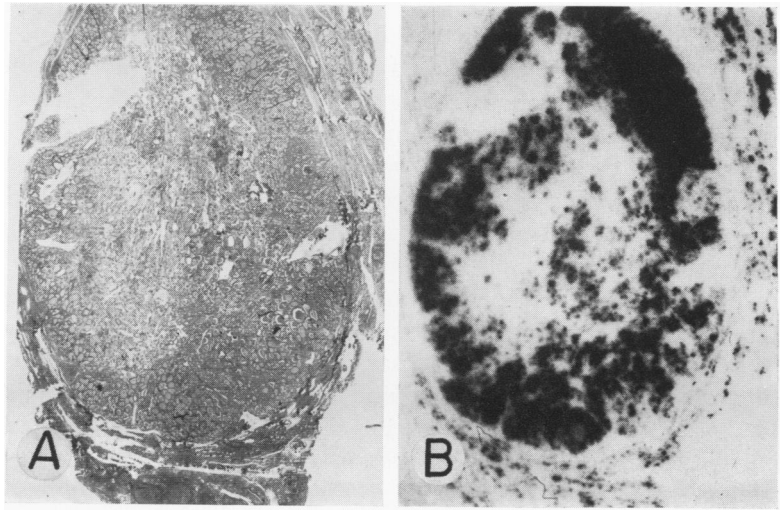

FIG. 2. A discrete encapsulated lesion of the thyroid with necrosis in its center.

A. Tissue section of a benign adenoma from an individual given ^{131}I before operation. Magnification from 6×.

B. Autoradiograph prepared from tissue section.

A sample of tissue taken from the area of necrosis and poor uptake of ^{131}I in the center of the neoplasm might give the impression of a nonfunctioning neoplasm on tissue counting, whereas a sample of the tissue from immediately within the capsule, where the blood supply is satisfactory, would reveal that this lesion picks up considerable ^{131}I and is most likely a benign lesion.

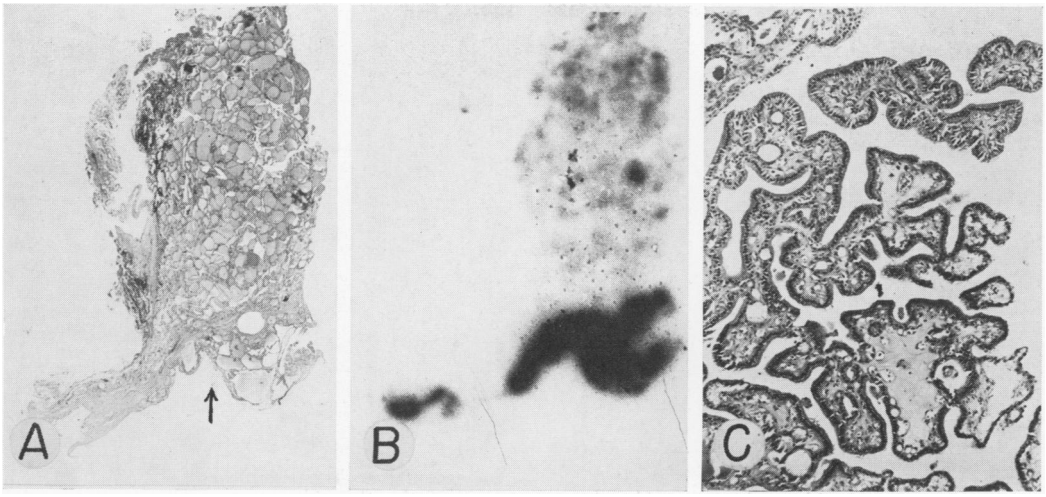

FIG. 3. A hot papillary lesion of the thyroid (benign).

A. Tissue section from an individual given ^{131}I before operation showing the wall of a cystic lesion with a rind of surviving neoplasm but within the capsule (neoplasm identified by arrow). Magnification from 6×.

B. Autoradiograph prepared from tissue section showing high concentration ^{131}I in the papillary neoplasm.

C. Papillary lesion with excessive function, shown in A & B. Magnification from 120×.

or mixed papillary and follicular adenocarcinomas; however, in this group with higher uptakes, some anaplastic and solid cellular lesions were encountered. Evidence suggested that some of these counts were in error.

When both autoradiographs and data on gross counting were available on the small masses of tissue, two reasons for error were found and have been largely overcome. In the case of highly malignant infiltrating carcinomas, small islands of functioning normal follicles may be trapped by the spreading cacinoma as shown in Figure 1. Upon gross counting of such a mass of tissue, the carcinoma may be credited with an uptake that was actually contained in the trapped normal follicles. Thus, in the case of a non-encapsulated lesion, the small sample of tissue should be obtained from as near the center of the lesion as possible to avoid normal follicles. A second reason for error in tissue counting arises in the encapsulated lesion which proves to have spontaneous necrosis in its center (Fig. 2). In encapsulated lesions the tissue lying just beneath the caspule is usually the most viable and displays the most reliable uptake. The counting of tissue from the center of a discrete adenoma may give a falsely low value and arouse undue concern. Thus where there is a discrete capsule the sample should be taken just beneath the capsule.

These observations serve to emphasize, 1.) importance of the careful selection of the sample of neoplasm for counting and 2.) the avoidance of manual contamination of the sample with the blade of an instrument. Despite errors in counting during the early experience (errors that are probably included in Table 1), the data suggests that more than 90% of thyroid carcinomas have less than 1/100 of the uptake of the accompanying normal thyroid tissue.

It is well known that not all neoplasms of the thyroid with microscopic papillary structure are malignant. On frozen section there may be difficulty distinguishing between the benign and the malignant papillary lesions. In a large experience with autoradiographs of various papillary neoplasms, there have been none with intermediate degrees of uptake. Such lesions

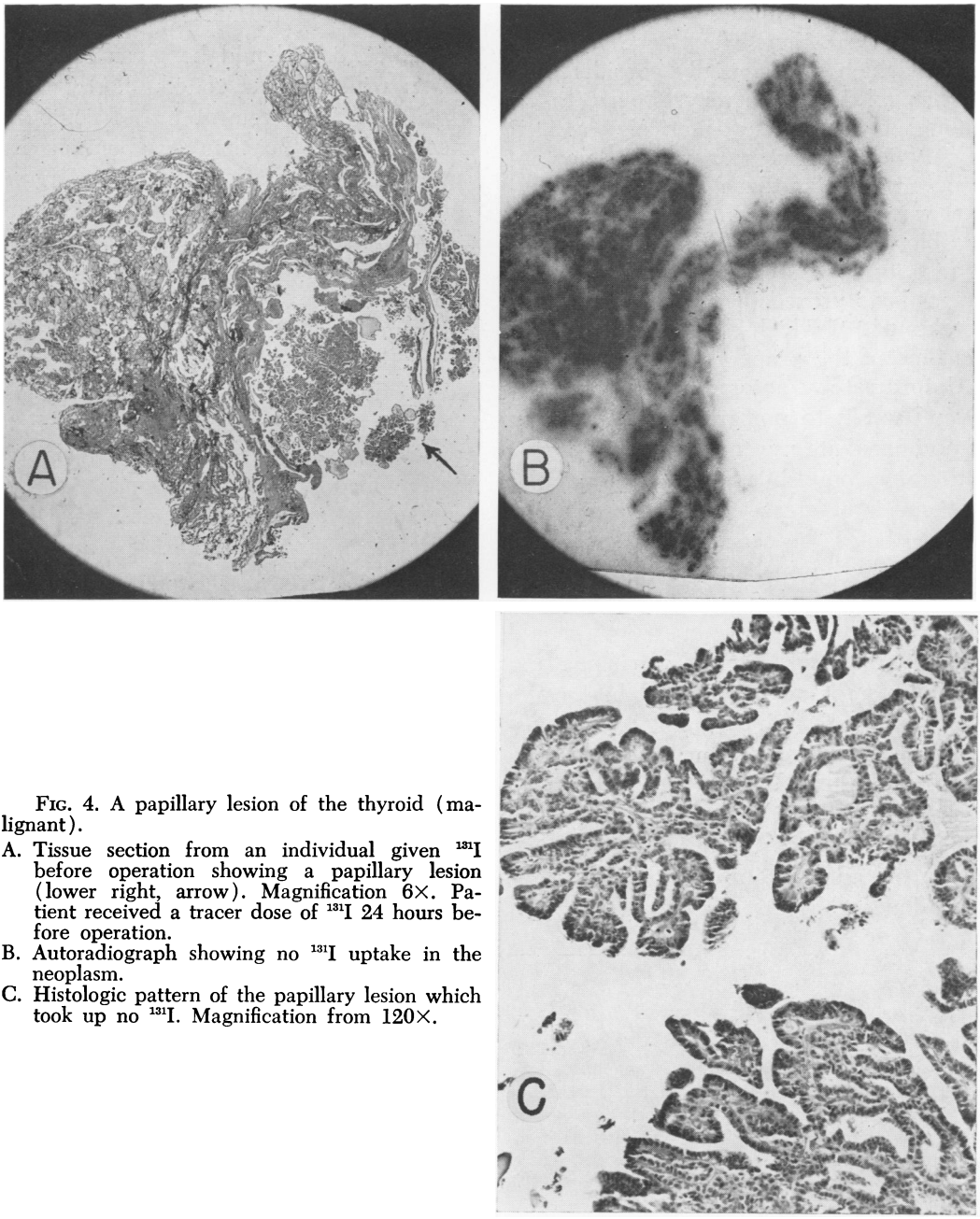

FIG. 4. A papillary lesion of the thyroid (malignant).

A. Tissue section from an individual given ^{131}I before operation showing a papillary lesion (lower right, arrow). Magnification 6×. Patient received a tracer dose of ^{131}I 24 hours before operation.

B. Autoradiograph showing no ^{131}I uptake in the neoplasm.

C. Histologic pattern of the papillary lesion which took up no ^{131}I. Magnification from 120×.

have either an excessive uptake as shown in Figure 3 or practically none at all as shown in Figure 4. Experience has shown that all of those that have metastasized or were subsequently regarded as malignant or microscopic study have proved to be "cold" papillary lesions. All "hot" papillary lesions have proved to be benign. Thus, when the frozen section diagnosis of a papillary neoplasm is in doubt, the measurement of the radioactivity immediately after removal may be of considerable assistance to the surgeon.

A few benign adenomas were found with considerably lower ratios than some of the most functional carcinomas. Although the

benign nature of most of these was ultimately proved, there were some follicular lesions which were initially considered to be benign, but ultimately proved to be malignant. Some were tentatively classified as "atypical" or "suspicious." In some instances a decision that a lesion was malignant was rendered some days later on finding blood vessel or capsular invasion, or atypicality of the cells. Most all of these lesions have proved to have extremely low uptakes of ^{131}I which can be recognized at the time of the primary operation.

Unfortunately autoradiographs require several weeks to prepare so that they are of no immediate use to the surgeon during a thyroidectomy, but counting of samples of tissue is of great value in warning the surgeon before he concludes the operation that he may be dealing with a carcinoma. The finding of a very low uptake in a neoplasm at the time of operation should arouse serious suspicion of carcinoma and should prompt, not only a further search for lymph nodes which might bear metastases, but also prompt a meticulously complete removal of the entire lobe from which such a neoplasm has been excised. If the final diagnosis then proves to be carcinoma, an adequate procedure will have been done at the first operation.

Summary

Radioiodine should be given to all patients with nodular goiters shortly before operation. Measurement of ^{131}I content of neoplasms at the time of operation is a useful adjunct to frozen section diagnosis of some questionable lesions of the thyroid. Approximately 90% of carcinomas of the thyroid encountered will be found to take up 1/100 or less ^{131}I than an equal weight of paranodular thyroid tissue. Being forewarned of the likelihood of a malignant lesion by precise counting, the surgeon takes particular precautions so that if the diagnosis of a malignant lesion is ultimately made, the most appropriate surgical procedure for that lesion will have been done at the first operation.

References

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Discussion

Dr. Oliver Cope (Boston): The experience that Dr. Dobyns has just recounted very, very briefly is the most extensive that is available. Two benefits which have resulted from this experience are impressive. The first tells about the biology of these tumors, and the second, explains its practical use in operation.

It is interesting that he has not identified a small percentage of carcinomas that fall into the more active group; if one observes the other endocrine glands he will find hyperfunctioning carcinomas which are encountered from time to time.

Of course, there are rarities, but the fact is interesting that in this enormous series Dr. Dobyns did not encounter a seemingly malignant tumor, which has a function greater than uninvolved tissue.

One of the so-called benign metastasizing tumors, so-called *metastasere adenoma* of the German pathologist, was not listed in Dr. Dobyns' report, unless it was not so identified. Of course, that theoretically should be the hyperfunctioning lesion and yet occasionally, it gives rise to metastases.

Since Dr. Dobyns is an able expert—an anatomist as well as a functional expert—I suspect he has not overlooked any of these lesions.

The second question is a practical one.

The practical use of this knowledge can be beneficial if the present technic can be developed. This will provide an added dimension at operation, a functional dimension which benefits beyond pathologic findings of frozen section. This usefulness, of course, depends upon rarity of exceptions. We can consider *metastasere adenoma* as a possible one.

The second possibility which is significant, is the functional capacity of the benign papillary tumors. A benign papillary tumor was seen with a high uptake and then a malignant one with zero uptake. Although the benign tumor had not metastasized, is it not possible that it was removed