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Thyroid Carcinoma and Radiation
some Difficult Problems in Screening Programs

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Abstract: Thus the data show a relationship between radiation and the development of thyroid carcinoma and imply that seeking and removing such tumors would be beneficial. As in most situations, however, this simple relationship is clouded by a variety of associated problems, which must be carefully considered.
The surgical procedure recommended for removal of a nodule in an irradiated gland was a total lobectomy on the contralateral side. If the contralateral side by a surgeon with a special interest in the field was found abnormal on inspection during the surgery, a near total thyroidectomy was indicated.
Discussion of problems and conclusion: Thyroid glands of patients coming to autopsy (usually above the age of 40) are sectioned with great care, over 6% are found to harbor tiny papillary carcinoma.

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These tumors are no larger than 1 cm, and 90% are less than 0,5 cm in diameter. It has been suggested that excessive concern over minor physical abnormalities in the thyroid, or abnormalities found on isotope scan, may lead to unnecessary operations with the detection of these tumors and falsely suggest an association of radiation exposure with carcinoma.

Several points can be raised against this hypothesis. The exact incidence of such tumors is not known in individuals between 20 and 40, who comprise the majority of patients seen for radiationassociated thyroid cancer, but it is probably less than 6% Among the irradiated individuals coming to surgery, not 6% but 30 to 40% have proven carcinoma. Further, the tumors associated with radiation are primarily larger than 0.5 cm, while 90% of the "spontaneous" tumors are less than 0.5 cm in diameter. DeGroot noted that it is porbable that some of the tumors thought to be associated with radiation are in fact the "spontaneous" variety. It is also possible, however, that the spontaneous tumors reflect the effect of unrecognized exciting events, including the 10 rads radiation to which we are all exposed by age 30. DeGroot and Frohman reported that these spontaneous tumors may be altered by radiation and be the sub-strate on which X-rays work to develop more aggressive tumors.

The actual percentage of irradiated thyroids harboring carcinoma is not known with certainty. At least 15% of individuals have definite nodularity after 700 rads exposure, and most series suggest that 5 to 7% of the total will have carcinoma. It is also probable that if more glands were resected, an even higher incidence of cancer would be detected.3,4

The radiation-associated tumors behave fundamentally like other thyroid carcinomas in young adults. Thus they are largely papillary on histology, metastasize primarily to the neck, and only rarely cause death. Current evidence suggests they are, if anything, slightly more aggressive than non-radiation-associated tumors, and more typically multicentric. One must, however, also acknowledge that thyroid carcinoma is slow growing,that patients rarely die from the tumor before age 40, and that in fact the incidence of death is very low.
The observation of a nodule in the thyroid, even in an irradiated person, does not convey the same ominous significance as does the observation of a fixed nodule in the breast. Delay in resection of a carcinoma is not desirable, but it is probable that some delay in decision-making, to allow definite confirmation of abnormality, rarely, if ever, leads to loss of control of the tumor.

What dose of X-ray is significant?Linearity of incidence of tumor and thyroid rad dose,between 100 and 700 rads,is indicated by the work of Beach and Dolphin,and studies by Hempelmann and co-workers suggest that there may actually be no threshold[6]. Certainly doses above 50 rads are tumorigenic. More recent studies by Modan and co-workers suggest that even seven rads to the thyroid may increase the incidence of thyroid carcinoma five-fold. Thus the question of a threshold dose becomes blurred. Most workers would suggest that a dose to the thyroid of about 50 rads would be definitely of medical significance. Current studies show that thyroid lesions become evident during 20 years and even up to 30 years after X-ray exposure. Even more prolonged latency is probable. The data of DeGroot suggest that the incidence

of new tumors, benign or malignant, is reduced after 35 years following radiation exposure.[8] It seems that 35 years is a safe time after which thyroid tumors will no longer develop, but further information is needed to define this latency period more adequately.

What sort of examination is indicated?Most "experts" believe a careful physical examination is the keystone in evaluation. The clinical study by palpation and thyroid scan resulted in the detection of nodular thyroid disease in more than one fourth of the subjects. Scintigram was responsible for detecting abonormalities in nearly half of the subjects with nodular disease who appeared normal on palpation performed without knowledge of the scintigram results. There is, however, the hazard of over-interpretation of minor abnormalities on poor quality scans, and the hazard of radiation if I^{131} is used as the isotope. Therefore, if scans are conducted, a gamma camera with pinhole collimator should be used, with the radionuclide ^{99m} technetium or ^{123} I as the agent (Fig.1). ^{99m} technetium delivers less radiation to the thyroid (2 per cent of that with ^{131}I) and is thus more suitable for use in screening procedures.

Other tests, including determination of T_4, FTI(Free thyroxine index), TSH, thyroglobulin, and antithyroid antibody are of interest in fully evaluating individual patients who will possibly go to surgery, but have no proven value in initial screening for carcinoma. Serum thyroglobulin, antithyroid antibodies, antimicrosomal antibodies and carcino-embryonic antigen(CEA) are more frequently positive in irradiated patients, but the tests do not provide definitive diagnostic information[10].

Thyroid needle biopsy or fine needle aspiration based on the recent report by DeGroot maybe done,but these te-- chniques are not widely available, and their utility in planning therapy for irradiated glands is yet to be established.

Initially, the decision to recommend surgical treatment for "abnormal" subjects was reported by Hempelmann et al. but there is no unanimity in this area. Some surgeons

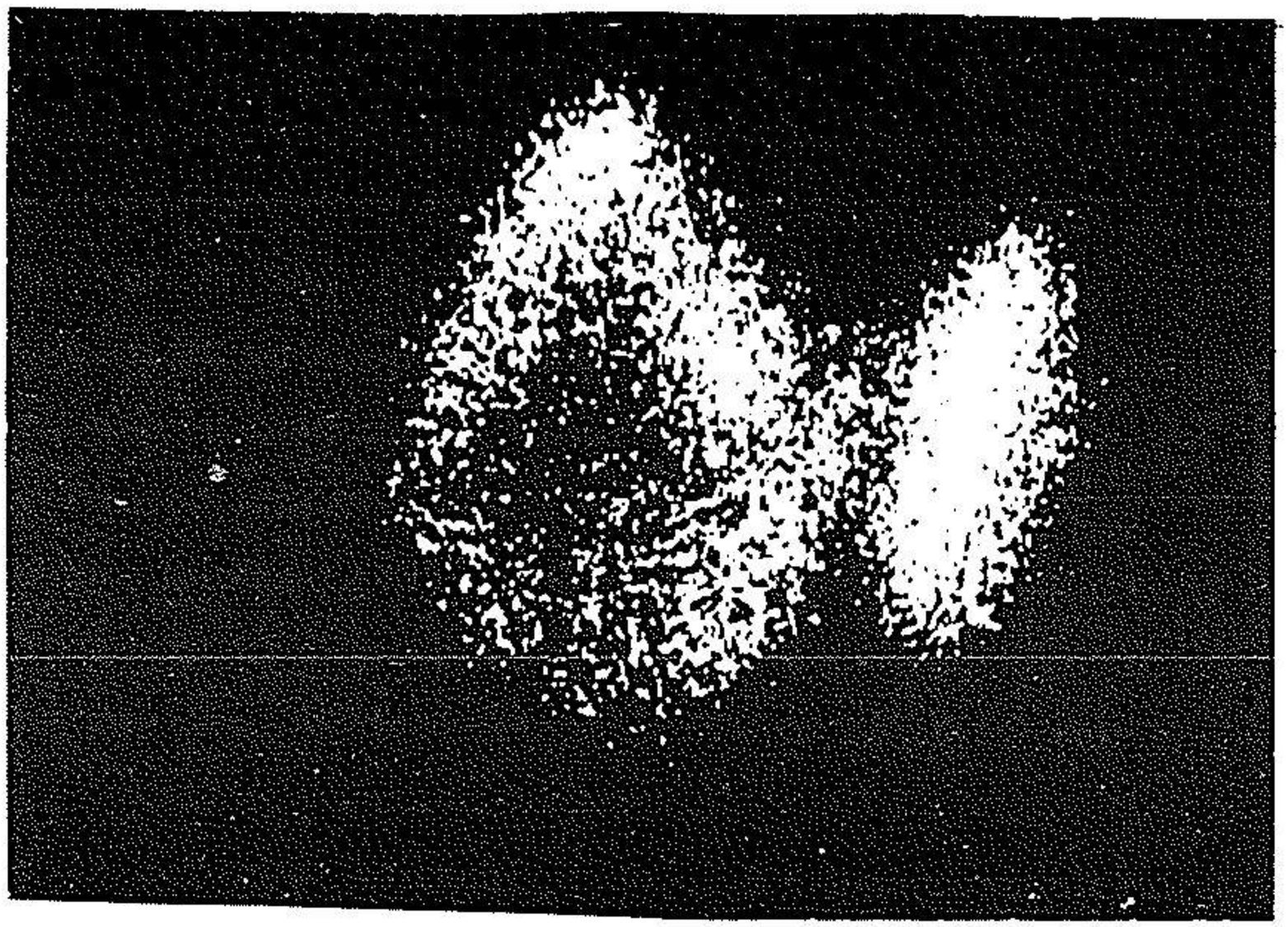

Fig.1 A clear-cut cold nodule involving the right lobe of the thyroid, as depicted by ^{123}I imaging using a gamma camera and pinhole collimator. The vast majority of lesions are much less obvious, and a significant hazard exists in overinterpretation of scans with vague reduction in uptake at the lower poles of the lobes (Photo provided by Thyroid Study Unit, University of Chicago).

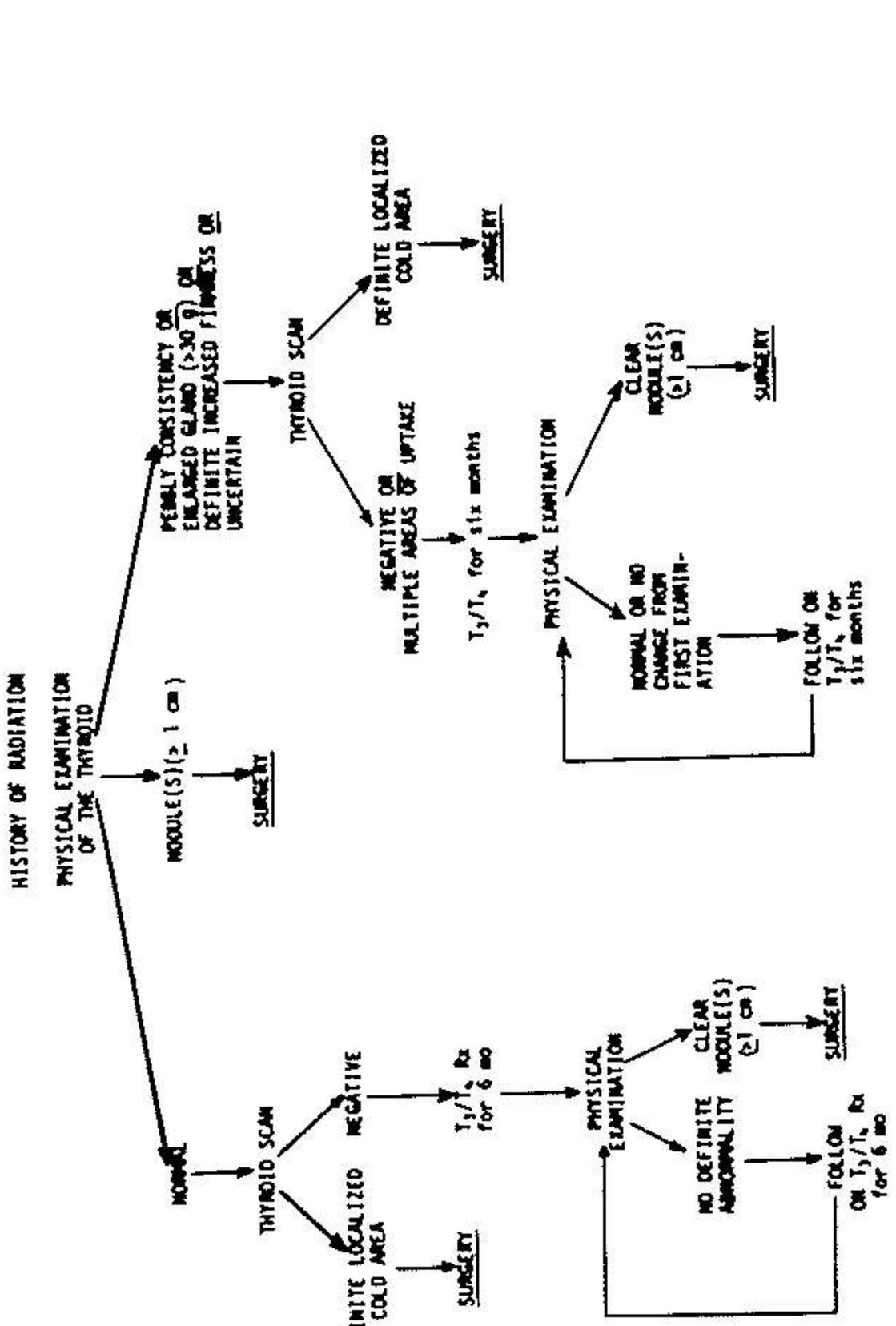

Fig. 2 Evaluation of patients with a history of radiation as currently conducted in the University of Chicago Clinics. Definite nodules, or a definite localized cold area on thyroid scan, is considered indication for surgery. Most individuals who have no abnormality are followed on suppressive therapy with thyroid hormone with examination at yearly intervals.

report that the tumors are frequently multicentric and involved both lobes. These observations have supported a near-total excision of the thyroid.

Other surgeons feel that such extensive resection for such a benign tumor is not indicated and may lead to an excess incidence of hypoparathyroidism, recurrent nerve injury and even death.

What is the role for thyroid hormone replacement therapy?Administration of thyroid hormone(thyroid suppression) is known to suppress development of cancers in irradiated animal thyroid glands[12].

Thyroid suppression of clinically "normal" irradiated subjects has been advocated[13] and appears to have a rationale based on the requirement of an intact pituitary for the development of thyroid carcinoma in rats after irradiation.

The evidence that suppression of TSH would be useful in preventing thyroid tumor formation in clinically normal subjects many years after radiation exposure,however, is unknown. Only a prospective study can answer questions such as the risk of thyroid carcinoma in subjects now "normal" and the value of thyroid suppressive therapy as well as the most effective therapy of clinically detectable nodules. Finally, is thyroid cancer and X-ray the only radiation-associated hazard we should be alert to? Ongoing studies show clearly that radiation exposure to the head and neck induces a variety of tumors, and screening should be best check for all of these. There is a definite increase in paratyroid adenomas [14] and parotid tumors, and in some studies by DeGroot and Kaplan it has been shown that there is also an increase in

neurolemma tumors and even in brain tumors. The cause of greatest concern at the moment is the association of these tumors with external radiotherapy. Fortunately, it is not proven that radioactive ^{131}I therapy for thyrotoxicosis, or ^{131}I used for radioactive iodine uptake (RAIU) or scan, are associated with an increased of malignancy, but should be alert. For this purpose we suggest to follow the simple tentative scheme currently conducted in the thyroid study unit at University

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