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SECTION I

INTRODUCTION : IRRADIATION AND THYROID CANCER

J.E. DUMONT

The demonstration of nodules and cancers in the thyroids of patients who had been subjected to X-ray therapy for thymic enlargement has brought the problem of radiation induced cancers to the forefront of medical and indeed public attention. Inevitably, the association of cancers with a previous treatment has stirred up public controversy about the consequences of medical and surgical procedures in general. Within this controversy there is little doubt that many would regard radiation induced thyroid cancer as the definitive example of iatrogenic cancer. It is also important to remember that the thyroid is subject to another form of iatrogenic disease, hypothyroidism, which frequently follows radioactive iodine therapy of the overactive gland. While this has not received the same attention as thyroid cancer, it is nevertheless important and the numbers now involved are very large.

The social and political issues raised by radiation induced thyroid disease have wide ranging consequences and must inevitably involve the community at large in determining and accepting criteria by which the benefits and risks associated with any procedure are seen to be balanced. Over and above these issues, radiation induced thyroid cancer and hypothyroidism are challenging and interesting medical and scientific problems in their own right. This monograph is primarily concerned with thyroid cancer, although questions relating to hypothyroidism are also raised when it is appropriate to do so. With regard to the cancer, it is of interest that it falls into the category of carcinoma, and although carcinomas represent 90 % of human cancers and share common epidemiological properties (1,2) their biology is much less studied than of sarcomas and leukemias. As with other carcinomas, thyroid tumors caused by irradiation have a well defined environmental cause and could thus be easily prevented. However, even though X-ray irradiation of the thymus has been the principal culprit leading to human thyroid irradiation, the latter organ can be and is exposed to a whole range of other medical and non medical irradiations : fallout of radioiodine after nuclear explosions, leakage of such isotopes from nuclear plants, industrial radiography, uptake of heavy radioactive elements such as radium, radiotherapy, radiodiagnosis, radioiodine uptake tests and other investigations of iodine dynamics with tracers, radioiodine therapy

in hyperthyroidism and cancer, etc. After irradiation, thyroid cancers are much more frequent than spontaneous carcinomas or tumors induced by other agents but their biology and evolution is similar and they constitute therefore the best models for such cancers. It is interesting in this regard that a particularly high incidence of thyroid cancers has been reported in China (3).

Though they are caused by X-ray or I^{131} irradiation, thyroid tumors are treated by high doses irradiation. This treatment requires the uptake of radioiodine by the cancer tissue and its metastases, which gives a very practical meaning to the concept of cancer dedifferentiation and redifferentiation. Indeed, it is the existence or recovery of iodide uptake by thyroid cancer which provides the best opportunity for treatment with I^{131}. Finally, thyroid cancers in general are a very suitable material for the study of cancer dedifferentiation;as all the individual steps of specialized metabolism of the tissue can be investigated using isotopes of an element which is only metabolized in the thyroid, iodine. As a purely radiobiological model, the thyroid allows the comparison of various types and modes of delivery of irradiation either external (X, γ irradiations) or internal (β and γ irradiation of I^{131}, etc...).

"The interest of good biological models for the investigation of irradiation and cancer is obvious. Whatever the reasons, the practical questions that have to be answered concern estimates of the increase in tumor incidence following relatively low doses of radiation in much the same way that genetic hazards have been evaluated previously.
Even in rodents, we cannot hope to measure directly the increase in tumor incidence that is associated with doses of the order of 1 rad/year or less, so that extrapolations will have to be made from higher dose levels, on which data are already available or can be obtained in the foreseeable future. These extrapolations will of necessity be performed over a broad range, i.e., from doses of the order of hundreds of rads per year down to 1 rad/year or even lower. Actually, such extrapolations should be termed predictions, and the only way by which these predictionscan obtain reliability is to base them on a demonstrated knowledge of the mechanisms involved in the induction of tumors by ionizing radiation. Different experimental

systems and conditions seem to provide us with different answers, and, from all of these seemingly conflicting data, we must derive the main mechanisms of the carcinogenic process" (4).

Because of its scientific and medical interest, radiation induced thyroid carcinogenesis has been widely studied at the experimental and clinical level. However, neither the possible specific relations of thyroid biochemistry with the primary radiation lesion nor the application of present day concepts of cancerogenesis to the thyroid have been explored to any great extent. Furthermore in many of the available studies, the dosimetry has of necessity been inexact and consequently intercomparison of such data or using it to extrapolate to human problems is fraught with difficulty. The aim of the present monograph is to present, for the clinically oriented reader, a short and readable review of the clinical problem of thyroid irradiation followed by more detailed dosimetric, radiobiological and experimental cancerogenesis fundamentals, to outline and define the physiopathology of its consequences, the rationale for prevention and treatment, and the important questions still to be solved.

The clinical problems of thyroid irradiation and cancer have been extensively reviewed in L.J. Degroot "Radiation Associated Thyroid Carcinoma" (5), origins of human cancers in general in "Origins of Human Cancer" (2). Thyroid dosimetry and radiobiology have been treated by J.F. Malone (6), experimental thyroid carcinogenesis by K. Christov and R. Raichev (7), thyroid cancer in general in "Thyroid Neoplasia" (8) and in a full issue of "Annales de Radiologie" (9). Our present day knowledge on the clinical aspects of irradiation and cancer have been reviewed in a United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (10) and the experimental aspects in another UNSCEAR report (11). The biology of radiation is extensively discussed in"Biology of Radiation Carcinogenesis" (12). Sources of industrial, medical and environmental irradiations are described in UNSCEAR reports (13,14,15).

CLINICAL OVERVIEW

SECTION II IRRADIATION INDUCED PATHOLOGIC STATES OF THE THYROID GLAND IN MAN

Andre J. VAN HERLE

INTRODUCTION

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INTRODUCTION

The information available regarding the relationship between irradiation exposure of the thyroid gland and ensuing pathologic states is vast and has recently infiltrated the lay press in the United States. As a result, the irradiation effects caused by nuclear weapons and nuclear plants, as well as treatment modalities used for thyroid and other disorders in man, are constantly under scrutiny.

Experimental studies of radiation effects on the thyroid gland and the important issue of dosimetry will be discussed in separate chapters. The present review emphasizes the incidence and the clinical aspects of thyroid-induced disease following all forms of irradiation exposure, and, where possible, recommendations are made for subjects exposed to such irradiation. The first section deals with the functional disturbances induced by irradiation.

I. Hyperthyroidism and Ophthalmopathy

A transient, but occasionally severe form of thyrotoxicosis is sometimes seen in patients with Graves' disease following a therapeutic dose of radioactive iodine (^{131}I) (16,17). This is believed to be the result of a massive release of thyroid hormone caused by thyroidal injury following isotopic treatment. The state of thyrotoxicosis following ^{131}I administration is rare and usually temporary in nature.

A more permanent form of thyrotoxicosis, indistinguishable from the hyperfunction described in Graves' disease, has been recently reported by Wasnich and coworkers (18). These authors observed the occurrence of hyperthyroidism associated with ophthalmopathy in four patients and ophthalmopathy alone in three patients following external irradiation to the neck and cervical or axillary areas for neoplastic diseases. The disorders in these patients included breast carcinoma (2 cases), Hodgkin's disease (2 cases), laryngeal carcinoma (1 case), nasopharyngeal epithelioma (1 case), and histocytic lymphocytic lymphoma (1 case). The hyperthyroid state in the four cases was most likely not related to the involvement of the thyroid by the primary pathologic process which can also occasionally lead to a thyroid toxic state (19)

In the cases described by Wasnich and coworkers (18), the first symptoms of thyrotoxicosis were observed with a mean interval of 6 years after the irradiation therapy, and the ophthalmopathy developed between 18 and 84 months after the irradiation therapy. The fact that none of the five Caucasian patients tested revealed an HL-A8 type antigen (an antigen found in about half of the Caucasian patients who spontaneously developed Graves' disease (20)) suggested to these authors that thyroidal injury by x-ray therapy plays an important role in the etiology of a syndrome which is indistinguishable from Graves' disease, with the exception of the above mentioned histocompatibility antigens.

II. Hypothyroidism

A. Incidence of spontaneous hypothyroidism in a normal population

In order to discuss the incidence of primary hypothyroidism in patients who received external and/or internal irradiation therapy, it is important to assess first the incidence of spontaneous primary hypothyroidism in a population and its progression with age. A recent survey in the North American population indicated the incidence in newborns to be 0.017% or 1.7 per 100,000 (21). The true incidence of hypothyroidism with progressive age is not known, but a recent study by Turnbridge and collaborators in England (22) indicated it to be 0.8% in the total sample studied and 0.2% (females and males combined) in a community studied in Finland (23). The mean age at the time of the diagnosis in the English study was 57 years. An assumption is made that the increments of hypothyroidism are linear with advancing age.

From the data of these reports one can estimate the rate incidence of spontaneous hypothyroidism at 0.013% per year in a normal population. Everything exceeding this rate in a population would be in excess of the spontaneous incidence of hypothyroidism.

B. Incidence of hypothyroidism following external irradiation therapy

Table 1 summarizes the information concerning hypothyroidism following external irradiation from several studies

Table 1. Published Series of Radiation-Induced Thyroid Dysfunction Following External Radiation to the Neck (34)

Author and reference	Disease	Estimated thyroid dose (rads)	Period followup	Incidence of thyroid dysfunction	Thyroid functions tested
Felix et al (24)	Ca of larynx	11500 r in air	6 yr	1	BMR, ^{131}I uptake, cholesterol
Koulumies et al (25)	Ca of larynx	5000	1-14 mo	0/118(0%)	PBI, ^{131}I uptake
Greig et al. (26)	Ca of larynx	3700-6500	1.5-6 yr	0/20(0%)	PBI, ^{131}I uptake, 48 hr PB^{131}I
Markson & Flatman (27)	Ca of hypopharynx, breast; lymphoma	2900-4850	4 mo-3 yr	5	BMR, cholesterol, ^{131}I uptake
Einhorn & Wikholm (28)	Ca of larynx and hypopharynx	5700-6000	18 yr	3/41 (7.3%)	PBI, ^{131}I uptake $\pm$ TSH stimulation*
Bosch et al (29)	Ca of head & neck	2900-6600	1-3 mo	0/27(0%)	PBI, ^{131}I uptake & conversion
Glatstein et al (30)	Hodgkin's disease & lymphoma (post-LAG)†	4000-4500	1-5 yr	77/174 (44%)	TSH only
				25/174 (14%)	TSH, T_4, T_3. BEI. cholesterol
	Ca of head & neck (no LAG)	6000-6600	1-6.5 yr	2/9(22%)	TSH
Prager et al (31)	Hodgkin's disease (post-LAG)	3900-4600	6-12 mo	5/23(22%)	T_4, ^{131}I uptake $\pm$ TSH stimulation
Murken & Duval (32)	Ca of larynogopharynx	3800-5500‡	2-74 mo	8/12(66%)	T_4, PBI
		3800-7000§	2-74 mo	1/6(16%)	T_4, PBI
Brase & Sippel (33)	Ca of larynx	5500-7000	$\geq$ 5 yr	10/72 (14%)	PBI, T_3, T_4, ^{131}I uptake
Fuks et al (34)	Hodgkin's disease post-LAG	4000-5000§§	--	150/235 (64%)	T_4,TSH
	Non-Hodgkin's lymphoma post LAG	4000-4500§§	--	36/62(58%)	
	Hodgkin's and non-Hodgkin's lymphona post-LAG	--	--	2/14(14%)	
	Carcinoma of head & neck	5000-6500§§	--	20/52(38%)	

* ^{131}I uptake following TSH stimulation-decreased in all 41 patients.

† In another 48 patients, TSH before LAG and irradiation was within normal limits in 47. LAG-lymphangiogram

‡ Radiation followed by laryngectomy and hemithyroidectomy

§ No hemithyroidectomy

§§ Radiation dose to the neck (rads)

(24-34). Analysis of these data (excluding data from those patients who received a lymphangiogram) shows an incidence of 31 in 357 cases studied, or 8.6% In some of these studies additional factors besides irradiation played a role, such as the involvement of the thyroid gland in the original disorder. Also, the use of iodinated agents to perform lymphangiograms in patients with malignant disorders plays an important role in the genesis of hypothyroidism.

One study showed the high incidence of elevated serum thyroid stimulating hormone (TSH) levels which supposedly reflects decreased thyroid reserve or frank hypothyroidism and is dependent on the amount or irradiation that was delivered and the extent of the field which was used (30). It is likely that the incidence of hypothyroidism in patients whose thyroid has been exposed to external irradiation is higher than can be expected in a nonexposed population.

C. Incidence of hypothyroidism in Graves' disease treated with ^{131}I and ^{125}I.

A totally separate issue is the group of patients in whom ^{131}I therapy has been applied in a therapeutic attempt to control hyperthyroidism. The treatment of Graves' disease with isotopes of iodine has been extensively used in the management of the disorder. Follow-up studies after such therapy have scrutinized the functional as well as the anatomical state of the thyroid gland in these patients. The high incidence of hypothyroidism occurring after such treatment became apparent, and occasionally tumor development was reported (35-39)

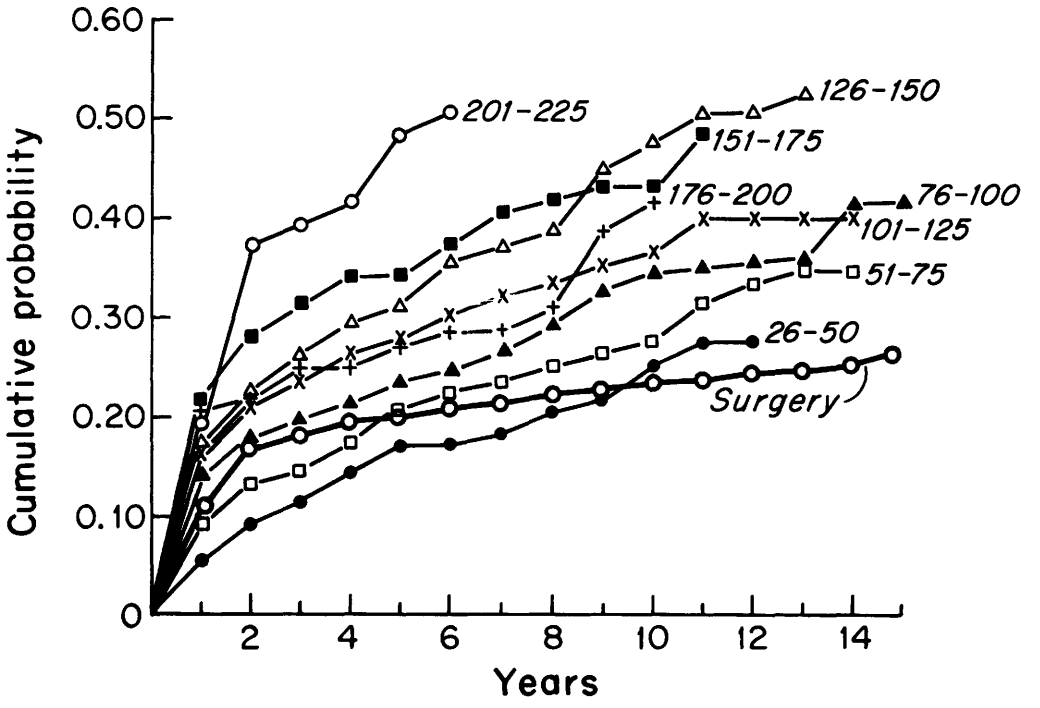


FIGURE 1. Probability of hypothyroidism with a single dose of ^{131}I for Graves' disease. The numbers indicate the dose of ^{131}I administered in microcuries per gram of thyroid tissue. (From Becker, D.V., et al In : Thyroid Research 1, 603-609, 1971 , with permission of the authors and editors) (35).

The present study reviews data dealing with the irradiation effects of ^{131}I and ^{125}I for therapeutic purposes in subjects with Graves' disease. Radioactive iodine (^{131}I) has been used for many years to control the hyperthyroid state of Graves' disease in man. In recent years the use of ^{125}I as an isotope to treat this disorder has been suggested because of the high incidence of hypothyroidism following ^{131}I therapy (35).

The results of the cooperative thyrotoxicosis follow-up study are summarized in Figure 1. This study indicates that the probability of becoming hypothyroid is the highest in the first 2 years after therapy and the cumulative probability increases continuously thereafter. This Figure also indicates that factors other than radiation play a role in the development of hypothyroidism after ^{131}I therapy. Indeed, the constant increment in the cumulative incidence of hypothyroidism is observed even following surgical therapy for Graves' disease. This is probably a reflection of the further deterioration of the function of the thyroid remnant due to the underlying autoimmune processes. The slope of the curve showing patients treated surgically suggests that a number of these patients may have become hypothyroid due to these underlying factors alone. The latter

is not a theoretical concept since the study by Wood and Maloof (40) demonstrates the development of hypothyroidism as a late sequel in Graves' disease patients treated with antithyroid drugs alone and suggests a rate of incidence of spontaneous hypothyroidism of the order of 0.7% per year. This figure has been quoted by others to indicate the rate of spontaneous hypothyroidism in a population with Graves' disease (41).

Becker et al (35) clearly indicate in their study that a positive relationship exists between the cumulative incidence of hypothyroidism and the ^{131}I dose retained by the pathologic Graves' disease gland (μCi/g of estimated thyroid weight). Indeed, a linear correlation between the radiation dose of the thyroid from ^{131}I and the probability of hypothyroidism above a dose of 2500 rem exists. Extrapolations suggest that a 60,000 rem thyroid dose would render all Graves' disease patients hypothyroid after 5 years. This dose is in close agreement with the mean dose of 49,000 rem required to render euthyroid cardiac patients hypothyroid with ^{131}I therapy (42).

Very few data are available concerning the lower doses of ^{131}I (<2500 rem). Rallison et al (43) found two cases of bona fide hypothyroidism in 1378 children exposed to ^{131}I fallout. The average dose delivered to the thyroid gland was 18 or 48 rems, depending on the estimate. When these data were compared with the incidence of hypothyroidism in non-radiated control groups (4 out of 3801), the difference was

not significant. A long-term follow-up study of the therapeutic use of radioactive iodine in children with Graves' disease, indicates the incidence to be 46% (44).

In order to avoid the high incidence of hypothyroidism with ^{131}I in children and adults, a trial with ^{125}I has been attempted in patients with Graves' disease (45-48). The concept behind ^{125}I therapy was derived from the characteristic features of the emitted electron irradiation of ^{125}I. The low penetrating potential in tissue of the majority of the electrons (less than 0.5 μm) and the fact that a small minority of the highest energy electrons travel up to 30 μm were thought to be of special importance in the thyroid gland. The ^{125}I located in the colloid should irradiate the hormonogenetic regions of the follicular cells much more than the nuclei or stroma. In contrast with ^{131}I, ^{125}I therapy should have a primary effect on the hormonogenetic part of the cell and less on the cell division. The nucleus would thus be protected from radiation sterilization which is regarded as the most important causal factor of radiation-induced hypothyroidism.

The first report by Greig et al (45) was encouraging, but did not definitely settle the issue of whether or not ^{125}I is more advantageous than ^{131}I regarding the long-term hypothyroidism state following treatment. Later studies reporte by the same group led to the conclusion that using ^{125}I in doses of 400 μCi/g of thyroid weight would provide better results than conventional doses of ^{131}I in the treatment of

Graves' disease (46,47). However, a recent review of 355 patients by the same authors showed that, after an average follow-up of 49.4 months, 63.4% of the total group of patients became euthyroid, 33.5% became hypothyroid, and 3.1% were still hyperthyroid (48). Therefore, in most published reports with a sufficient follow-up an unacceptable high incidence of persistent hyperthyroidism is found when the dose of isotope is too low, while a higher dose causes an increased incidence of hypothyroidism (see also Section V).

From these finding, it is concluded that ^{125}I should not be used for the routine treament of hyperthyroidism (48). The theoretical advantage of ^{125}I over ^{131}I as an isotope in the treatment of hyperthyroidism due to Graves' disease may become less appealing if one realizes that labelled ^{125}I thyroglobulin is eventually introduced into the thyroid cell as colloid droplets via the endocytic process. These colloid droplets, prior to hydrolysis of their content, travel towards the capillary site of the cell and consequently deliver radiation to the thyroid nucleus when in close proximity of the latter.

III. Thyroid nodules after irradiation of the thyroid gland

In order to evaluate the incidence of thyroid nodules in a given population exposed to irradiation, the following questions arise.

1. What is the incidence of thyroid nodules in a non-exposed population or in a population immediately prior to a planned irradiation (i.e., ^{131}I therapy for Graves' disease)?

2. What correlation exists between the number of nodules that develop in a given population treated with irradiation (external or internal) and the dose of irradiation given to the patient?

The answers to these two questions are discussed in this section in addition to the incidence of malignant nodules in normal and irradiated people.

A. Incidence of thyroid nodules in a control population

Several studies have attempted to provide figures on the incidence of thyroid nodules. These figures, however, are variable depending on the ages of the subjects studied and whether or not pathologic data have been included. Mortensen et al (49) found, in a post-mortem study, an incidence of 20.9% of palpable thyroid nodules (uni- or multinodular). The average age of this population was 60 years. Rallison and coworkers (50) who studied 2271 normal children in Arizona, found an incidence of 1.5%. The age of these subjects varied from 11 to 18 years. A recent survey by Trowbridge et al (51) of children between the ages of 9 to 16 years found the incidence of thyroid nodules to be 0.22%. The Framingham study reported an overall incidence of thyroid nodules of 4.2% (52).

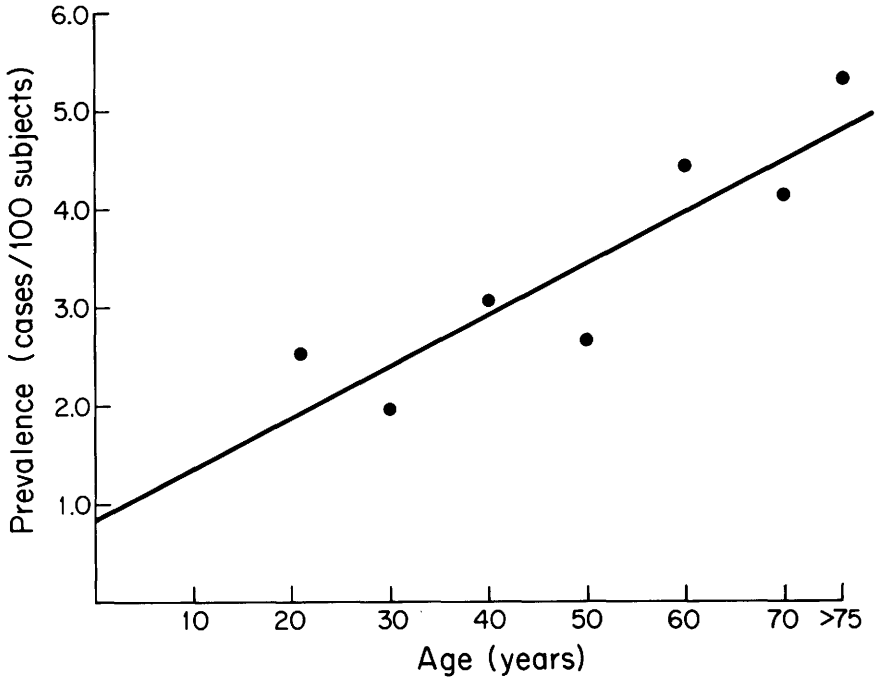


FIGURE 2. Prevalence of spontaneous thyroid nodules in an English population. A positive correlation (r=0.88) between the incidence of thyroid nodules and increasing age is observed (From Tunbridge, W.M.G., et al. Clin. Endocrinol. 7, 481 , 1977, with permission of the authors and editors) (22).

The data obtained in a recent study carried out in England by Turnbridge et al (22) is shown in Figure 2 and indicates that a good correlation exists between the advancing age of the participating subjects, both male and female, and the increased incidence of thyroid nodularity discovered. These data may provide a partial explanation of the discrepancy between the low incidence of thyroid nodules in a young population (50,51) and the higher incidence found by Mortensen et al (49). Also, the varying methodologies used in studying these separate groups certainly contributed to the differences.

The spontaneous rate of incidence of nodules in the general population was calculated recently by Maxon et al (41) on the basis of data in the literature and was estimated to be 0.08% per year; the rate of incidence of thyroid malignancies was estimated to be 0.01% per year. The latter figure is higher than the 0.004% per year suggested by the Second and Third National Cancer survey which is largely based on death certificates and the Cancer registry data (53).

B. Incidence of thyroid nodules and thyroid cancers in Graves' disease

For several decades, ionizing radiation has been employed as a form of therapy for Graves' disease. Thus, an evaluation of any thyroid nodule present is indicated prior to such therapy.

Dobyns and coworkers (39) reported that 15.5% of the patients with surgically treated Graves' disease had palpable thyroidal nodules. The mean age of this group was 40.1 years. The incidence of spontaneous thyroid nodules in subjects who were about to be treated with radioactive iodine was 16.4% in the same study, but the mean age was higher at 49.7 years. These figures are certainly higher than the 2.9% incidence reported in the normal population in a British study with a similar mean age (22). The spontaneous total rate of incidence of palpable nodularity in patients with Graves' disease is estimated to be 0.36% per year, and the rate of incidence of malignant palpable nodules is 0.002% per year (41).

The incidence of thyroid nodularity post-treatment with ^{131}I was also analyzed by Dobyns et al (39). In this study 16,042 cases of patients with Graves' disease were analyzed. The authors found that 86 subjects who had no palpable nodules at the time of ^{131}I therapy had detectable nodules later at surgery. Of these 86 patients, 9 had a malignancy, that is 10.5% of the operated group. Since 494 additional patients had developed a nodule after ^{131}I therapy, but had not undergone surgery yet, one could assume that an equal incidence of carcinoma occurred in these nonoperated cases with nodules. An additional discovery of 52 cases of thyroid malignancies leads one to estimate the rate of incidence of thyroid cancer at 0.05% per year and a total rate of incidence of nodularity of 0.45% per year.

If the data reported by Safa et al (44) are combined with the cases reported by the Cooperative Thyrotoxicosis follow-up study, a total of 304 children treated with ^{131}I was analyzed. In this group 17 cases were found with benign nodules and 2 with carcinoma. Follow-up time and doses received in these patients were, respectively, 11 years and 9000 rem. The observed rate of incidence of cancer is consequently 0.06 cases per million persons per rem per year, a mean value that is not different from normal values in the adult population (0.05 cases). The absolute risk of nodularity in contrast is 0.23 cases per million persons per rem per year which is slightly higher than the adult group (0.11 cases)(41). Sheline et al (37) and Dobyns et al (39) both called attention to the propensity of young individuals for the development of nodules after treatment with ^{131}I.

In adults receiving ^{131}I ablation (32,000 rem (39)) for cardiac disease no nodules were found in 20 patients who were euthyroid before ablation (54,55). In a group of children exposed to small doses of ^{131}I from fallout (46 rem) Rallison et al (43) found no difference in the prevalence rate of benign and malignant nodules when compared with a control population in a 14-year follow-up study.

The incidence of death from thyroid carcinoma was compared by Dobyns et al (39) in patients treated with surgery and those treated with ^{131}I for Graves' disease. Their data indicate that the risk of death due to thyroid neoplasm in

Graves' disease is indeed small and does not differ between the modalities of treatment used. Although the risk of development of malignant tumors in a population is low, the relative high risk of the young patients to develop nodularity after ^{131}I therapy indicates that a long-term follow-up of these patients remains necessary.

C. Incidence of nodules and tumors in patients exposed to external radiation therapy

1) Accidental or nuclear weapon exposure

Since the use of atomic weapons in Hiroshima and Nagasaki, several studies have shown that survivors have been exposed to substantial amounts of irradiation and have developed a number of malignant tumors including thyroid carcinoma. A study conducted by Jablon et al (56) found a high incidence of thyroid carcinoma in a subsample of the population.

In March of 1954, the Marshall Islands were accidentally exposed to fallout radiation from the detonation of a high yield thermonuclear device during experiments at Bikini in the Pacific Proving Grounds. The inhabitants of Rongelap Island received the largest fallout exposure (175 rads of whole body gamma irradiation) (57). In addition to the gamma rays, these subjects were exposed to iodine isotopes as the result of the fission process. The average thyroid dose received for an adult in the island of Rongelap, including the gamma dose, is calculated to have been 335 rads. The thyroid dose

delivered to a 3-year old child on the island was calculated to be in the range 700 to 1400 rads. The first effect observed after this exposure of radiation was stunted growth in two boys who had developed symptoms of myxedema, and demonstrated low serum thyroxine levels. Nine years after the exposure, the first thyroid nodules were found in a 12-year-old girl. Subsequently, thyroid nodules developed in subjects of other less exposed islands. At present, 40 of the 243 exposed Marshallese or 16.5% are affected. Recent studies have shown that, in addition to the nodularity, the incidence of hypothyroidism is high (50%) in the Rongelap group.

The latency of tumor occurrence appears to be dose related with a period from 11 to 22 years. Analysis indicates that thyroids receiving lower doses developed tumors later than those receiving higher doses. This inverse relationship between thyroid dose and latency had not been observed in x-ray treated children (58). Since the latent period for the development of thyroid tumors may be as long as 30 years, long term follow-up studies will probably disclose further abnormalities of thyroidal function and structure.

2) External irradiation in man for therapeutic purposes

Since the early decades of this century, external radiation was delivered to anatomical sites such as the

thymus (59) and the tonsils (60), to treat the so-called "status lymphaticus" and chronic tonsillitis or pharyngitis. Later, dermatologic conditions, such as hemangiomas and acne vulgaris, were added to the list of therapeutic indications. In 1950 Duffy and Fitzgerald (61) suggested the existence of an etiologic link between a previous history of childhood irradiation to the thymus and the occurrence of thyroid carcinoma. Since that report, a number of investigators studied subjects who had received irradiation for thymic hyperplasia and other benign conditions (58, 62-68). Factors, such as sex, irradiation dose, and age at treatment, are important variables in the evaluation of subjects affected by this treatment.

The mean dose of irradiation delivered is variable. Hempelmann et al (58) studied a group of subjects who received x-ray treatment during childhood and reported in his fourth survey in 1975 on 2872 subjects who received an average air dose of 225 R and an average thyroid dose of 119 R. In subgroup C, reported in this same survey, a substantially higher air dose was used (461 R) with an average thyroid dose of 399 rads. A higher amount of irradiation was delivered to the 261 patients in this subgroup via larger anterior and posterior ports. A smaller study published the same year by Refetoff et al (66) disclosed an exposure to a mean dose of 388 rads in 30

subjects who were treated for thymic hyperplasia. Patients in this study were irradiated to the tonsils or to the face for acne and received a substantially larger mean dose ranging from 860 rads (tonsils) to 1500 rads (tonsils and adenoids). Finally, a large study conducted by Favus et al (67) on 1056 patients who received irradiation for various inflammatory diseases of the upper respiratory tract disclosed that a mean total dose of 807 rads was used in the subjects who were irradiated to the tonsil and pharyngeal site. These studies indicate the possibility of a wide variability in the irradiation dose to which the thyroid was exposed. Of interest is the study of Modan and collaborators (68) where irradiation was administered to the scalp for tinea capitis and where doses to the thyroid were estimated to be only 6.5 rem (68). Of note is that thyroid carcinoma has been reported in subjects who have been irradiated for other benign skin conditions such as hemangiomas (66, 69) and acne of the face (70).

If the various studies mentioned above are analyzed (58, 62, 65-68) it is possible to observe that the incidence of thyroid nodules and thyroid cancer is increased, when compared with a control population. Recently, the data of Colman et al (71), Modan et al (72), Albert et al (73), and Hemplemann et al (58) were combined and analyzed by regression analysis (41). This analysis revealed that

there was a good correlation between the incidence of thyroid nodules and thyroid cancer on the one hand and the total dose in rem received by the thyroid gland on the other. Absolute risk for the thyroid cancer and total nodules appeared to be 4.2 and 12.3 cases per million/rem/year, respectively.

It is also clear that the 33% incidence of thyroid cancer in subjects who received irradiation and underwent surgery because of the presence of a detectable lesion (67) is higher than that reported in the American autopsy series (13%) accumulated by Nishiyama et al (74). The incidence, however, is lower than that found by Sampson et al (75) (28.4%) in a Japanese population and Fukunaga et al (76) in Hawaii (24%). From studies previously reported (77 - 79), it is apparent that the incidence of thyroid cancer is low when the irradiation dose administered exceeds 2000 rem. To explain this phenomenon, one must assume that the protective mechanism is based on complete destruction of the mitotic capability of thyroid cells.

The type of histologic lesions encountered in radiated subjects who subsequently underwent surgery are shown by the data in Table 2 (67). Of interest is the fact that in this study 49 of the 60 cases who were operated on had a thyroid tumor smaller than 15 mm which was consequently considered as occult thyroid carcinoma or

Table 2. Histologic Diagnoses in Subjects Operated on.

Diagnosis	No. of Cases	
Carcinoma	60	
Papillary		23
Papillary-follicular		34
Follicular		3
Benign	120	
Multiple adenomas		86(40)†
Single adenoma		18(6)
Hürthle-cell tumor		3(3)
Colloid cyst		10(2)
Thyroiditis		3(15)
Other*	2	
Hyperplastic lymph node		1
Schwannoma of recurrent laryngeal nerve		1
Totals	182	

*Associated with normal thyroid histology

†Figures in parentheses indicate secondary diagnoses in subjects with >1 histologic diagnosis.

(From Favus, M.J., et al. N Engl J Med 294:1019, 1976. Reproduced with permission of the authors and editors) (67).

"minimal carcinoma." Twenty-one of the carcinomas found were smaller than 0.6 mm and were discovered neither by palpation nor by scan. Of additional interest is that in this study by Favus (77) 72% of the thyroid carcinomas were actually associated with benign adenomas. Distant metastases were not observed, but lymph node involvement was present in 28% of the patients who underwent surgery (table 3).

The average latency of the malignant tumors is variable. In the study of Hempelmann et al (58) the minimum latent period was 5 years for thyroid cancer and 10 years for benign lesions. The data reported by these authors also suggest that with smaller doses of irradiation there was a longer latency period before benign lesions developed. In the study by Favus et al (67) the mean latency in the examined group was 27.5 years year. They define latency as the length between the time of therapy and the year of 1974 when their survey was conducted. The latency in the study of Refetoff et al (66) was comparable, namely 24.4 $\pm$ 5.2 years.

It is apparent from the studies of Hempelmann et al (58) that the incidence of thyroid nodules predominates in females. The female:male ratio was 1.9:1 for malignant thyroid lesions and 2.3:1 for benign lesions in that study. In subgroup C a higher incidence of thyroid cancer was found in the Jewish population (7.2%) than in

Table 3. Characteristics of Thyroid Carcinomas in Irradiated Subjects

Characteristics	Totals	Papillary tumors	Mixed papillary & follicular tumors		Follicular tumors
All cases	60	23	34		3
Size of largest tumor:					
Microscopic	15	10	4	*	1
1–5 mm	6	3	3		0
6–15 mm	28	6	20	*	2
>15 mm	11	4	7		0
Coexisting benign tumors	43	21	22*		2
Centricity:					
Unicentric	32	19	10		3
Multicentric	28	4	24†		0
Lobes involved					
1	45	20	22		3
Both	15	3	12		0
Thyroid-capsule invasion	12	1	10*		1
Blood-vessel invasion	5	0	4		1
Lymph-node involvement	17	2	15*		0

*$P < 0.05$ by chi-square analysis (papillary vs mixed)

†$P < 0.01$ by chi-square analysis (papillary vs mixed)

(From Favus, M.J., et al N Engl J Med 294:1019, 1976. Reproduced with permission of the authors and editors) (67).

the non-Jewish population (2.9%). The fact that the Jews in subgroup C were 1 year older and had received a slightly higher dose of irradiation did not explain the higher incidence of thyroid carcinoma in this population.

IV. Methods of Evaluation in Subjects with a History of Irradiation Exposure

A. Necessity of evaluation

A number of screening programs have been established in the United States to recall subjects who had received external irradiation in the past (66, 67). Since the number is large, this represents a serious problem. The proceedings of a recent Conference in Chicago (5) devoted to the subject clearly stated that the screening programs are justified, and recommendations were made concerning the diagnostic techniques to be utilized to analyze the subjects at risk. These methodologies are summarized hereafter.

B. Clinical evaluation

The physical examination of the neck area with special attention to the thyroid is considered of primary importance. However, one must bear in mind that up one-third of the small thyroid cancers (< 6 mm) reported by Favus et al (67) were undetectable by the thyroid scan and by physical examination. In addition, non-thyroidal tumors of importance developed, such as salivary gland tumors (81) and parathyroid adenomas (82,83). Whether or not thyroid

scans should be used in addition to physical examination, to detect lesions in exposed patients was extensively discussed at the previously mentioned symposium (80). It is certainly true that a certain percentage of thyroidal lesions, which could not be uncovered by physical examination alone, is picked up by such techniques.

Discrete regions of increased or decreased radionuclide uptake were identified in 278 scintigrams or 26.3% in the study of Favus et al(67). The scintigraphy of the thyroid failed, on the other hand, to demonstrate in a small percentage of cases an abnormality which was found on physical examination. The data seem to indicate that the use of scintigraphy on a first visit basis may be a useful tool to investigate patients exposed to neck or chest irradiation in the past. Subsequent follow-up evaluations should not include scintigrams except in those subjects where new palpable abnormalities became apparent The isotopes of choice with which to perform these studies are ^{123}I and ^{99m}technetium (80).

Physical examination is required on a yearly basis or when lesions develop because of the latency shown by these tumors. As far as other tests are concerned, no specific markers for thyroid tumor differentiation are available. The measurement of serum thyroglobulin (Tg) has been extensively investigated in the patients who had been exposed to irradiation previously (84). The conclusion reached by these authors indicate that there is a difference

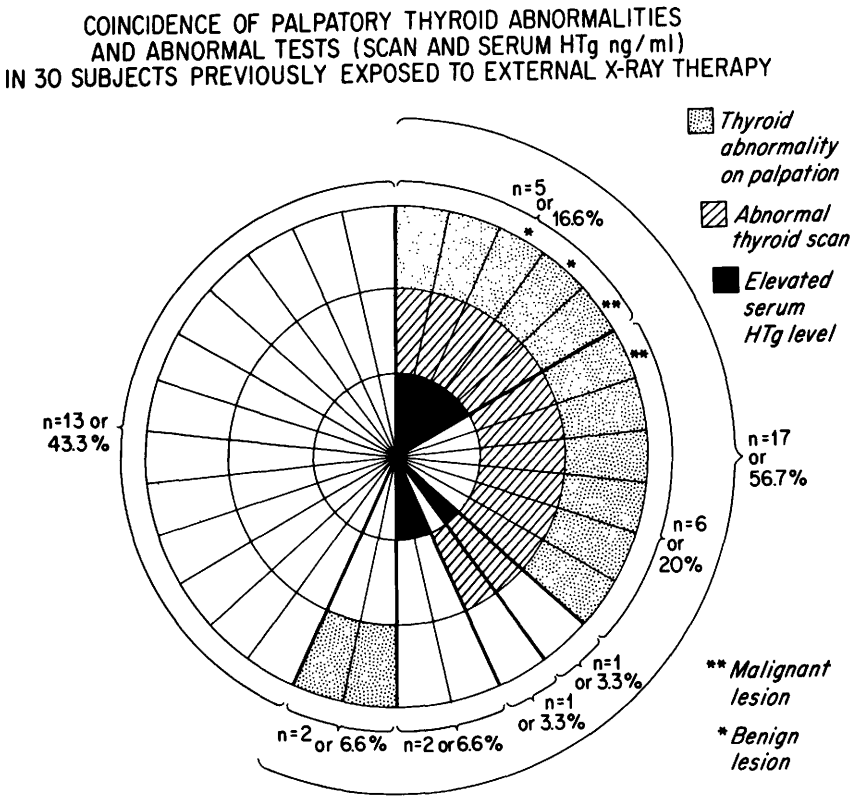


FIGURE 3. Incidence of abnormal tests in patients who received external x-ray therapy in the past. White areas represent normal findings or tests. Note that 56.7% of this small population had one or another abnormal finding.

in plasma thyroglobulin levels when subjects with nodules in the thyroid gland are compared with those without such lesions in the thyroid gland. However, the measurement of Tg does not allow a distinction between those patients who have a benign or a malignant tumor of the gland. Consequently, the assay provides no information regarding the histologic classification of the lesions. Of importance, however, is the fact that a subgroup of subjects was found representing 13% of the population analyzed in which an elevated plasma thyroglobulin is found in subjects with otherwise normal thyroid glands. Whether or not these patients represent a high risk subgroup among the irradiated population is not known and will only become apparent after prolonged follow-up studies.

Additional studies performed in our own institute concerning testing procedures concur with the findings of Schneider et al (84). Indeed each individual test, including a palpation of the thyroid gland, when applied to subjects who have received irradiation in the past, will reveal abnormalities in certain subjects that will not be revealed by other tests (Fig. 3) (85).

V. Treatment

A. Surgery

Once a lesion is detected in the thyroid of a patient who has received external irradiation, most experts would agree that surgery is mandatory. The final conclusions

of the conference in Chicago (80) can be summarized as follows:

1. A nodule greater than 1 cm or a dominant nodule in a multinodular goiter should be considered for surgery.

2. Pre-operative suppressive therapy is not necessarily recommended but may be selected by the surgeon to render the operation technically easier.

3. Total lobectomy and isthmectomy of the affected lobe with subtotal thyroidectomy on the contralateral lobe is considered a minimal operation for a benign or malignant nodule.

4. Total thyroidectomy is recommended if obvious metastatic disease or bilateral disease is present.

5. Modified neck dissection should be used if involvement of the lateral lymph node chain is present.

6. Thyroidectomies should only be performed by experienced surgeons in the field.

7. Postoperative thyroid ablation with ^{131}I depends on the individual and should be used: a) when obvious residual tissue is present in the neck, or b) when suspicious disease is present in the neck or metastases are present in the neck or elsewhere.

Since patients will have permanent hypothyroidism after surgery, the administration of thyroxine is indicated.

B. Thyroid hormone therapy

Three possible indications for administering thyroid hormone to suppress thyroid function after irradiation can be summarized as follows : 1) to prevent the development of new nodules or neoplasma, 2) to shrink existing nodules, and 3)to prevent further growth or neoplastic transformation of such nodules.

The experimental evidence obtained in animals indicates that radiation-induced thyroid tumors are prevented by TSH suppression. On the basis of these experimental data, the following recommendations were made by the panel at the Chicago Conference (5,80).

1) Patients with normal thyroid glands who had been exposed to sufficient amount of irradiation during childhood or adolescence be considered for the prophylactic administration of thyroid hormone.

2) In patients in whom thyroid abnormalities have developed and who are considered for surgery, a trial with hormone administration to shrink the nodule may be considered. Usually this therapy should not exceed 6 months.

3) All patients with radiation-related abnormal thyroid glands, who for some definite reasons cannot undergo surgical excision, should receive suppressive therapy with thyroid hormone.

4) All patients who have been thyroidectomized should receive thyroid hormone therapy.

5) Therapy with any form of thyroid hormone is acceptable, and a full replacement is the goal.

These recommendations also obviously apply largely to the patient who has been exposed to other forms of irradiation in whom a nodule develops.

CONCLUSIONS

From the analysis presented in the present chapter, it is clear that in any form of irradiation therapy used in man, be it internal or external or administered therapeutically or accidentally, long-term sequelae must be expected. The development of nodules (benign or malignant) is of great concern, and a physician should definitely request information with respect to previous exposure to irradiation when a patient presents with this clinical problem. Such information is sometimes difficult to obtain since the irradiation often occurred in early childhood and many of the patient records are not available for scrutiny. One important rationale for evaluating these patients is that the irradiation can lead to functional, as well as structural abnormalities of the thyroid gland which are likely to occur with a great latency.

At the present time, it is not known whether these lesions continue to occur with a certain frequency beyond 25 and 30 years after irradiation. However, it must be assumed that continuous development of tumors occurs in these patients and that a careful physical examination to evaluate Their metabolic status as well as the structures in the neck is

required to detect any structural or functional abnormalities. Therapy must ensue in cases where definite structural or functional abnormalities are present.

In view of the significant incidence of radiation-induced thyroidal disorders, careful exclusion of the thyroid from radiation fields, is indicated whenever feasible.

BASIC SCIENTIFIC CONSIDERATIONS

RECENT DEVELOPMENTS IN DOSIMETRY OF RADIONUCLIDES IN THE THYROID

SECTION III

J.F. MALONE

I. Introduction.

II. Physical Aspects of Dosimetry

A. The Traditional Method.

B. The Revised MIRD Schema.

C. Nuclear Disintegration Data.

III. Determination of Thyroid Parameters.

A. Thyroid Mass

B. Cumulated Activity

1) Uptake

2) Effective Half-life

C. New Methods of Determining Cumulated Activity.

IV. Microdosimetric Considerations in the Thyroid

A. Influence of Mass

B. Interfollicular Inhomogeneities

C. Inhomogeneities at the Cellular Level.

V. Doses to the Thyroid in Practice.

1. INTRODUCTION.

The thyroid is probably the internal organ that is most frequently subjected to significant doses of ionizing radiations. This has already been illustrated by other contributions to this volume and is reinforced by Table 1, which highlights the glands' susceptibility to irradiation by nuclides of iodine. The circumstances in which exposure can occur range from occupational exposure and nuclear accidents (86,87) through a wide range of diagnostic medical procedures that may or may not involve the gland itself (88,89) to therapy of hyperthyroidism and thyroid carcinoma (90,91).

Despite the widespread irradiation of the gland in medical procedures and its high susceptibility to accidental irradiation, the dosimetry of nuclides of iodine in it and its radiobiological response have not been exhaustively studied (6). The reasons for this are difficult to assess, but probably relate to the feeling that thyroid dosimetry is technically difficult, if not impossible. Furthermore, many workers have been of the opinion that the radiobiological response of the gland is inherently unstable and unpredictable (92). Hence the value of good dosimetry, even if it were achievable , has been regarded as questionable. This line of reasoning eventually led to both thyroid dosimetry and radiobiology becoming trapped in a closed loop. The radiobiology could not be explored quantitatively as the dosimetry was poor, and the dosimetry was not refined and developed because the available radiobiology did not suggest well defined patterns of response. This loop has recently been broken, as there are now reasons to believe that the radiobiological response of the gland is relatively well defined (6,93-96,99). In view of this, and the substantial radiation burden to which the gland is exposed, the case for attempting to refine thyroid dosimetry by applying modern techniques and knowledge to it, is a strong one.

This chapter attempts to bring developments in the basic physics of dosimetry and the techniques of measurement that are particular to the thyroid together.

NATURE OF PROCEDURE		RADIATION TYPE
Therapeutic Medical	Treatment of thyroid carcinoma	^{131}I
	Treatment of Hyperthyroidism	^{131}I and ^{125}I
	Partial or Complete inclusion in Radiotherapy Fields	X and γ Rays
Diagnostic Medical	Radionuclide Scanning	$^{99}Tc^{m}$, ^{131}I, ^{123}I
	Uptake Tests	^{131}I, ^{125}I, ^{99m}Tc, ^{123}I
	Iodine Kinetics	^{131}I, ^{125}I, ^{99m}Tc, ^{123}I
	Uptake of Nuclides used to investigate other organs	Multiple
	Partial or Complete Inclusion in Diagnostic Radiology Fields	X-Ray.
Occupational Exposure and Nuclear Incidents	Ingestion of Materials	Multiple, Principally nuclides of I and T_c
	External Irradiation	Multiple

TABLE 1: Circumstances in which Thyroid is irradiated.

Initially the basic physical considerations that are important in good dosimetry are outlined, paying particular attention to the scheme followed by the Medical Internal Radiation Dose (MIRD) Committee in the U.S.A. (97,98). This is followed by a discussion of the measurements which must be performed to apply the scheme to the thyroid, including some novel approaches to determining the integral under the activity - time curve. The complex distribution of iodide in the thyroid requires that the microscopic distribution of dose be studied, and this is outlined in Sections III,IV. Finally the sizes of doses encountered in practice are reviewed. The consequences of these doses including radiation induced neoplasia and broader aspects of the gland's radiation response are discussed in Sections II and V.

II. PHYSICAL ASPECTS OF DOSIMETRY.

The physical aspects of dosimetry outlined in this section relate to how absorbed dose calculations are performed for a nuclide distributed through a thyroid assuming that both its mass and radionuclide kinetics are known. The methods used to determine the latter parameters in practice are discussed in the next section. The approaches available for determining the dose due to internally distributed radionuclides may be broadly divided into two categories. (Table 2). They are the traditional approach due to Marinelli (100,101) and the Revised Schema due to the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine in the U.S.A. (97,98).

The traditional method separates the dosimetry of electrons (β^+, β^- etc.) from that of photons (X and γ-rays). It has been widely used with ^{131}I in the thyroid, (102-104). Although in many cases the data available to support it are not extensive, it is still popular and is frequently cited in the thyroid literature (102,105). The MIRD scheme unifies the dosimetry of photons and electrons in a conceptually simple way (97,98). Furthermore, extensive documentation has been produced to support application of this system in humans (106-114). Both methods are outlined below, together with details of nuclear disintegration data appropriate for use in dosimetry and a brief discussion of the new S.I. Radiation Units, in so far as they are relevant to the material in hand. It is important to note that both methods assume that the activity giving rise to the dose is uniformly distributed through the volume of interest. Frequently this will only be approximately true in the thyroid. The consequences of non-uniform distribution of activity will be discussed in IV.

A. The Traditional Method.

In the traditional method the dosimetry of electrons and photons is considered separately. Electrons (β^+, β^-, etc) emitted by most commonly used nuclides have such a short range in tissue that they may be assumed to

METHOD	* FORMULAE	DOSE FROM ^{131}I for 1 μCi/g
Traditional (Marinelli)	β Dose = 73.8 C T_{eff} $\overline{E}_{\beta}$ γ Dose = 0.0332 C T_{eff} $I\chi_{\delta}^{\overline{g}}$	100.9 rad
MIRD	Dose = A Δ Φ or = Q τ S	106.2 rad

* The formulae are discussed in detail in the text.

TABLE 2 : The Traditional and MIRD approaches to dosimetry with a typical thyroid dose calculated by each method.

be totally absorbed in adult human organs in which they are emitted (101,103, 115). Hence it is commonly assumed that an organ containing a β-emitter absorbs all the energy associated with the emitted β particles. Using this assumption the absorbed dose from a nuclide completely decaying in an organ is (Tables 2 and 3):

$$\text{Dose} = 73.8\ C\ T_{eff}\ \bar{E}_{\beta} \quad \text{rad}$$

where the symbols in the equation are defined as follows:

C: Concentration of radionuclide in the organ, in μCi/g.

T_{eff}: Effective Half-Life of the nuclide in the organ of interest, in days. (This is a composite of the physical half-life T_p and the biological half-life T_b, and is equal to $T_p\ T_b\ /(T_p + T_b)$).

$\bar{E}_{\beta}$: Mean β energy emitted per nuclear disintegration, in MeV

The definition of these parameters, and numerical values associated with them for ^{131}I in the thyroid, are summarized in Table 3.

Photons of X and γ-radiation are much more difficult to absorb than β-particles. They are rarely completely absorbed even in large organs. To allow for this in dosimetry calculations a factor $\bar{g}$ is defined and used to account for the proportion of the photon energy that will be absorbed in a given organ of specified composition and geometry(103,116). The quantity $\bar{g}$ is frequently referred to as the "geometrical factor", since it will obviously depend on the size and shape of an organ. It is difficult to compute accurately, as it is a volume integral containing terms to account for the effects of absorption and the inverse square law(6,103). However, it has been evaluated for idealized shapes such as cylinders, and tables of values are available that may be used with nuclides emitting photons whose energy is in the range 60 keV to 2 MeV.(103,116,117). Outside this range special calculations must be made for each particular case as no general approach has been developed.

Using $\bar{g}$ the absorbed dose from photons emitted by a radionuclide in organ is (Table 2 & 3):

SYMBOL	SHORT DESCRIPTION	UNIT	TYPICAL VALUE
C	Initial Activity/Unit Gland Mass	μCi/g	Depends on Administered Dose
T_{eff}	Effective Half-life	days	6-7 *
$\overline{E}_{\beta}$	Mean β energy per nuclear disintegration	MeV	0.180 to 0.188 *
I_{γ}	Specific γ-ray Constant, i.e. Dose Rate at unit distance from unit activity.	$RmCi^{-1}hr^{-1}cm^{-2}$	2.18*
$\overline{g}$	Geometrical Factor to account for absorption of γ-rays in gland	cm^2	15.7

* for ^{131}I only.

TABLE 3: Parameters associated with the traditional method of calculating dose from radionuclides.

$$\text{Dose} = 0.0332\ C\ T_{eff}\ I_{\gamma}\ \bar{g}\quad \text{rad.}$$

where C, T_{eff}, $\bar{g}$ are defined as above and I_{γ} is defined as follows:

Iγ : Specific Gamma Ray Constant, that is the exposure dose rate at unit distance from unit activity. In this case it is specified in Roentgens per mCi- h at 1 cm.

These parameters and numerical values associated with them for ^{131}I in the thyroid are summarized in Table 3. The value 0.0332 for the constant in the above equation is slightly less than the value 0.0346 sometimes quoted. The difference is accounted for by a factor 0.96 used to convert Roentgens in which I_{γ} is specified to rads,in which absorbed dose is quoted (118).

The combined dose from a β-γ emitting nuclide in the thyroid is therefore given by

$$\text{Dose} = 73.8\ C\ T_{eff}\ \bar{E}_{\beta} + 0.0332\ C\ T_{eff}\ I_{\gamma}\ \bar{g}\quad \text{rads}$$

Inserting the values for the parameters quoted for ^{131}I in Table 3, and assuming that the initial concentration of activity is 1 μCi/g and that the effective half-life is 7 days,gives a β-dose of 92.98 rad and a γ-dose of 7.95 rad. Thus the total dose is 100.9 rad (Table 2). The fact that the absorbed dose in the gland is about 100 rads for an activity of ^{131}I of 1 μCi/g may be used as a useful aide memoire(93). In many respects the traditional method of dosimetry outlined here has been superseded by the MIRD approach. Nevertheless, it is still necessary to be aware of it for a number of reasons. For example, it is still used and most of the thyroid dosimetry presented during the last 30 years is based on it (6,105). Furthermore, the fact that the results it gives are slightly different from those obtained with the MIRD scheme is of importance when surveying earlier literature.

B. The Revised MIRD Scheme.

In 1968 the MIRD Committee published the first in a series of pamphlets that outlined a revised scheme for calculating the absorbed dose from biologically distributed radionuclides (97). The original publication has been followed by comprehensive support literature on the dosimetry of photons

and electrons, nuclear disintegration scheme data, and applications to a particular adult human phantom (106,114). The committee has also prepared a series of reports on dose estimates from particular radionuclides, and those on $^{99}Tc^{m}$ and iodine are particularly relevant to the thyroid (119,120). Recently the scheme has been updated and improved to render it easier to use and to take explicit account of biological models in dose calculations (98,114).

The scheme initially appears complex as it is presented using a formal mathematical approach (97,98). For example exact definitions of and suitable symbols for about 30 quantities or units are required. These define the radiation type, the absorbing material, the source and target organs and basic physical quantities. In the interests of brevity this discussion will be confined to the three central concepts in the method, and two new concepts recently introduced to simplify usage. Well presented introductions of a more detailed nature have been published (122-123), and are helpful when approaching the primary literature (97,98).

In the MIRD scheme the absorbed dose from a biologically distributed radionuclide is computed as the product of three factors as follows (Table 2):

Dose = { Concentration of Radionuclide X Duration of its Presence } Symbol $\tilde{A}$

X { Energy Emitted by a unit concentration of the nuclide present for unit time. } Symbol Δ

X { Fraction of the emitted energy absorbed in a unit mass of the organ being examined } Symbol Φ

$\therefore$ Dose = $A \Delta \Phi$ rad

The three components in the dose equation will be briefly discussed outlining their main features.

The quantity $\tilde{A}$ is referred to as the "Cumulated Activity". In essence

it is the integral under the activity-time curve for the organ and nuclide in question, and is specified in units of microcurie-hours (μCi-h). One μCi-h of cumulated activity could be the consequence of, for example, a mean activity of 1 μCi being present in an organ for 1 hour, or a mean activity of 0.1 μCi, being present for 10 hours. In an organ which instantaneously takes up a single bolus of Q μCi and eliminates it with an effective half life of T_{eff} hours the cumulated activity is

$$\tilde{A} = 1.44\ Q\ T_{eff} \quad \mu Ci\text{-h}.$$

The second term Δ in the dose equation above is the total energy emitted by the nuclide for 1 μCi-h of cumulated activity. This is sometimes referred to as the "equilibrium dose rate constant" (97,98). Obviously Δ will be the sum of the energies of the individual photons and particles emitted by the nuclide during transformation. As such it is frequently written as

$$\Delta = \Delta_1 + \Delta_2 - - + - - - \Delta_i - - + - - \Delta_n$$
$$= \sum_i \Delta_i$$

where Δ_i is the energy associated with the i th photon/particle emitted. The individual values of Δ_i must take account of both the energy (E_i) of the emission involved and its relative abundance (n_i) in the disintegration process. When due account is taken of the change in units Δ_i can be written as

$$\Delta_i = 2.134\ n_i\ E_i$$

and hence

$$\Delta = 2.134 \sum_i n_i\ E_i$$

Extensive tables of values for Δ_i, n_i and E_i have been compiled (112).

The units in which Δ is expressed are rather unusual (Tables 4 and 10). Its basic definition is as energy emitted per μCi-h. However, the unit of energy used is not one of the conventional ones such as the Joule or MeV. Instead a unit based on the definition of radiation dose is applied. This is the gram-rad (g.rad) and is the amount of energy deposited by a dose of 1 rad in a mass of 1 g. Therefore, the unit in which Δ is specified is g.rad per μCi-h. When the S.I. System of Units is adopted in radiation studies

SYMBOL	SHORT DESCRIPTION	UNITS
A	Cumulated Activity = Integral under Activity - Time curve	μCi-hr
Δ	Equilibrium Dose Rate Constant - Energy Emitted per μCi-hr.	$\frac{g - rad}{\mu Ci-hr}$
Φ	Specific Absorbed Fraction = Fraction of Emitted energy abosrbed per g of absorber	g^{-1}
S	Absorbed Dose per unit Cumulated Activity	rad/ μCi-hr
τ	Residence Time (see text)	hr
Q	Administered Activity	μCi

TABLE 4: Parameters associated with the MIRD method of calculating dose from radionuclides.

ENERGY MeV	ORIGIN
0.179 to 0.180	Mean Energy of β particles per Disintegration
0.188	Mean Energy of Principal β Particle Emitted during disintegration.
0.192	Mean Energy of β particles, internal conversion and Auger Electrons, per disintegration.
0.193 to 0.194	Mean Energy of β particles, internal conversion and Auger Electrons per disintegration plus allowance for radioactive daughter product.

TABLE 10: Values of Mean $\overline{E}_{\beta}$ which have been used for ^{131}I and their probable origin.

the need for this anomolous unit will disappear (Table 10).

The final term in the MIRD dose equation is Φ, which is called the Specific Absorbed Fraction. It is defined as the energy deposited, per unit mass, in the organ of interest divided by the energy emitted by the radionuclide The <u>total</u> energy absorbed in the organ is its mass (m) multiplied by Φ. This is designated ϕ and referred to as the Absorbed Fraction. Thus :

$$\phi = m \Phi$$

The absorbed fraction must be assessed separately for photons and particles of differing energies, as the extent to which they are absorbed is energy dependent. Hence an individual absorbed fraction term ϕ_i is associated with each emission of energy E_i. Thus the total energy absorbed from a radionuclide will be

$$2.134 \sum_i n_i E_i \phi_i = \sum_i \Delta_i \phi_i \quad \text{g.rad/ } \mu\text{Ci-h.}$$

To convert this to absorbed dose it must be divided by m, the mass of the organ giving

$$\sum_i \Delta_i \frac{\phi_i}{m} = \sum \Delta_i \Phi_i \quad \frac{\text{rad}}{\mu\text{Ci-h}}$$

Extensive tables of ϕ are available for photons and particles of various energies (106-110). However, for simplicity the absorbed fraction for particles and non penetrating photons (<11.3 keV) is usually taken as unity (96,100). This approximation is true to within a few per cent in adult organs. However, as will be pointed out in IV, in the thyroids of small children, in the foetus, or in experimental animals it is unlikely to be sufficiently true to provide useful results.

Using the three quantities A, Δ and Φ it is possible to compute the dose from any nuclide to any organ for which the support documentation has been prepared. The calculation process is tedious as the product of Δ_i and ϕ_i must be determined separately for each type of photon and particle emitted. The number of such emissions for nuclides of iodine and $^{99}Tc^m$ is listed in

Table 7. All of these products must then be summed before the dose can finally be determined. To simplify this process a new quantity was introduced This is designated "S" and is the absorbed dose per unit cumulated activity (98,113). It is evident that S is in fact equal to the sum of the above products, divided by the mass of the organ of interest, i.e.

$$S = \frac{1}{m}\sum_i \Delta_i \phi_i$$

$$= \sum \Delta_i \Phi_i \qquad \text{rad/ Ci-h.}$$

Values of S are available for over 110 radionuclides distributed through 19 organs in a standard human phantom (113). Those for some nuclides of iodine and $^{99}Tc^{m}$ in the thyroid are summarized in Table 5. From the above it is clear that the equation for dose may now be reduced to

$$\text{Dose} = \tilde{A} \cdot S \text{ rad}$$

A second refinement recently introduced to the MIRD schema is concerned with $\tilde{A}$, the cumulated activity (98,114). The new concept is defined as the cumulated activity per unit administered dose, and is referred to as the residence time (τ). The unit for τ is hours. From the definition

$$\tilde{A} = Q \cdot \tau \qquad \mu\text{Ci-h.}$$

where Q is the activity administered to the subject in μCi. Residence time takes account of both the duration of nuclide stay in an organ and the proportion of a given dose that enters the organ. Values for τ for some nuclides of iodine and $^{99}Tc^{m}$ in the thyroid are given in Table 6. It should be noted that these values were computed on the basis of a particular biological model, and may not be suitable for general application (114). Values for the thyroid are also plotted in Fig.1, as a function of the physical half life of those in Table 6. The resulting curve is smooth.

From the figure it is evident that once the shape of the residence time curve has been determined it allows values of τ for nuclides with intermediate physical half-life to be interpolated reasonably accurately., This indicates the major advantage of the concept of residence time, in that it allows for easy transferability between nuclides in dosimetric calculations when there

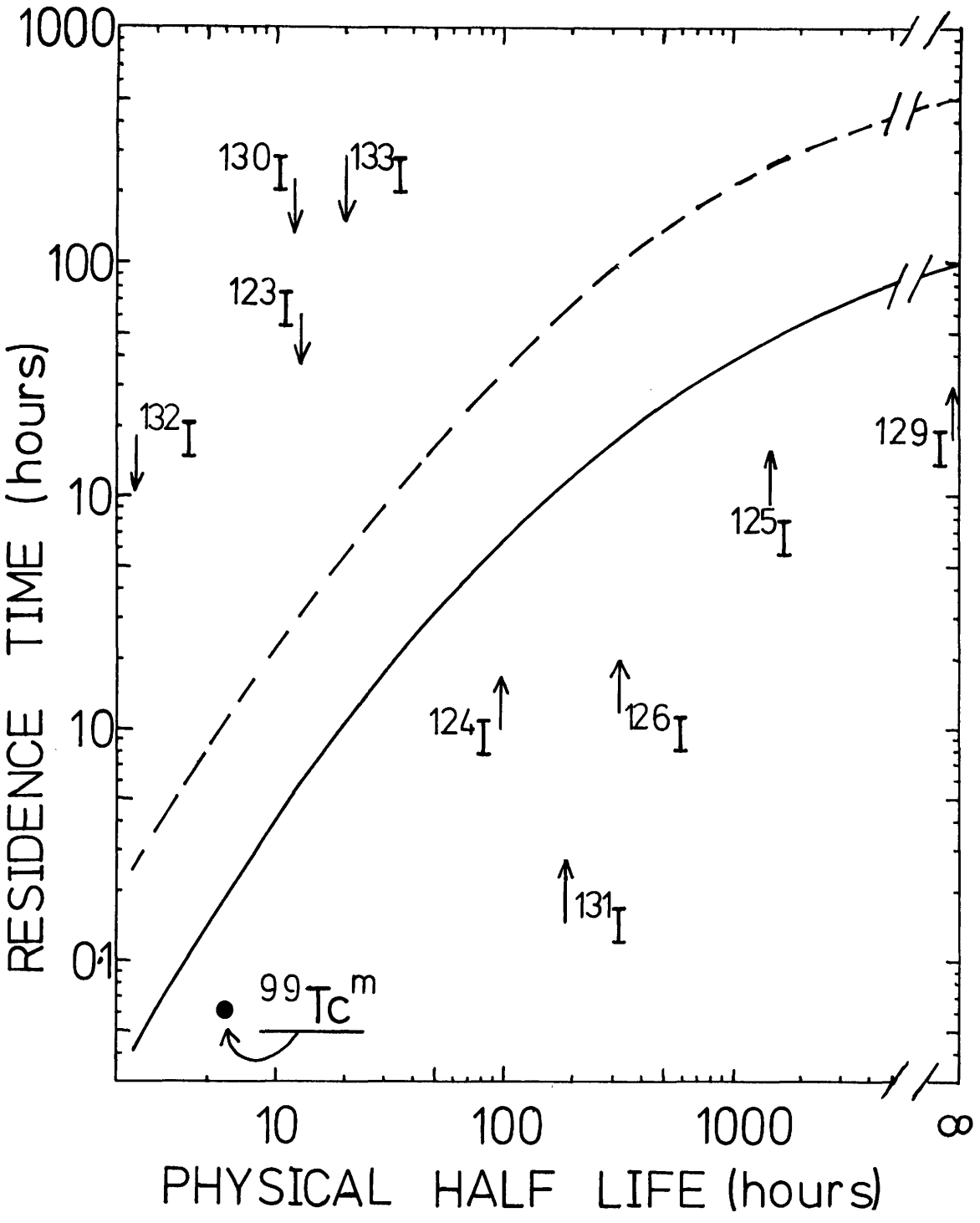


Fig. 1 : Residence time (τ) for nuclides of iodine plotted as a function of their physical half-life, using a particular model of iodine kinetics. The curves correspond to uptake values of about 5 percent (lower) and 25 percent (upper). The form of presentation is based on an original by Berman (114).

NUCLIDE	PHYSICAL * Half-Life	RESIDENCE TIMES (HOURS) Uptake 5%	Uptake 25%
^{123}I	13.0 h	0.6°	3.3°
^{124}I	4.2 d	6.7°	33°
^{125}I	60.2 d	52.1+	263°
^{126}I	13.0 d	17.8°	88.9°
^{129}I	15.7×10^{6} y	98°	490°
^{130}I	12.5 h	0.58+	3.1°
^{131}I	8.06 d	12.52+	59.1°
^{132}I	2.38 h	0.04+	0.22°
^{133}I	20.8 h	1.1°	6.1°
$^{99}Tc^{m}$	6.03 h	0.06°	

* Values from MIRD Pamphlet No. 10. (112)

\+ Values from MIRD Pamphlet No. 12. (114)

o Values Calculated by Authors.

TABLE 6: Physical Half-Lives of various nuclides and residence times (τ) in thyroid assuming uptake values of 5 and 25 percent.

NUCLIDE	POSSIBLE EMISSION TYPES		ENERGY EMITTED AS X-RAY
	NUCLEAR	NUCLEAR X-RAY, I.C. & AUGER ELECTRONS	I.C.and AUGER ELECTRONS (% of Total)
^{99m}Tc	3	16	13.1
^{123}I	14	27	28.6
^{124}I	70	85	1.7°
^{125}I	1	14	96.2
^{126}I	13	32	3.3°
^{129}I	2	15	41.2
^{130}I	31	48	0.4
^{131}I	20	37	1.8*
^{132}I	116	144	0.5
^{133}I	39	44	0.4*

* Contribution from radioactive daughter products neglected.

o Not inc luding annihlation radiation.

TABLE 7: Possible Types of Emission including X-rays, Internal Conversion and Auger Electrons, and percentage of total emitted energy associated with the latter.

is no change in the chemical-biochemical nature of the material being used.

Using the concept of residence time gives the final equation for absorbed dose within the MIRD schema:

$$\text{Dose} = Q \cdot S \quad \text{rad.}$$

Values of the thyroid dose computed for nuclides of iodine and $^{99}Tc^{m}$ are listed in Table 5, assuming the activity in the gland is 1 μCi/g.

The concepts, units and equations discussed above are summarized in Tables 2 and 4. However it is likely that all dosimetric systems will soon be adapted to take into account the newly formulated S.I. Radiation Units. These units and their present equivalents are listed in Table 8. Fortunately the present revision of the MIRD schema is relatively independent of the system of units in which it is formulated, and hence the impending transition should be relatively painless (98).

C. Nuclear Disintegration Data.

Both the traditional and MIRD Systems of dose calculation are dependent on the accuracy and appropriateness of the nuclear disintegration data used in the dose formula outlined above. One would expect that the standard decay schemes in sources such as "Nuclear Data" or "Tables of Isotopes" would be adequate (124,125). Indeed much of the published dosimetry of ^{131}I in the thyroid relies on such data (102,103). However, in sources of this type details are only given of the X , β and γ rays, emitted during nuclear transformation They do not include the multiple X-rays, internal conversion and Auger electrons that may be ejected from the atom due to the perturbations it experiences during disintegration (126). Table 7, indicates the number of different types of nuclear emission associated with the decay of various nuclides of iodine and $^{99}Tc^{m}$. It also indicates the total number of emissions when X-rays, internal conversion and Auger electrons are accounted for. Clearly the latter are important, and in many cases account for a significant portion of the emitted energy. This is particularly true when disintegration is by electron capture. For example with ^{125}I and ^{129}I, the non-nuclear emissions account

NUCLIDE	S* (Rad/ μCi-hr)	DOSE FROM 1 μCi/g+ INITIAL ACTIVITY (rad)
^{123}I	4.0×10^{-3}	1.0
^{124}I	2.7×10^{-2}	69
^{125}I	3.0×10^{-3}	59
^{126}I	1.8×10^{-2}	126
^{129}I	7.1×10^{-3}	273
^{130}I	3.9×10^{-2}	8.9
^{131}I	2.2×10^{-2}	105
^{132}I	6.0×10^{-2}	0.9
^{133}I	4.6×10^{-2}	21
^{99m}Tc	2.3×10^{-3}	0.017

* Values from MIRD Pamphlet No. 11 (113)

+ Depends on iodide kinetics.

TABLE 5: S, the Absorbed Dose per μCi-hr, and dose from a single administration assuming the initial (and maximum) activity is 1 μCi/g.

QUANTITY	SYMBOL	PRESENT UNIT	NEW S.I. UNIT	EQUIVALENCE
Activity	Q, q	Curie (Ci) Microcurie (μCi)	Becquerel (Bq)	1 μCi = 3.7×10^{4} Bq
Absorbed Dose	D	rads	Gray (Gy)	1 rad = 0.01 Gy
Dose Equivalent	H	rem	Sievert (Sv)	1 rem = 0.01 Sv
Cumulated Activity	A	μCi· h	Becquerel-Second (Bq·s)	1 μCi·h = 10.3 Bq·s
Half Life Effective Half-Life Residence Time	T	hour	Second (s)	1 h = 3600 s
Energy (Photon)	E	MeV	Joule	1 MeV = 1.6×10^{-13} J
Energy (Occasional Unit)		g·rad	Joule = kg·Gray	1 g.rad = 10^{-5} kg.Gy = 10^{-5} Joules
Specific Absorbed Fraction	Φ	per/gram (g_{-1})	per Kilogram (kg^{-1})	1 g^{-1} = 10^{3} kg^{-1}
Equalibrium Dose Constant	Δ	$\frac{g - rad}{\mu Ci-hr}$	$\frac{kg \cdot Gy}{Bq \cdot s}$	$\frac{1g \cdot rad}{\mu Ci-hr} = 9.7 \times 10^{-7} \frac{kg \cdot Gy}{Bq \cdot s}$

TABLE 8: New SI (Radiation) Units and their Present Equivalents.

for 96 per cent and 42 per cent of the radiated energy respectively.. Table 9 lists the basic decay scheme for both of these nuclides together with the full scheme necessary for dosimetry purposes. The difference between the two is dramatic.

As well as revising the basic schema for dose calculations the MIRD Committee have undertaken a detailed study of relevant events associated with nuclear disintegration. As a result comprehensive documentation has now been published on over 120 nuclei including those listed in Table 7 (112). This does not include all the radionuclides of iodine, but those not listed are rarely encountered in practice.

Another example of value of comprehensive and appropriate nuclear decay data is given in Table 10. This lists various values of the mean energy of ^{131}I that have been quoted in dosimetry calculations, and the probable origin of each value. Clearly figures such as .180 and .188, which have been widely used, are significantly lower than they should be. This in part at least, accounts for the difference between the results obtained for the traditional and the MIRD dose calculations in Table 2.

^{125}I			^{129}I		
* NUCLEAR DISINTEGRATION DATA					
Transition	Mean No. per Disintegration	Transition Energy (MeV)	Transition	Mean No. per Disintegration	Transition Energy (MeV)
Electron Capture 1	1.0000	0.1420	Beta (Minus) 1	1.0000	0.1500
Gamma 1	1.0000	0.0354	Gamma 1	1.0000	0.0395
*EMITTED RADIATIONS					
Radiation	Mean No. Per Disintegration	Mean Energy (MeV)	Radiation	Mean No. Per Disintegration	Mean Energy (MeV)
Gamma 1	0.0666	0.0354	Beta (Minus) 1	1.0000	0.0484
K I.C. Electron	0.8000	0.0036	Gamma 1	0.0801	0.0395
L I.C. Electron	0.1142	0.0309	K I.C. Electron	0.8018	0.0050
M I.C. Electron	0.0190	0.0346	L I.C. Electron	0.0884	0.0345
K Alpha-1 X-Ray	0.7615	0.0274	M I.C. Electron	0.0294	0.0386
K Alpha-2 X-Ray	0.3906	0.0272	K Alpha-1 X-Ray	0.3814	0.0297
K Beta-1 X-Ray	0.2056	0.0309	K Alpha-2 X-Ray	0.1968	0.0294
K Beta-2 X-ray	0.0426	0.0318	K Beta-1 X-Ray	0.1052	0.0336
L X-Rays	0.2226	0.0037	K Beta-2 X-Ray	0.0221	0.0345
KLL Auger Electrons	0.1416	0.0226	L X-Rays	0.1134	0.0041
KLX Auger Electrons	0.0597	0.0264	KLL Auger Electrons	0.0639	0.0244
KXY Auger Electrons	0.0096	0.0301	KLX Auger Electrons	0.0277	0.0285
LMM Auger Electrons	1.5442	0.0029	KXY Auger Electrons	0.0045	0.0326
MXY Auger Electrons	3.6461	0.0008	LMM Auger Electrons	0.7087	0.0031
			MXY Auger Electrons	1.7026	0.0009

* Values from MIRD Pamphlet No.10 (112)

TABLE 9: Nuclear Disintegration Data (Top) and Emitted Radiations (Bottom) for ^{125}I and ^{129}I.

III. DETERMINATION OF THYROID PARAMETERS.

As outlined in the previous section the thyroidal parameters that influence the macroscopic dose to the gland are its mass and the cumulated activity or the integral under the activity-time curve. In this section the procedures that may be followed to measure these properties are reviewed with respect to their applicability and usefulness . Gland mass may be estimated by palpation, scintiscanning or ultrasonar methods. Surprisingly, as will be demonstrated in III,A, the three approaches appear to be about equally accurate. The cumulated activity has traditionally been derived from measurements of the uptake and effective half life of radionuclides in the gland. There are many pitfalls in uptake measurements, and estimation of the effective half life can be greatly simplified using a thermoluminescent techniques. The main features of both of these parameters are discussed in B. Using the uptake and effective half life represents at best an approximate approach to determining cumulated activity. More direct approaches to this problem which are potentially more powerful and accurate exist and are briefly reviewed in C. Any physiochemical factor that modifies iodine kinetics in the thyroid will also obviously interfere with the cumulated activity, and hence the absorbed dose. The influence of such factors are discussed elsewhere in this volume (see Section III, IV).

A. Thyroid Mass

Traditionally it has been felt that one of the limiting factors in thyroid dosimetry is the accuracy of gland mass estimation (92). However, some reports in the literature indicate that surprisingly good mass determinations can be made using relatively crude techniques (127-130). The methods on which objective studies, have been performed are palpation, scintiscanning and ultrasound B scanning. In each case the validity of the method has been assessed by comparing the measured mass with the actual mass of thyroids subsequently removed at surgery. Consequently there is an inherent bias in

the populations studied towards subjects with larger glands, as this is a feature of patients referred for thyroid surgery.

The potential of palpation may be assessed from studies by Soley (127)and Smith et al. (129). Results from the latter are summarized in Table 11. It is evident that almost 70 per cent of the mass estimates lie within 25 to 30 per cent of the surgical value, and that over 90 per cent of the cases are within 50 per cent of the true value. However it is clear that agreement with the surgical estimate is reduced significantly when only those with a gland mass of less than 40 g are considered.

The use of scintiscans to provide thyroid mass estimates gave results that were generally regarded as unsatisfactory during the 1950's and 1960's (92,131,132). A recent study reviewed 19 formulae used for this purpose, and re-evaluated the potential of the method (128). The formula finally selected to calculate mass was relatively simple, being:

$$M = 0.86\ A^{1.26}$$

where M is the mass of the thyroid in grams and A is its area on a scintiscan in cm^2. The results obtained using this relationship are surprisingly good and are summarized in Table 11. The overall accuracy is about equal to that obtained with palpation, and may be slightly better for glands of 40 g or less. It is entirely possible that scintigraphic mass estimates can be significantly improved using specially designed collimators (133,134). Fig. 2, indicates that the cros-sectional area of sources can be measured with these collimators to a high degree of precision when large sources approximating the size of the spleen are used. The right side of the figure indicates that a correlation which is not quite as good, but is nevertheless useful, is obtained even with very small sources. Application of these techniques to the thyroid should improve mass estimation.

Although the accuracy to date of the scintigraphic method is only equal to that of palpation, the technique has three significant advantages to recommend it. First,it is independent of the experience of the observer.

ALL CASES			
Deviation from Surgical Estimate %	Cases within Deviation (%) Palpation	Scintigraphy	Ultrasound
25	67	69	68
50	91	95	91
75	96	99	96
100	99	99	96
Total No. of Cases	104	74	22
Cases with thyroids less than 40 g.			
Deviation from Surgical Estimate	Cases within Deviation (%) Palpation	Scintigraphy	Ultrasound
25	47	64	62
50	80	71	92
75	90	93	92
100	97	93	92
Total No. of Cases	30	14	13

TABLE 11: Accuracy of Thyroid Mass Estimates by various techniques. The percentage of the cases examined that lie within specific deviations from the surgical value is presented (128-130).

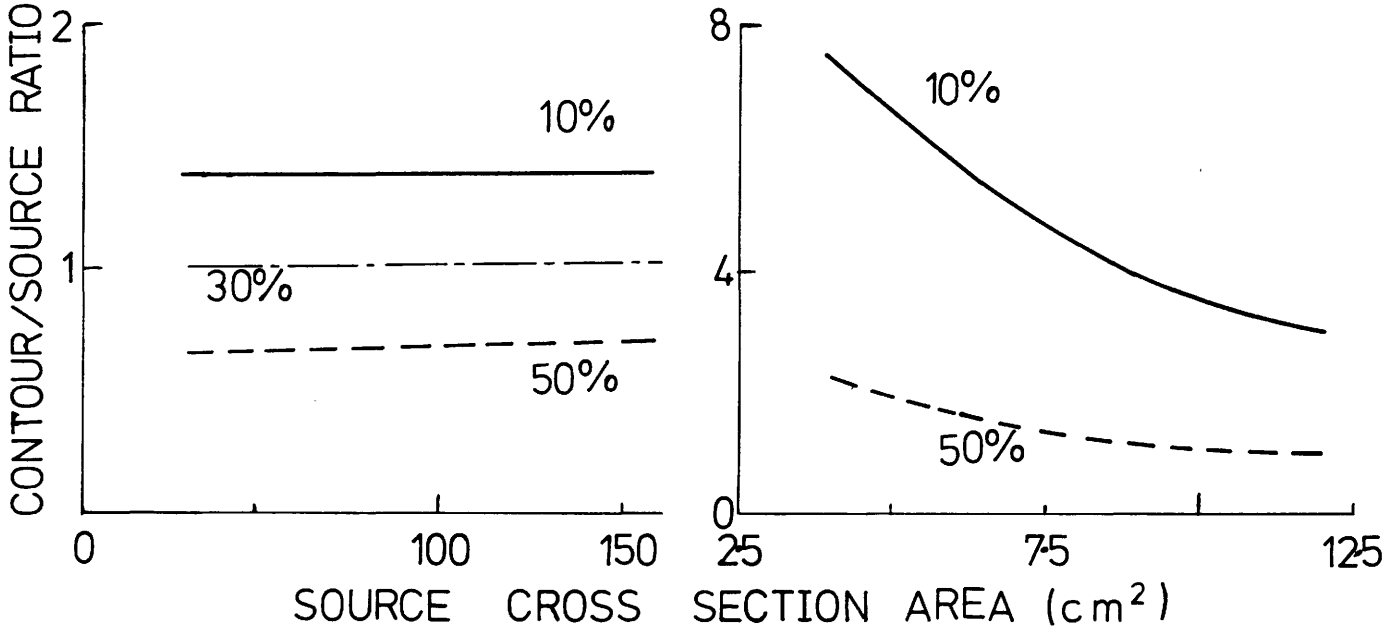


Fig. 2 : The ratio of the area of a scintigraphic image to the source area for specific isocount contour levels. Special collimators were used. For large areas approximating the size of the spleen the 30 percent contour is suitable (left)and for small areas the 50 percent contour gives reasonable results (right). Redrawn from originals by L.P. Clarke (133-134),

Second it is reproducible from day to day and from place to place. Finally it is relevant to note that scintigraphic mass estimate refers only to tissue through which activity is distributed and this from a dosimetric point of view is all that is required. The disadvantages of the method obviously relate to its cost and inconvenience.

Gland mass estimates using ultrasound B-scanning were evaluated by Rasmussen and coworkers (130). They used serial tomographic sections of the thyroid to determine its volume and hence its mass (Fig.3) Their results, illustrated in Table 11, are approximately the same as those reported for palpation and scintigraphy, and may be slightly better for glands less than 40 g. However, there is probably considerable room for improvement in the ultrasonar method. For example in the above study the transducer and scanning arm used were primarily designed for large scale abdominal work. A higher frequency transducer and a more refined scanning arm would probably give significantly better results, particularly with smaller glands. Furthermore the scanning technique most appropriate for mass determination is quite different from that used in conventional thyroid ultrasound examinations, and is still open to improvement.

Figure 4 summarizes the results for mass determination listed in Table 11. The heavy line represents the mean accuracy of the three techniques, as there is little difference between them. The shaded area represents the accuracy for glands less than 40 g, with ultrasound lying towards the top and palpation toward the bottom. The most appropriate method to use in a particular case will depend on the accuracy required and the staff and facilities available. However, in cases where a subject is suspected of having ingested radionuclides of iodine there is a lot to be said for using a scintiscan, which can be performed with as little as a few μCi in the gland provided sufficient time is taken. From the point of view of future developments in gland mass estimation it is clear that ultrasound, scintigraphy and possibly CAT Scanning could with refinement, yield

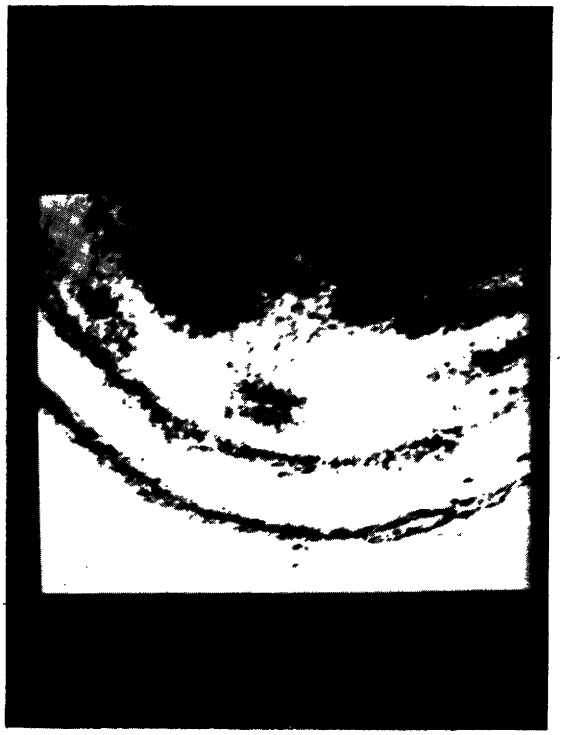


Fig. 3 : Ultrasound B scan of thyroid showing a tomographic section through the gland that clearly outlines its crossection.

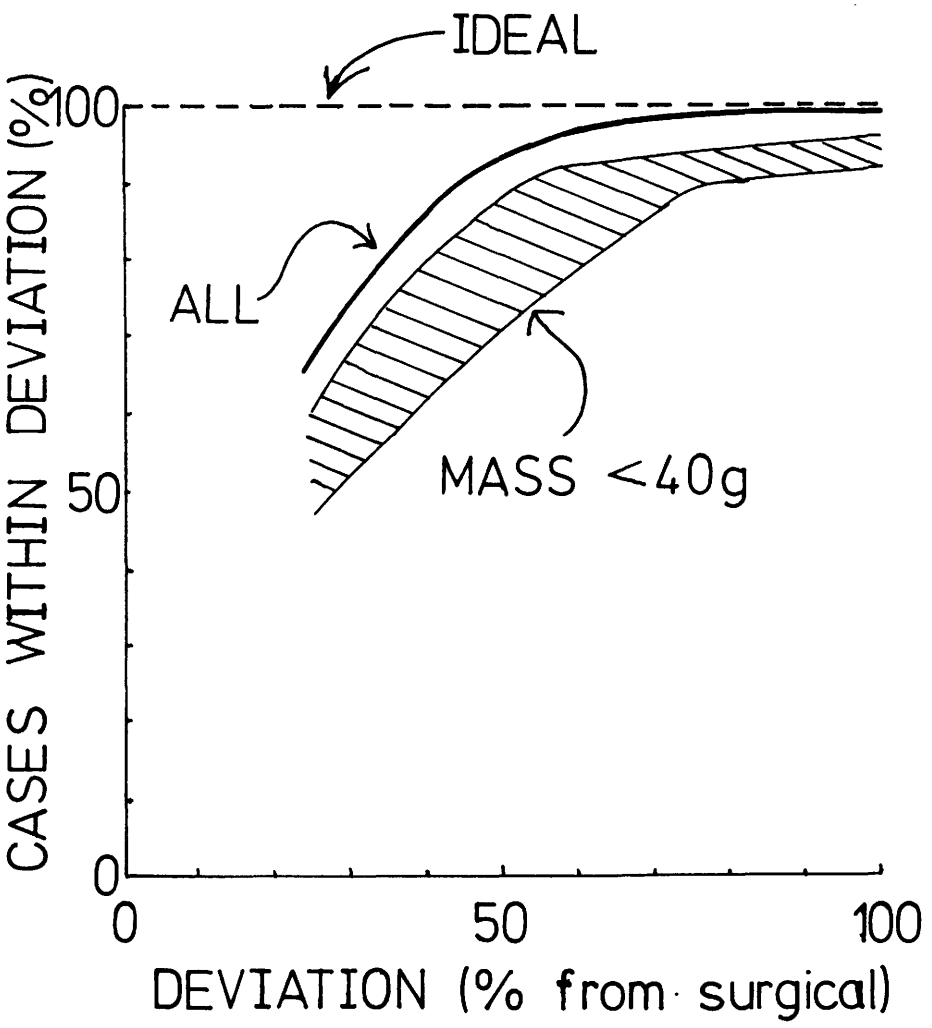


Fig. 4 : The percentage of gland mass estimates that lie within a fixed deviation from the surgical value, for the three techniques : palpation, scintigraphy and ultrasound. The full line is for all glands while the shaded area is for glands less than 40 g. Based on the data in Table 11, which was derived from Refs:128-130.

more accurate results.

B. Cumulated Activity

Cumulated activity, or the integral under the activity-time curve, has traditionally been determined in thyroid investigations from measurements of the 24 h uptake and the effective half life of the nuclide in question. The methods used to measure these parameters and their validity have recently been subject to investigation and will be reviewed here.

1) Uptake

The thyroid uptake of a radionuclide is commonly measured using a single stationary collimated probe. The activity in the gland is determined by comparing the count rate obtained over it with that obtained from an activity standard in a neck phantom (135). The uptake value calculated from this type of measurement will only be true to the extent that the phantom actually represents the geometrical and attenuation conditions present in the subject's neck. It has long been recognized that differences in thyroid geometry could give rise to large errors in activity determinations with low energy nuclides such as ^{125}I (121) while it was felt that such errors would be small with higher energy nuclides such as $^{99}Tc^{m}$ or ^{131}I. However, Fig.5 indicates that this is not the case (136). The figure, based on phantom studies, indicates the correction factor by which an observed uptake must be multiplied to compensate for variations in depth of the gland below to neck surface. Over the range of depths studied the apparent uptake can vary by a factor of 2 for ^{131}I and $^{99}Tc^{m}$, and a factor of 4 for ^{125}I. The range of thyroid depths encountered in practice is presented in Table 12, which indicates a mean value of about 3 cm and a very large standard deviation.
Therefore, gland depths vary to such an extent in practice that the corrections presented in Fig.5 are essential when accurate uptake measurements are required. The underlying causes for these corrections are attenuation and the inverse square law in about equal proportions (136).

To apply the correction factors in Fig.5 gland depth must be measured.

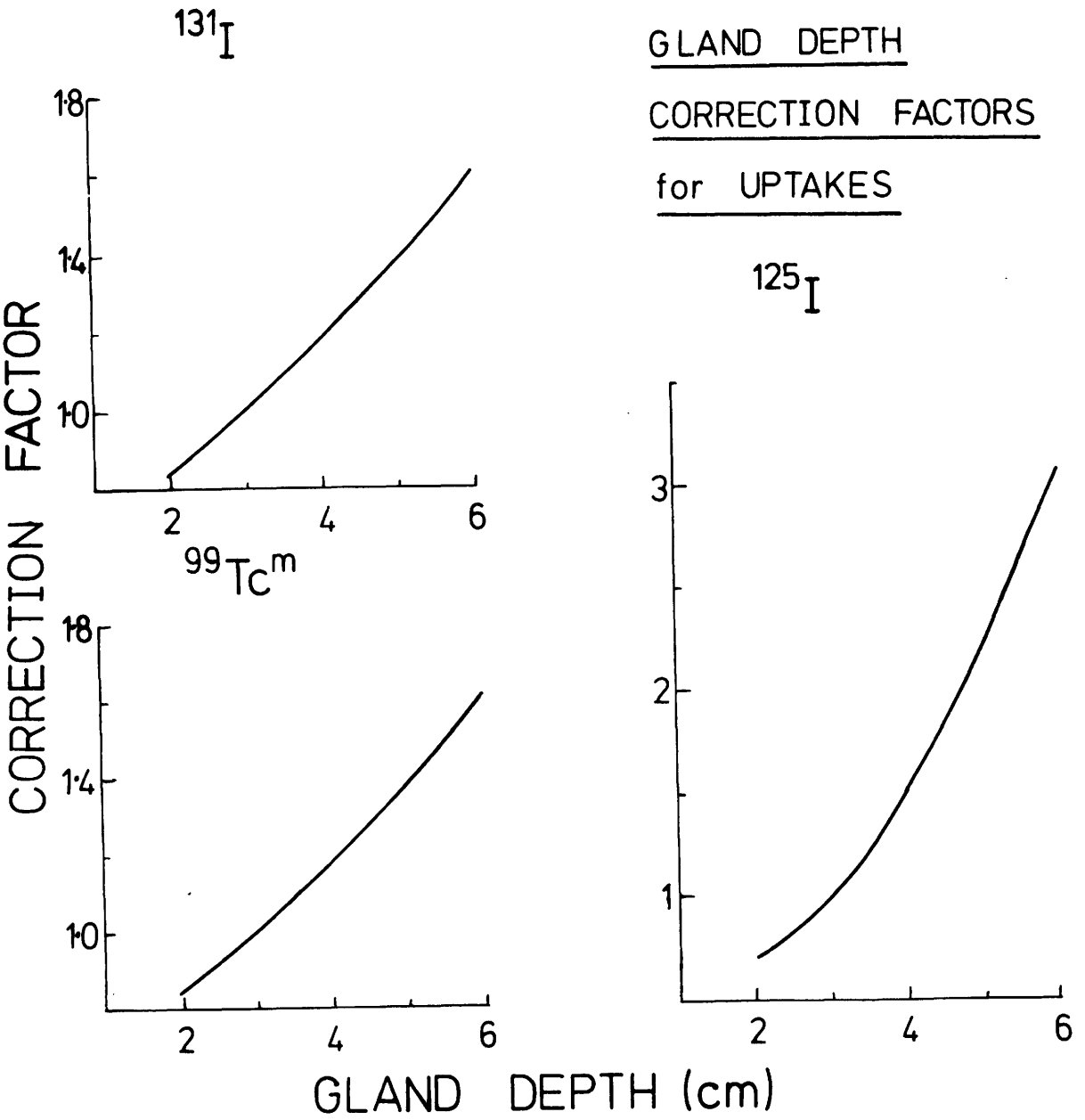


Fig. 5 : The correction factor by which an observed uptake must be multiplied to give its true value, as a function of gland depth. A "normal" thyroid was assumed to be 3 cm deep. Adapted from O'Connor and Malone (136).

NO. OF CASES	THYROID DEPTH (Mean ± 1s.d.)	MEASUREMENT OF DEPTH to	REFERENCE
92	3.85 ± 1.60	Centre of Gravity of thyroid	Schulz and Rollo (137)
100	3 ± 2	Centre of Gravity of thyroid	Vennart (201)
53	2.6	To anterior of lobe	Wellman et al (202)
42	2.1 ± 1.1	Centre of Gravity of thyroid	This study (probe)
21	2.2 ± 0.9	Centre of Gravity of thyroid	This study (TLD)

TABLE 12: Thyroid Depths from various studies.

This can be achieved in a number of ways. For example the ratio of the counts obtained at 2 distances from the neck surface is sensitive to variations. in gland depth (137). Fig.6 gives a plot of this ratio for neck-detector distances of 30.4cm and 50.4 cm, using ^{131}I, Determination of the thyroid counts at these distances from a subject allows its depth be read off from the figure. The advantage of this method is that no special equipment over and above an ordinary uptake counter is required. Its disadvantage is that relatively long counting times are needed to give statistically significant results. Alternative methods that could possibly be employed to determine gland depth include use of the ratio of Compton scattered counts to the counts in the main peak (138,139), use of a lateral radionuclide scan, or an ultrasound scan (136). It is also possible to construct both stationary and moving detectors whose response is relatively independent of depth, and there is a good case for applying such instruments to quantitative uptake measurements in the thyroid (139-146).

The dependence of thyroid activity measurements on gland depth is the main source of error in conventional uptake methodology. Smaller errors of the order of 10 per cent and 2 per cent may arise from variations in lobe separation and gland mass respectively. In very accurate determinations these may also be corrected for (136). The level of circulating extra thyroidal activity seldom presents serious problems in practice, except shortly after a dose is administered or when the uptake is very low (144).

When a very precise value of the thyroid uptake is not required it may be estimated using thermoluminescent discs fixed with BAND AID dressings to the subjects anterior or posterior neck surface for a 24 hour period. This type of measurement is very easy to perform in remote situations in which direct access to equipment or laboratory facilities may not be easily available. The minimum measurable quantities of activity for ^{125}I and ^{131}I using LiF or $CaSO_4$ (Dy) thermoluminescent discs are listed in Table 13. Clearly activities of the order of 1 μCi are well within the range of these materials. The

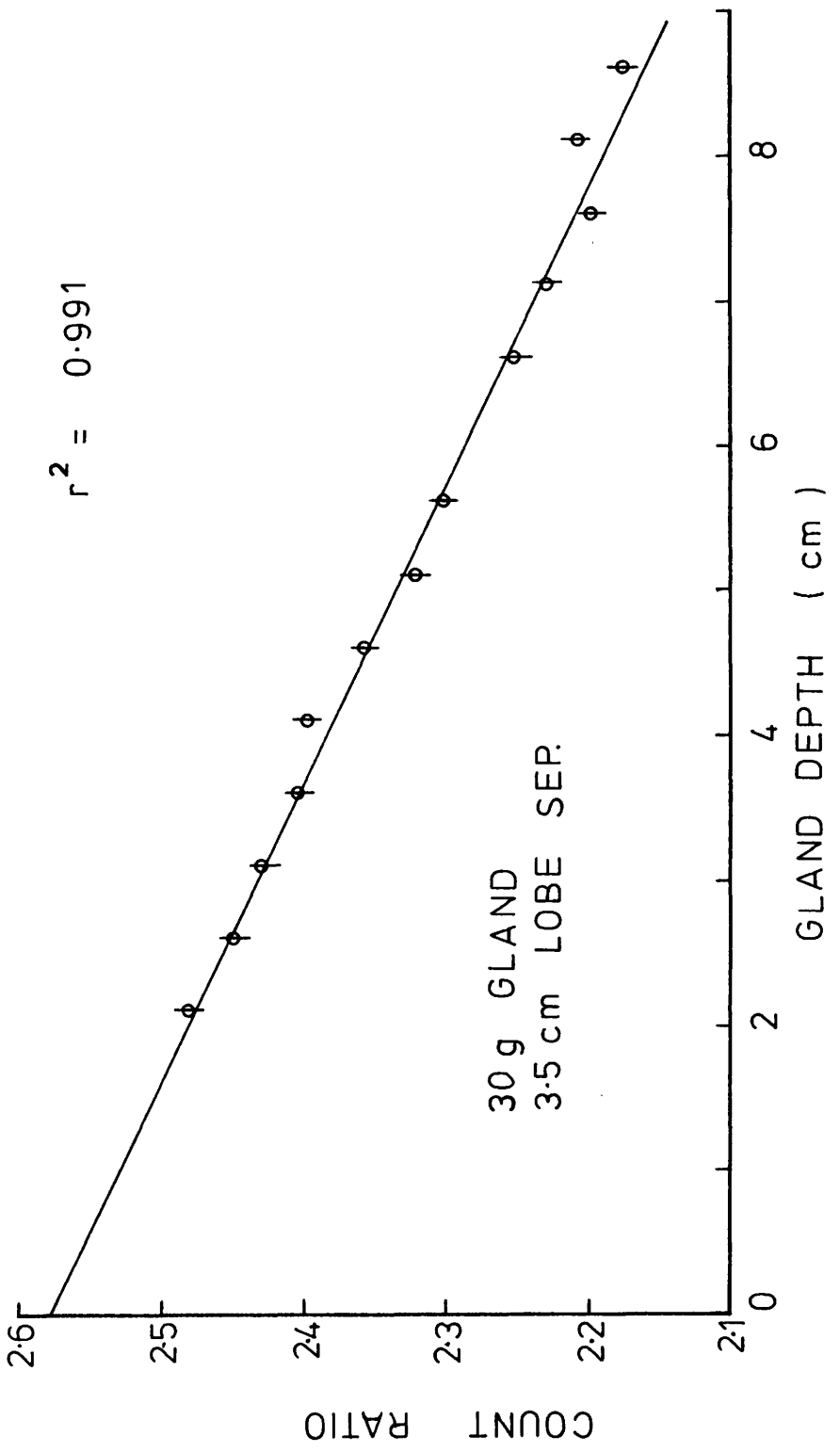


Fig. 6 : The ratio of counts obtained at two distances from a neck phantom surface as a function of thyroid depth. The nuclide used was ^{131}I.
Courtesy of M.K. O'Connor (146).

Thermoluminescent Discs	Nuclide and Activity ^{131}I (μCi)	^{125}I (μCi)
LiF	4.4	8.3
$CaSO_4$(Dg)	0.32	0.13
Selected Batch of $CaSO_4$ (Dy)	0.1	0.04

TABLE 13: Minimum measurable thyroid activities in μCi of ^{125}I and ^{131}I with thermoluminescent discs placed for 24 hours on the anterior neck surface. Values for posterior neck surface are about 10 times less.

selected batch of $CaSO_4$ discs was chosen to minimize the interdisc variability in radiation response and background. Consequently it is more sensitive as the limiting factor in sensitivity in these studies is the standard deviation of the background reading (145).

As with the uptake probe, thermoluminescent disc measurements of thyroid activity will depend on gland depth. Fig.7 shows the correction factor which must be applied to the back of neck TLD reading so that it provides a representative activity estimate. This curve neglects errors that arise because of variations in gland mass and lobe separation between subjects. However, these errors will not be large for gland masses in the range 20-60 g and lobe separations up to 4.5 cm. As illustrated in Fig.8 very few thyroids lie outside these limits.

The requirements that gland depth be determined for TLD uptake measurements would destroy its usefulness in remote situations if conventional high technology methods of depth determination had to be used. Therefore, a method of estimating depth using the discs themselves has been developed. Fig.9 illustrates the ratio of the reading from discs placed on the front and back of a neck phantom plotted against the depth of the gland. These curves allow gland depth be determined to within about 1.0 cm (146), and hence would allow the corrections of Fig.7 to be applied in practice without recourse to more sophisticated equipment.

In Fig. 10 the uptake measured by the TLD technique is plotted against that obtained using a conventional probe. Both measurements have been corrected for gland depth. The correlation between the methods is good, although a best fit to the data points indicates that the TLD method gives results that are on average about 20 per cent lower than those from the uptake probe. This is probably, in part at least, accounted for by the fact that the disc readings represent the average activity present during the first 24 hours after a dose is administered, which will inevitably be lower than the point measurement of activity made at 24 hours by the probe. The right panel

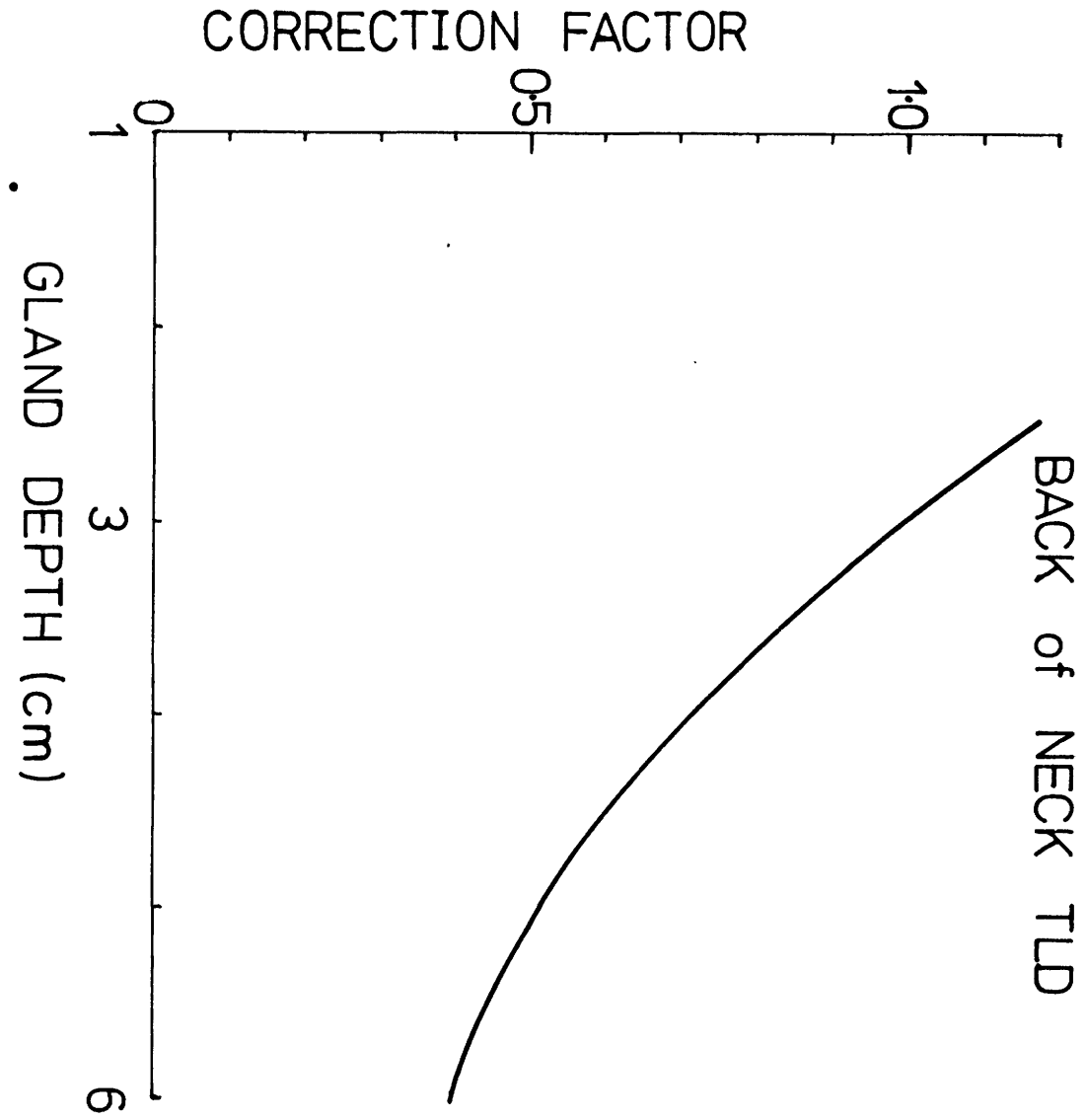


Fig. 7 : The correction factor by which a back of neck thermoluminescent disc reading must be multiplied to give a value that is representative of thyroid uptake of ^{131}I. The gland depth in the phantom is measured from the front of the neck. Corrections for gland mass and lobe separation are not included. A "normal" thyroid was assumed to be 3 cm deep. Adapted from an original by M.K. O'Connor, with his permission, (146).

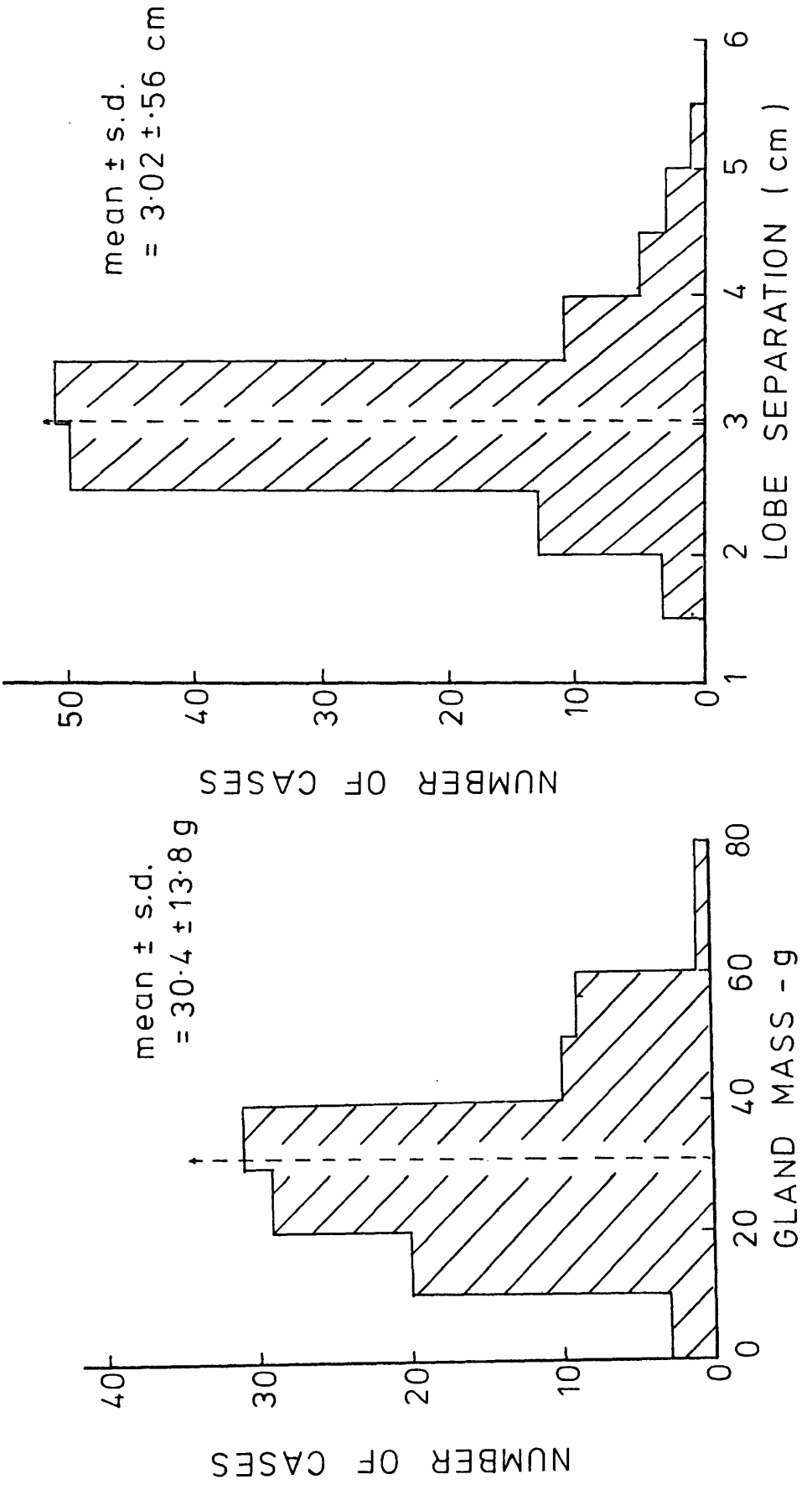


Fig. 8 : Distribution of gland masses and lobe separations in patients seen at a thyroid clinic. Courtesy of M.K. O'Connor, (146).

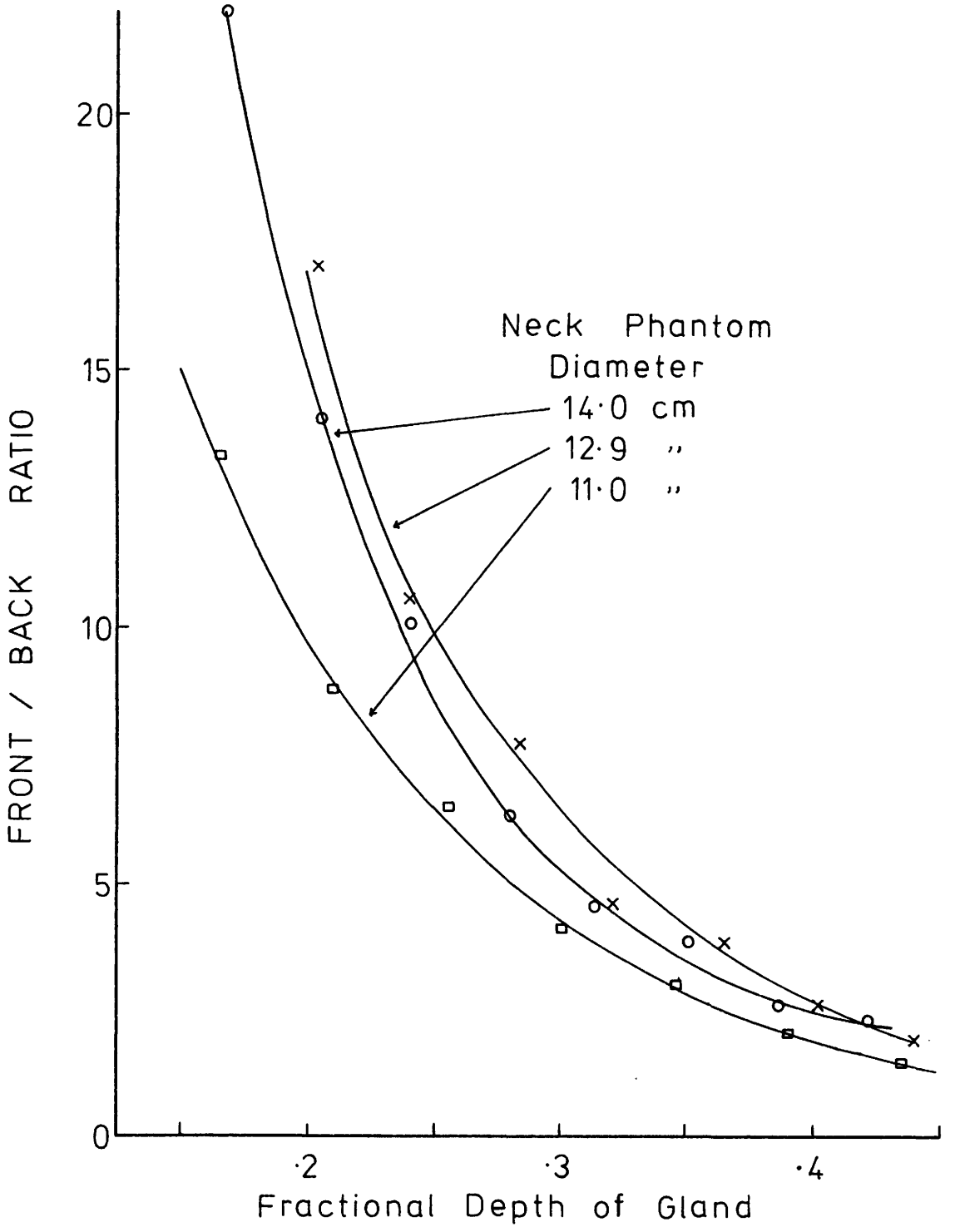


Fig. 9 : The ratio of readings in thermoluminescent discs placed on the front and back of a neck phantom as a function of fractional gland depth for neck phantoms of differing diameters. Courtesy of M.K. O'Connor, (146).

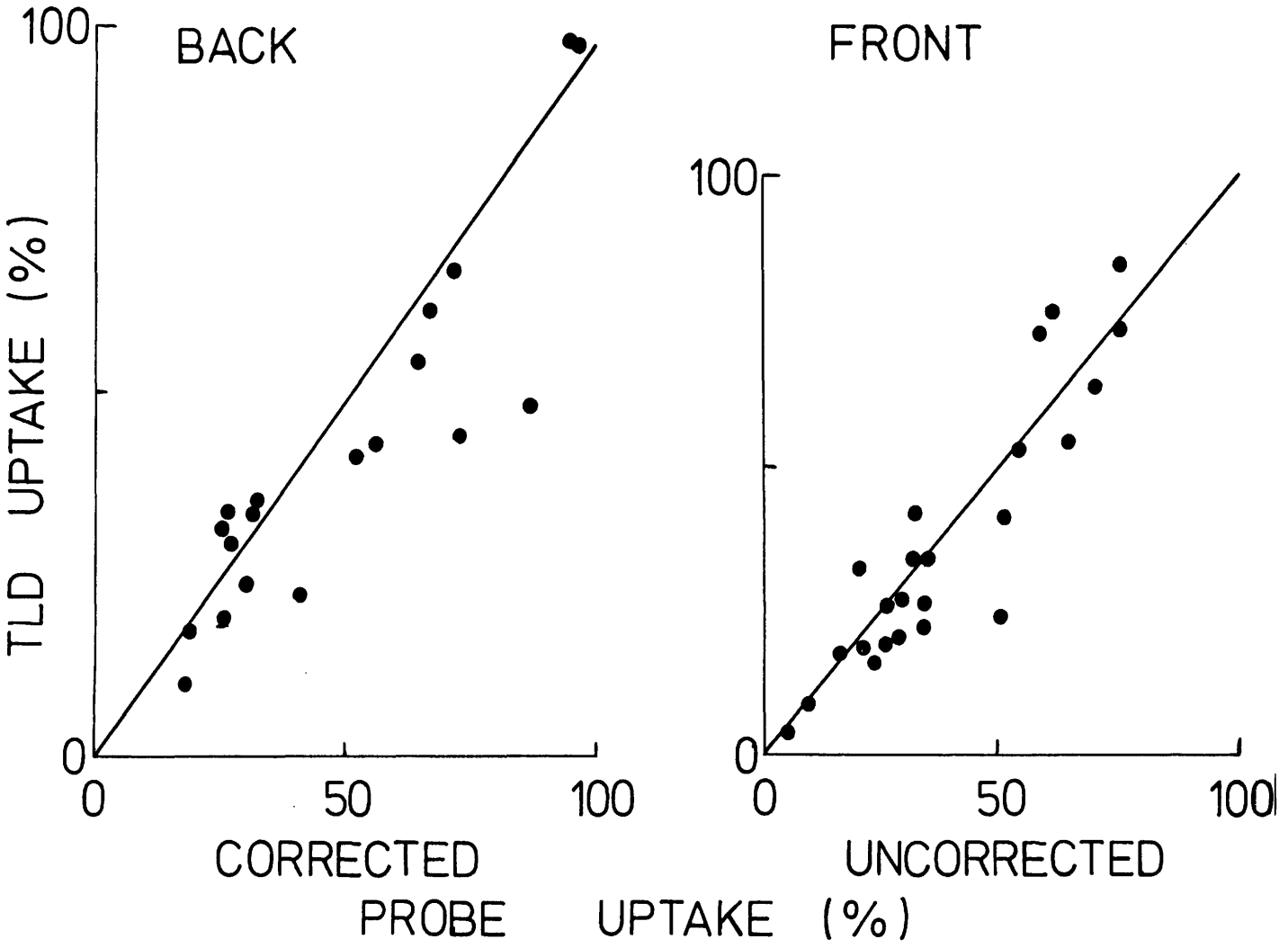


Fig. 10 : Comparison of uptake values obtained using a conventional probe and thermoluminescent discs. In the left panel the TLD discs were placed on the back of the neck and both the uptake probe value and disc value were corrected for gland depth. In the right panel the discs were placed on the front of the neck and no corrections were applied to disc or probe measurements. Adapted from originals by M.K. O'Connor, with his permission, (146).

in Fig.10 demonstrates a surprisingly good correlation between the uncorrected TLD reading obtained on the front of the neck and the uncorrected value of uptake obtained with a probe. This correlation simply reflects the fact that in this case, the magnitude and direction of the errors from both techniques are similar.

The approaches outlined to uptake measurement indicate that it may be studied at a number of levels. However, it is absolutely clear that if accurate data are required for dosimetric work gland depth and geometry must be corrected for. For work demanding less accuracy such as diagnostic medical investigations or epidemiology the same rigorous techniques need not be applied, and in these circumstances there may be occasions when the simplicity and portability of thermoluminescent discs has much to commend them.

2) Effective Half Life

The effective half life of a radionuclide in the thyroid may be determined from sequential counts performed with an uptake probe. This method is time consuming and obliges the subject to make numerous visits to the laboratory. Consequently effective half life measurements have frequently been omitted from dosimetry regimes on practical grounds and assumed values have been used. For example, it is commonly assumed that the effective half life of ^{131}I in the thyroid is 6-7 days (92,103).

An alternative approach to effective half life estimation, using thermoluminescent discs has been developed in recent years (147-149). with uptake measurements the technique involves fixing the discs to the anterior neck surface for sequential 24 hour periods. Effective half life measurements do not require absolute activity determinations. All that is necessary is relative measurements of the activity present from day to day, and this eliminates the need for most of the geometrical corrections that must be introduced when uptake is being estimated. Furthermore, while positioning the discs reproducibly on the neck surface is important, small

variations from one day to the next are tolerable without substantially influencing the results obtained (145). Therefore, determination of effective half life is technically easier than uptake.

Fig. 11 illustrates the results of a comparison between the effective half life of thyroidal ^{131}I determined using thermoluminescent discs and that obtained using an uptake probe. The correlation is excellent, indicating that for practical purposes the TLD method is an adequate substitute for traditional methodology (148,149). The most striking feature of the technique is its convenience, as after a short period of instruction most of the measurements can be made by the subjects being monitored in their own home. The discs may be returned to the laboratory in person or by mail (149) This is clearly a considerable advantage when monitoring out patients from a hospital clinic or healthy subjects who have accidentally ingested radioiodine. Its benefits for those living in remote regions are also evident.

The range of effective half lives encountered in practice depends on the iodine kinetics in the subjects and the radionuclide being used. With ^{131}I a range from approximately 2 to 8 days has been encountered (149,150) in patients being investigated or treated for hyperthyroidism. In these patients an excellent correlation is obtained between the effective half lives of tracer and therapy doses, a feature which may be usefully availed of in dose prescription (149). Shorter values of effective half life down to 12 hours, have been noted in patients with thyroid carcinoma (151). As indicated in Table 14 these changes give rise to very substantial changes in the dose the thyroid would receive from a fixed initial level of radioiodine. The table also indicates that the dose due to nuclides with longer physical half lives is subject to greater variation than that from their shorter half life counterparts. This table highlights the need for more extensive data on iodine kinetics in normal human subjects, particularly in view of the possibility that small relatively stagnant pools of iodide can develop even in normal

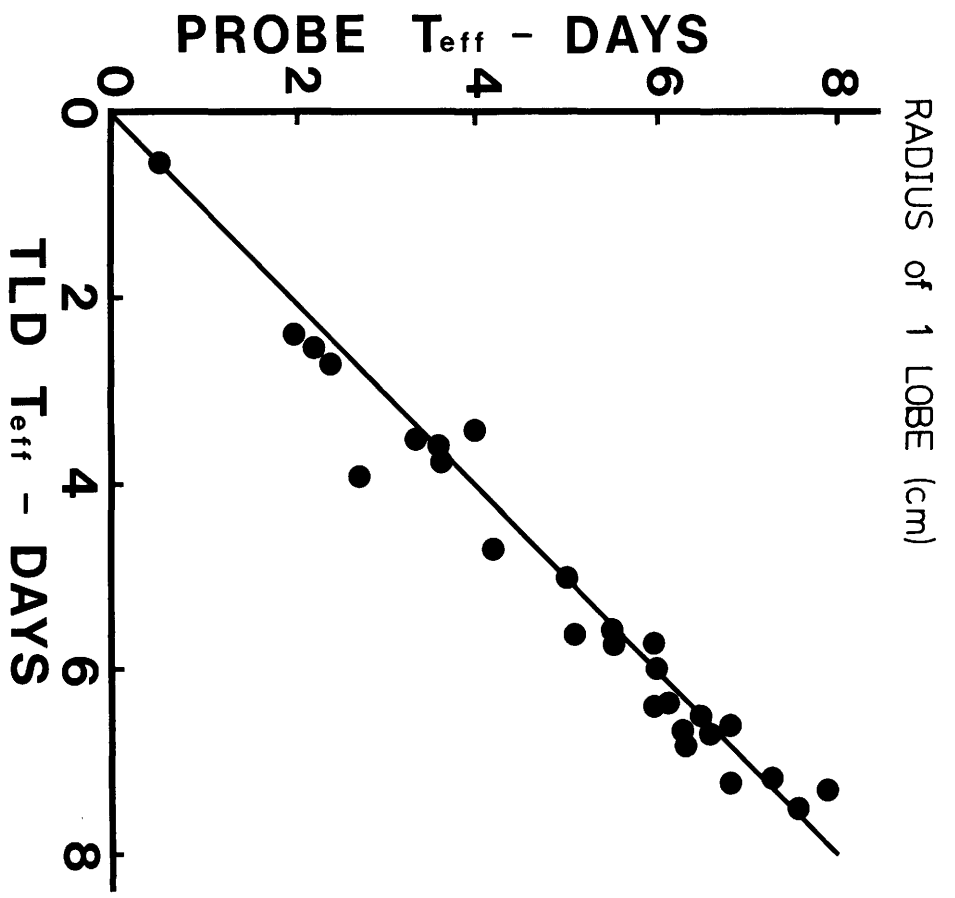


Fig. 11 : Correlation of effective half lives measured with a conventional probe with those obtained using thermoluminescent discs.

BIOLOGICAL HALF-LIFE (days)	MEAN GLAND DOSE (RADS)			
	^{126}I	^{131}I	^{125}I	^{129}I
2.7	83	29	10	5
50	100	100	100	100
104	100	109	139	208

TABLE 14: Change in thyroid dose associated with change in biological half-life of iodide, assuming a dose of 100 rads is associated with a biological half-life of 50 days. Uptake was assumed to be instantaneous.

thyroids (IV,, B).

Determining cumulated activity from measurements of uptake and effective half life as outlined above is at best an approximate method. For example the method takes no account of the uptake phase or its duration, and will thus systematically overestimate the cumulated activity from this portion of the activity-time curve. Furthermore, iodine kinetics can frequently be complex and the curve indicating loss of radioiodine from the gland often has several components. Determining the correct method of fitting such curves is difficult and prone to errors. For the above reasons there is a need to develop a more direct approach to the estimation of cumulated activity using concepts such as residence time, or those outlined in the next section (114,152,153). In the mean time the results obtained using uptake and effective half life are useful and will generally be within 20 per cent of the true value provided sufficient care is taken with the measurements.

C. New Methods of Determining Cumulated Activity.

The cumulated activity, as has already been pointed out is essentially an integral of activity over time for a particular area or volume. The most common methods of measuring it relies on accumulating single point counts in time and using the best fit curve to these points to estimate a value for the integral. Little attempt has been made to determine cumulated activity by applying the facts that some radiation detectors and many biological systems, under appropriate circumstances, operate essentially in an integral mode. This will be illustrated using two examples which should clarify the concept, and should indicate that a more direct approach to measuring cumulated activity is not only possible, but is also likely to be more powerful, convenient and accurate than present methods.

Thermoluminescent discs are integrating detectors. During effective half life determinations as illustrated in Fig. 12 A, they are used to provide point count measurements that are equivalent to those obtained with an

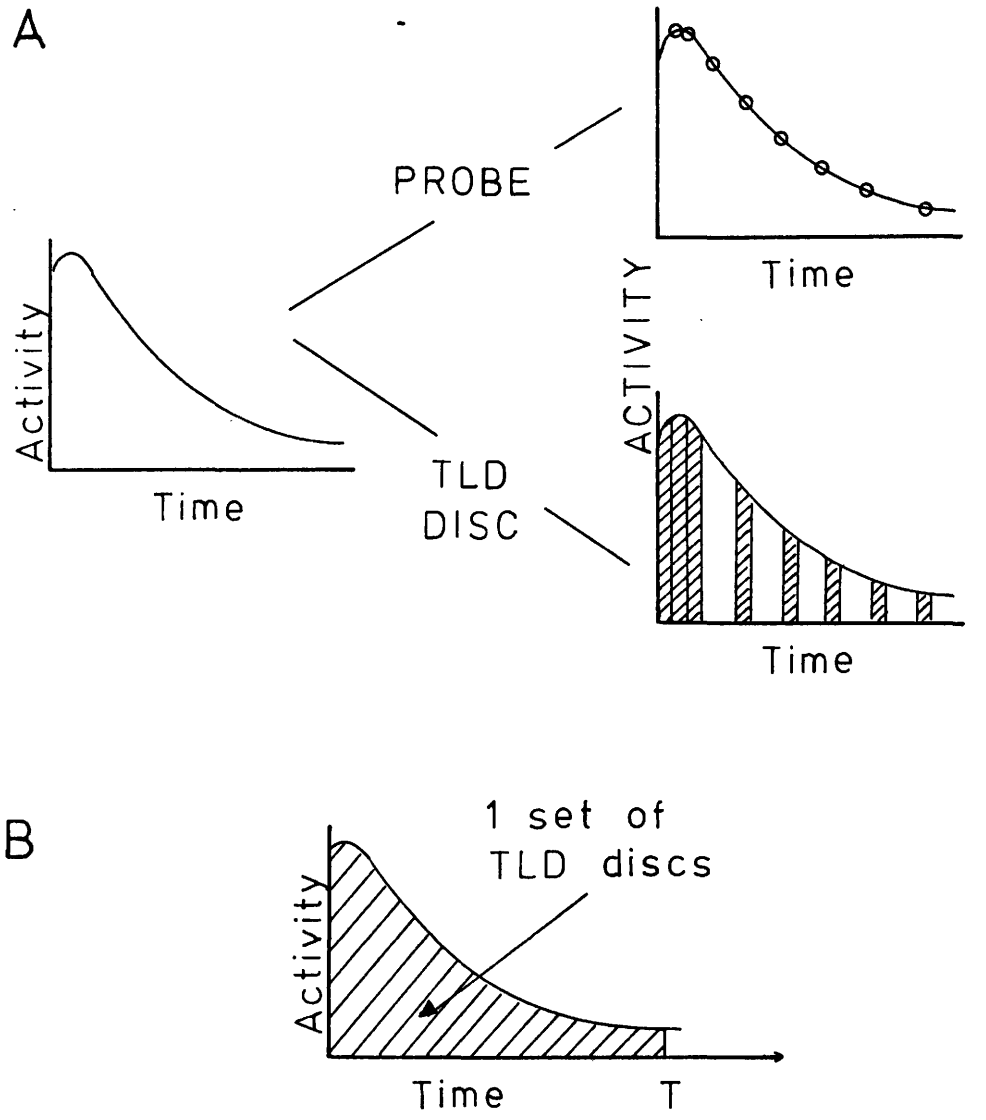


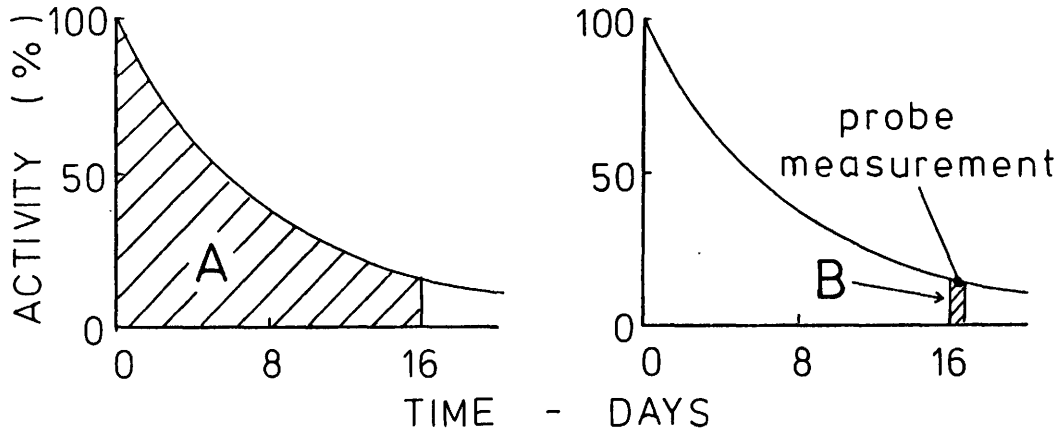
Fig. 12 : Illustration of conventional method of obtaining data for cumulated activity measurements (top), and the possibility of making a direct single measurement with thermoluminescent discs (bottom).

uptake probe. However, each TLD point actually represents the integral of the activity in the gland for the 24 hour period it is in position. There is no reason, in theory at least, why the discs could not be left in position for the entire period over which the integral is to be determined as illustrated in Fig. 12 B, If this were done the disc reading would be directly representative of the cumulated activity during that period. To convert disc readings to μCi-h a calibration protocol is necessary. This could take many forms, using for example a suitable set of phantoms or the procedure illustrated in Fig.13. In this a second set of discs is placed on the subjects neck surface for 24 h at the end of the period for which cumulated activity is being determined. During this time an accurate measurement of the activity in the gland is made using an uptake probe. This provides the calibration factor necessary to convert the reading in the long term discs to μCi-h.

In 4 subjects in whom the above method was applied to determine cumulated activity the results obtained were within about 10 percent of those calculated from the traditional approach using uptake and effective half-life. However, a number of technical problems must be resolved before the method can be widely applied. Some of these are relatively simple to cope with and concern fading of the signal in thermoluminescent discs and correction for the residual activity after the discs are removed (146,154). Others are more practical in character and are principally associated with finding a suitable and acceptable means of securing the discs to a subject's neck surface for a period of several weeks.

The second direct method of determining cumulated activity is based on continuous infusion of a *constant activity per unit time* instead of the single bolus normally injected. The method is based on a principle which may be stated as follows (152,153).

"The activity remaining in any organ, or the whole body, after a period of continuous infusion of constant activity per unit time, is equal to the



Probe measurement : Q μC

$\therefore B = 24Q$ μC - hrs

$\therefore A = 24Q \frac{A}{B}$ μC - hrs

Fig. 13 : Illustration of a method of calibrating a single thermoluminescent disc measurement of cumulated activity "A". A second set of discs "B" is positioned for a 24 hour period during which the activity in the gland, Q μCi, is determined with an external probe.

mean activity that would have been present over the entire period of infusion if all the activity were administered as a single bolus at the commencement of the infusion period"

The principle may not be intuitively obvious though mathematically it is very easy to prove (152). Furthermore, it has been validated in practice using ^{67}Ga in rats (153).

The principle is illustrated in Fig.14 . The left panel summarises data on the loss of a 13.5 μCi single bolus of activity from experimental animals over a 13.5 day (324 hr) period. From the elimation curve the mean activity present during the period, 3.1 μCi, can be calculated. If on the other hand the 13.5 μCi is administered at a uniform rate of 1 μCi/day, the right panel illustrates that the activity in the animals builds up until at 13.5 days their final activity is 3.1 μCi. This is equal to the mean activity present after the single bolus, and allows the cumulated activity be calculated as it is simply equal to the mean activity multiplied by the total time period involved. In practice continuous infusion is not necessary and a semicontinuous injection regime gives reasonable results although small errors are introduced These can be minimized if the injections are sufficiently frequent toward the end of the infusion period (152,153).

The above methods provide a direct approach to measuring cumulated activity. Both methods are quite independent of the shape of the activity time curve and consequently do not require assumptions about the most appropriate way to fit it. As a result they are also uninfluenced by the problems associated with the uptake phase of activity-time curves. Both methods require only a single measurement to be made, although ancillary calibrations may be necessary also(154) In practice this represents a substantial reduction in the amount of work involved in, for example, an effective half life determination. In human investigations the methods would reduce laboratory attendances and with experimental animals they would greatly reduce the numbers necessary for a particular investigation. The second method

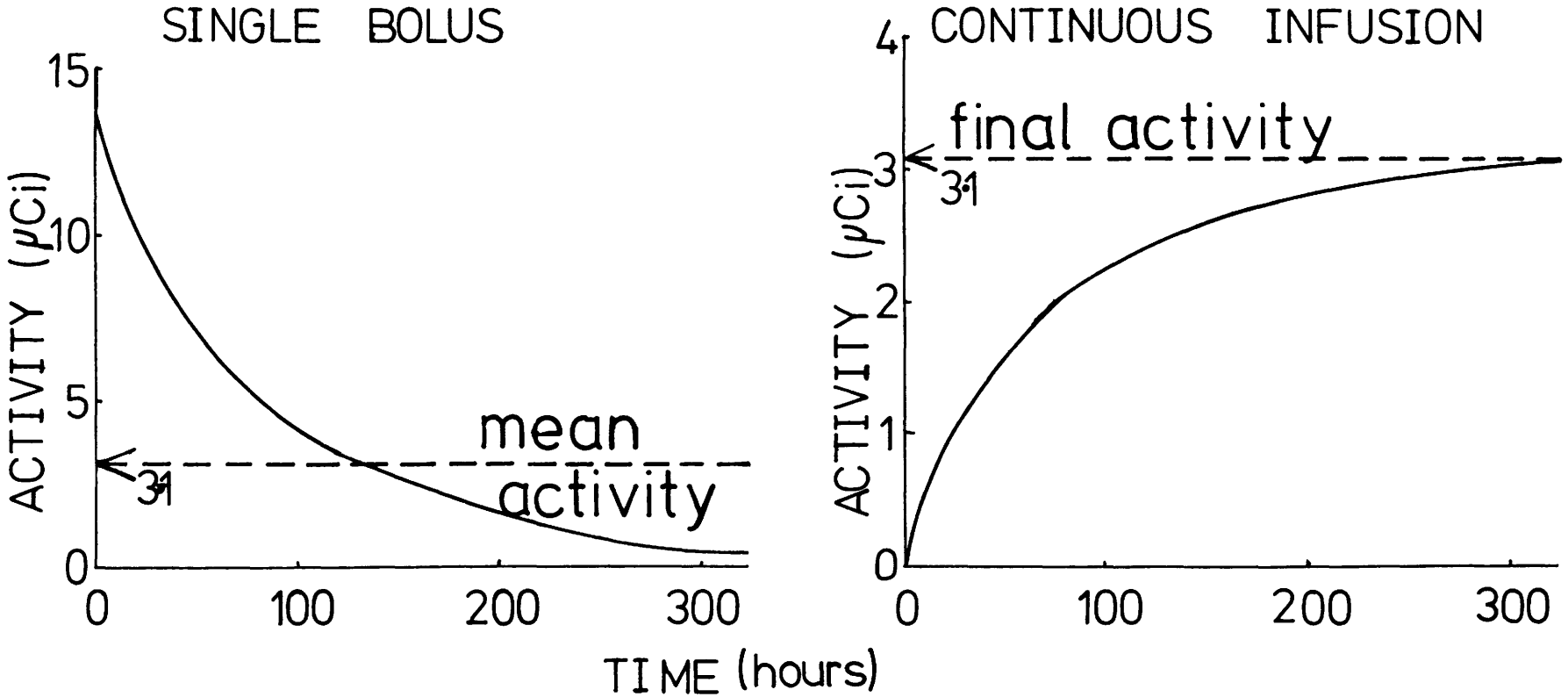


Fig. 14 : The left panel illustrates loss of a 13.5 μCi bolus of activity over a 13.5 day (324 h) period. The mean activity present during the period is 3.1 μCi. The right panel illustrates the build up of activity when 1 μCi/day is continuously infused over a 13.5 day period. Based on an original by Malone et al. (153).

also has considerable potential in microdosimetry (152). While neither method is widely used yet, their advantages are such that they should in their present form, or after adaptation for use with concepts such as residence time, become useful tools in dosimetric investigations of the thyroid. It is also evident that the above concepts and methods could be profitably employed in physiological studies.

MICRODOSIMETRIC CONSIDERATIONS IN THE THYROID.

In the discussion on physical aspects of dosimetry in II, it was assumed that activity was uniformly distributed through the thyroid and that it was sufficiently large to absorb almost all the β radiation emitted. It is evident that if either of these assumptions is untrue dose inhomogeneities will arise in the gland. These arise for a number of reasons. For example if the range of the emitted electrons in tissue is sufficiently long some of them will escape through the surface of the gland, thereby, reducing the surface dose and as a consequence the mean gland dose. Alternatively electrons with very short ranges may not be able to pass from one follicle to the next, or even across a cell. Hence another form of dose inhomogeneity arises. Finally iodine kinetics may vary from one area of the gland to another or from follicle to follicle and thereby give rise to a further dose variation through the gland.

The microdosimetric problems raised above have, with few exceptions, not yet been thoroughly investigated (155-157). However, sufficient data exist to gain a partial insight into them, at three levels. First at the macroscopic level, the loss of energy from an entire gland, or nodule, may be studied as a function of its size. Second at the level of an individual follicle the concentration of iodide and its kinetics give a useful insight into dose distribution. Finally at the level of the individual cell, some studies of dose distribution for nuclides such as ^{125}I exist (155-157).

A. Influence of Mass.

The problem of variation of absorbed dose with mass in small organs is a difficult one which has not yet been fully resolved (113). Studies of the dose distribution around point sources of β particles are available and can be used to obtain approximate solutions in individual investigations (109,158). In thyroid studies the masses of interest range from about 100 g for a large

human gland to about 1 mg for a mouse thyroid or small deposit of thyroid carcinoma. Between these extremes lie the rat thyroid, the foetal and juvenile human thyroid, nodules in the adult gland, well formed metastases of thyroid carcinoma and the normal human adult gland.

Fig. 15 illustrates the proportion of the β dose from ^{131}I that is absorbed in structures of various sizes. To present the data in this form it was assumed that the thyroid consisted of two spheres. The data are drawn from three sources that coincide for glands larger than about 1 g, but diverge for smaller organs (103,158,159). The figure indicates that about 93 per cent of the expected dose will be received in an infant's thyroid, about 80 per cent in the rat thyroid and 50-70 per cent in the mouse gland. These reductions are relevant to radioiodine treatment of thyroid carcinoma, which presumably is intended to be a systemic form of therapy. Thus while it may be easy to achieve a lethal tumour dose in a 10 to 20 g mass from 150 mCi of administered activity, it is much more difficult to do so in small metastases of 0.1 to 1 mm radius. Consequently there are sound dosimetric reasons for using such large doses.

Fig. 16 illustrates a more detailed experimental study, by Walinder, of the dose distribution from ^{131}I across the mouse thyroid (160). It generally supports the calculated results in Fig. 15. However, it also illustrates the severe dose inhomogeneity across the gland ranging from over 80 per cent of the expected dose at the centre to less than 40 per cent at the edges. While the dose distribution in large glands will be much more uniform there will still be a peripheral ring in which the dose is reduced to about half that at the centre due to escaping β particles (113). The width of this ring depends on the β energy. For ^{131}I it is the order of 0.5 mm (158).

The above discussion has concentrated on variation in β -dose with mass. The photon dose also varies but in a more complex fashion. For example it has been suggested that with photons of energy greater than 100 keV the variation is with $m^{-2/3}$ (113). In many practical cases however photons

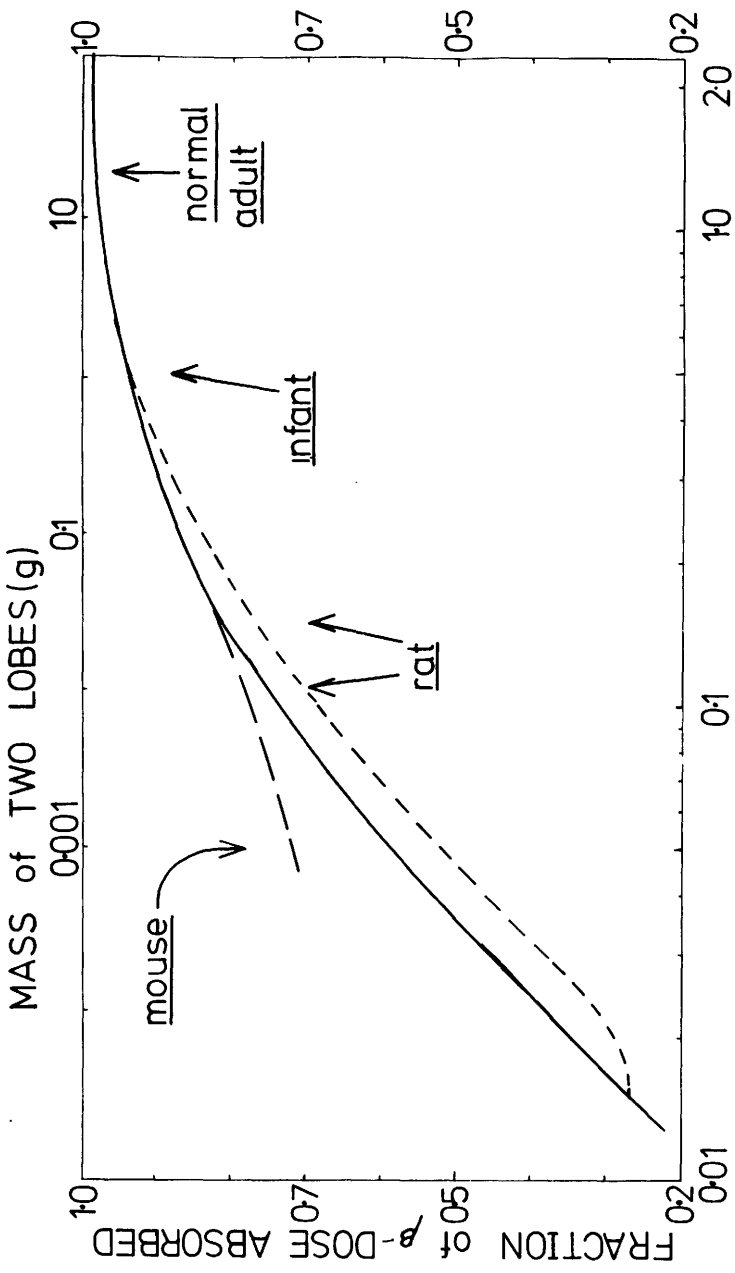


Fig. 15 : The fraction of the β dose from ^{131}I absorbed in thyroids of varying sizes, assuming the gland consists of 2 equal sized spheres. The curves are drawn from data presented in Refs:174, lower broken line;158, full line; and 159 upper broken line.

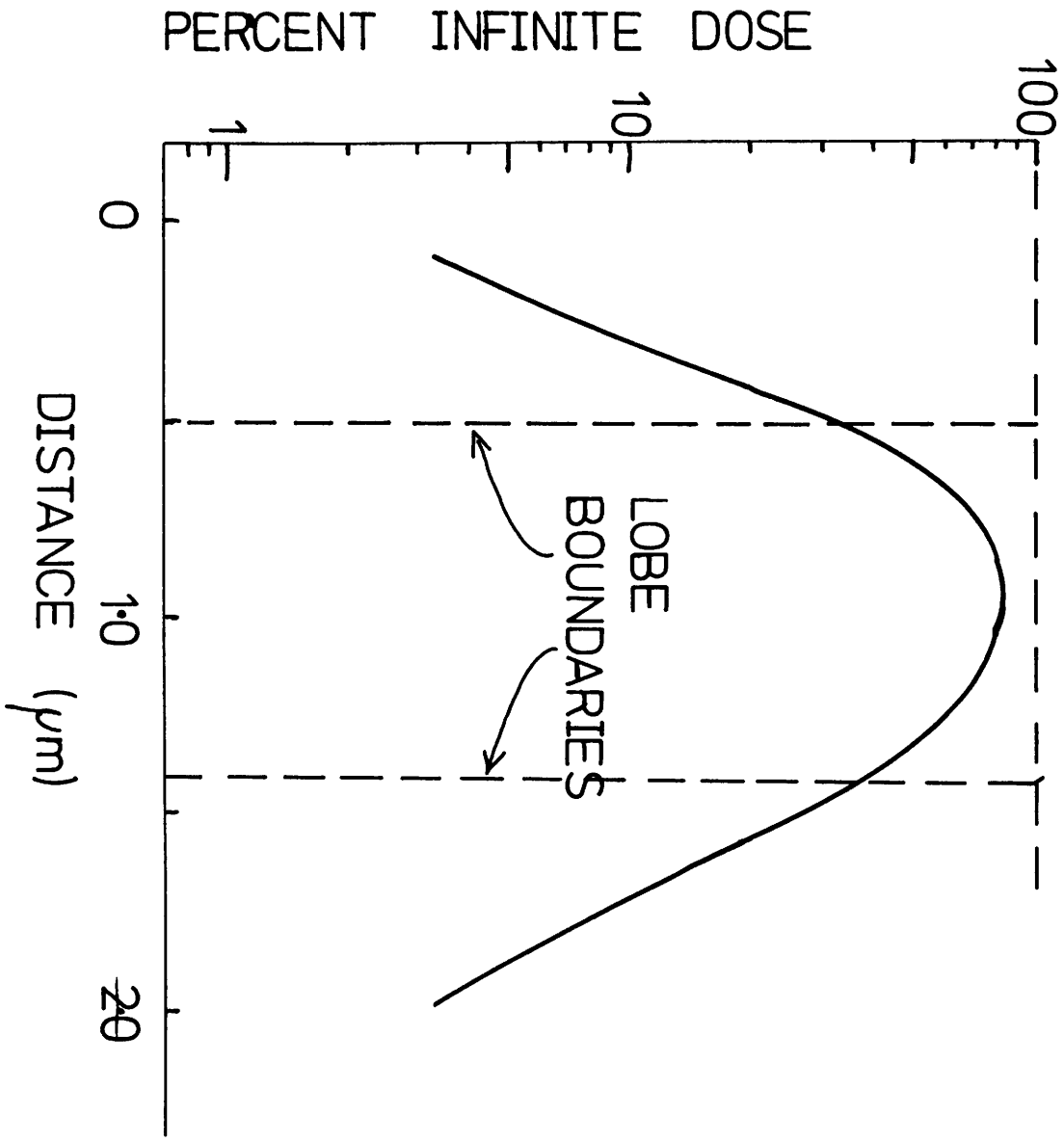


Fig. 16 : The dose distribution from ^{131}I across a lobe of mouse thyroid. On the abscissa the 100 percent value corresponds to total absorption of the β energy. Adapted from an original by Walinder, (160).

contribute only a small portion of the total dose. For example with ^{131}I it is less than 10 per cent in the adult human thyroid. Hence variations in this contribution will have a relatively small effect on the overall dose. In very small glands such as those in the rat or the mouse some authors neglect the photon dose from ^{131}I entirely (99).

B. Interfollicular Inhomogeneity.

Approximately 90 per cent of the iodine in the thyroid is concentrated in the follicular colloid (6). Therefore, when the gland contains radioiodine most of the radiation emerges from the colloid areas. As a result dose inhomogeneity will arise if the range of the β particles is on average less than the interfollicular separation. Another source of dose inhomogeneity lies in the observation that the amount of radioiodine taken up by each follicle does not appear to be constant. In early days after administering ^{125}I to rats the follicular activity and size appear to be inversely related in studies performed by Lowenstein and Wollman (161-163). On the other hand as illustrated in Fig. 17, Riviere and co-workers noted that follicular activity and surface area were directly related (164). This implies that the specific activity per unit volume will be less in large follicles than in smaller ones, and therefore goes some way toward explaining the the results of Lowenstein and co-workers(6,161,163).

The above picture does not remain constant, and with the passage of time there is some evidence to suggest, as illustrated in Fig.17, that activity is eliminated more rapidly from small follicles than from large ones (161-165). Because of this,attempts to base estimates of dose inhomogeneity on the distribution of activity over particular follicles or areas at a single time are misleading. The dose in a given area depends on the integral of activity over volume and time. From the above it is evident that in the thyroid the higher activity per unit volume in small follicles is in part compensated for by its more rapid turnover. Results obtained using the second method of estimating cumulated activity outlined in III, C also support this

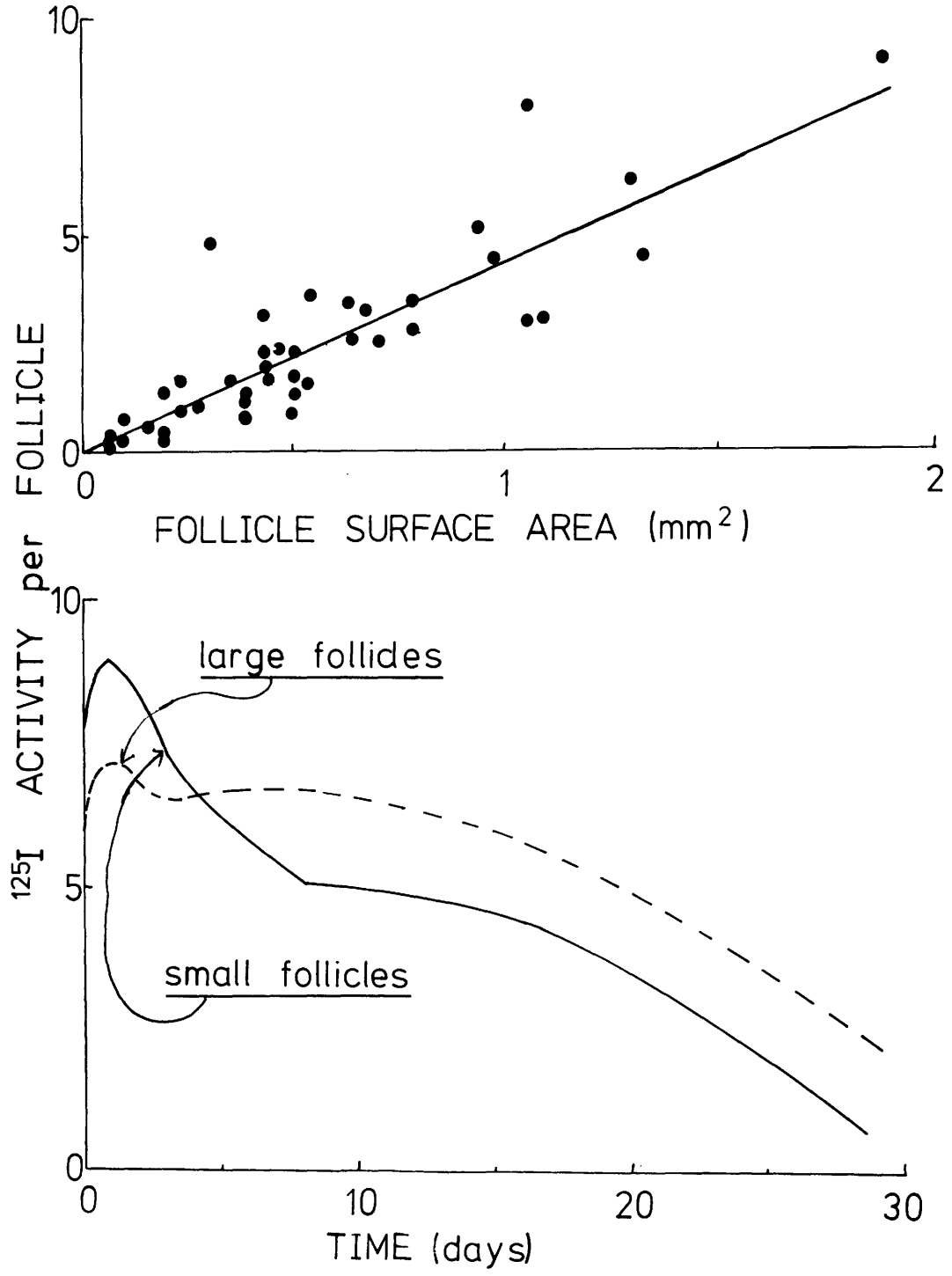


Fig. 17 : Top : ^{125}I activity in human thyroid follicles as a function of their surface area. Redrawn from an original by Riviere et al., (164) Bottom : uptake and loss of activity from large and small follicles in the rat thyroid. Redrawn and adapted from an original by Berjis et al., (165).

view ([152]). These considerations apply to normal glands or those with diffuse disease. However, when function is not uniformly distributed as in single or multinodular goitres it is obvious that larger dose variations will arise.

C. Inhomogeneities at the Cellular Level.

Even if all the emitted β radiation is totally absorbed in the thyroid and the activity is uniformly distributed through the colloid, dose inhomogeneities can arise because the range of some electron emissions is such that they will not completely traverse a follicular cell (155-157). If this is so, the portion of the epithelial cell close to the colloid-cell interface will receive a larger dose than the basal portion and the nucleus. An extensive study of the dosimetry of ^{125}I in this regard has been performed. Fig. 18 illustrates the calculated electron dose distribution across colloid, a follicular cell and stroma. The cell in this figure, which has been adapted from the work of Gillespie et al., is representative of a hyperthyroid rather than a normal gland (157). Table 15 presents the mean gland dose and the dose to the nuclei of follicular cells calculated for all ^{125}I emissions on the basis of a normal human thyroid model used by Fiege and co-workers (155,156). The calculations are in all cases dependent on the assumptions made about follicle size, cell size and the fraction of the gland occupied by colloid in the model thyroid used. Altering these assumptions will alter the computed dose values. For example increasing the colloid fraction will increase the portion of energy absorbed in it and thereby reduce the dose to the cell nucleus (6,155,157). Calculations have been performed for a number of normal and hyperthyroid human glands and for a normal rat thyroid (99 ,155,157).

The ^{125}I studies described above are in many respects classical. Little detail of a similar character is available for other nuclides with the possible exception of ^{129}I for which some results are given in Table 15 (156). There is scope for extending similar investigations to other nuclides and for a detailed study of the relevant structural aspects of the thyroid in healthy and diseased states (for the clinical aspect of using ^{125}I or ^{131}I in therapy see II, II,A and V).

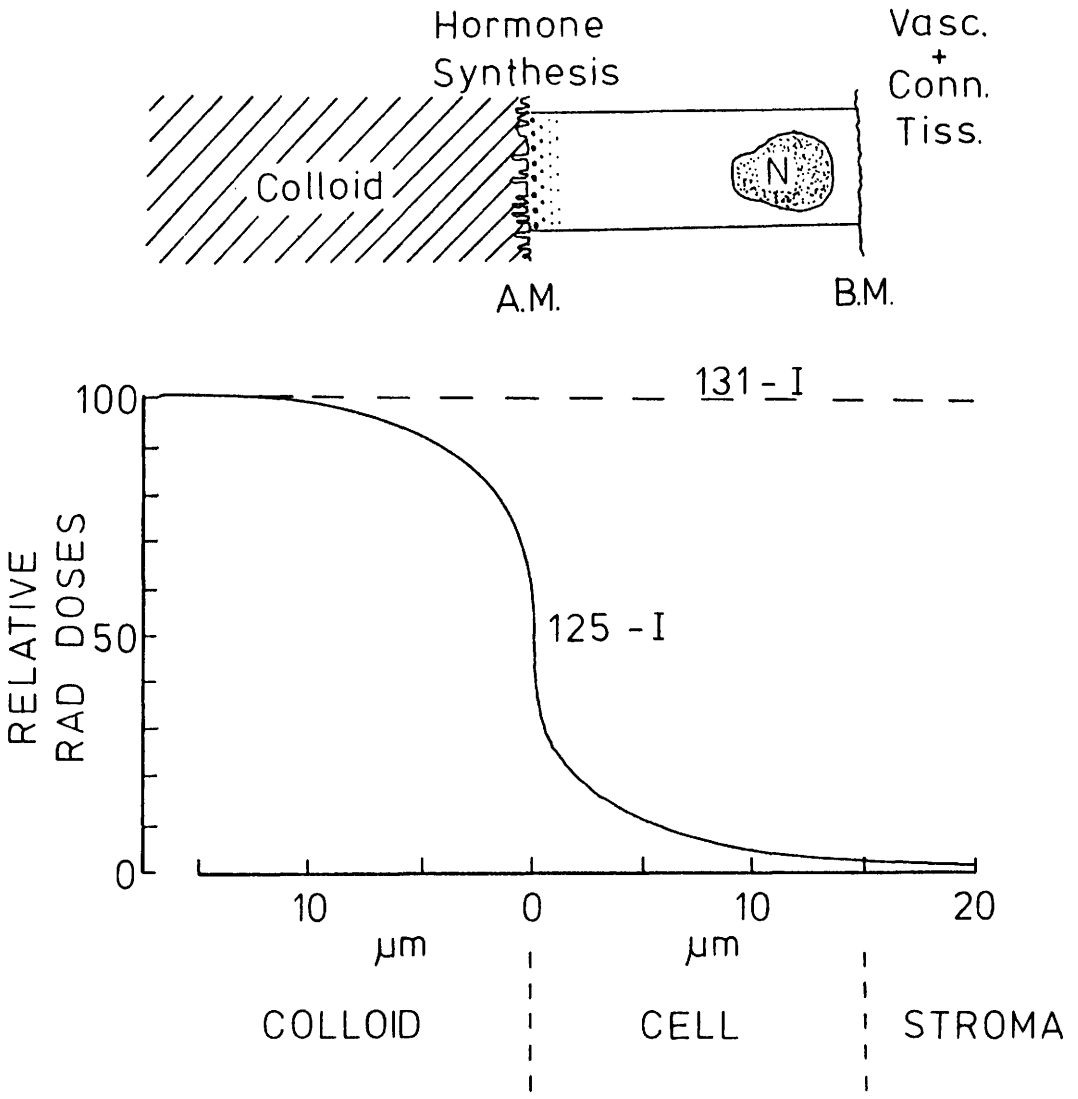


Fig. 18 : Dose distribution from ^{125}I across follicular colloid, elongated follicular cell and stroma. Redrawn and adapted from an original by Gillepsie et al., (157).

NUCLIDE	DOSE RATE (m rad/h)	
	Cell Nucleus	Mean
^{125}I	46.8	73.5
^{129}I	114.2	147.3

TABLE 15: Nuclear and Mean Gland dose rates from 1 μCi/g of ^{125}I or ^{129}I in a normal adult human thyroid.

V. DOSES TO THE THYROID IN PRACTICE

The methods discussed in II allow the dose to the thyroid to be calculated, subject to the qualifications raised in IV. In many circumstances it is not possible or even desirable, to perform all the measurements detailed in III in each individual case, as all that is required is an approximate dose estimate. To this end, lists of doses to the gland have been prepared based on the assumption that its mass is 19.6 g and using a particular model for iodide kinetics (113,119,120). From these results data on thyroid dose and whole body dose for a group of nuclides of iodine and technetium are summarized in Table 18. The nuclides were assumed to be administered as Sodium Iodide or Sodium Pertechnetate (119,120).

From the table it is evident that the dose per mCi of ^{129}I is the largest. This is in part due to its exceedingly long physical half life. This is closely followed by ^{126}I and ^{131}I and by ^{124}I and ^{125}I. A reduction of a factor of 5 to 10 takes place for doses from ^{133}I and ^{130}I. A further factor of 10 reduction is evident in the doses from ^{123}I and ^{132}I, accounted for, in part at least, by their short physical half lives. Finally the dose from $^{99}Tc^{m}$ is a factor of 100 down on that from ^{123}I or ^{132}I. From a radiation protection point of view, the ratio of thyroid to whole body dose is of interest. It is clear that this is most favourable for the nuclides giving the highest thyroid doses, and is the order of 1000:1 in all but the short lived nuclides (168). It is also of interest that there is little difference in the whole body dose per mCi from $^{99}Tc^{m}$, ^{123}I and ^{132}I.

In individual cases departures from these estimates may be dramatic due to variations in iodine kinetics and gland mass. For example the variation in the dose to the thyroid in a group of patients receiving identical therapeutic activities of ^{131}I has been evaluated and is greater than one order of magnitude (149). Such variations are particularly likely to occur to those whose glands are diseased, and consequently should be borne in mind when radioiodine therapy is being prescribed.

Therapeutic medical procedures requiring radionuclide irradiation of the thyroid are for the greater part confined to ^{131}I, although ^{125}I is occasionally used (90,91,92,105,169).The largest activities, of the order of 150 mCi, are admini stered during treatment of thyroid carcinoma and its metastases. The data in Table 16 is of little value in estimating the absorbed dose from this procedure,as the size of the mass being treated is highly variable (III, IV,A), and both uptake and effective half life can be in the region of an order of magnitude lower than normal (6,91,105). The latter properties may sometimes be favorably improved by medical management (91, 105). As indicated in Table 17 the absorbed doses achieved can range from about 1,000 to about 100,000 rads. The limitation on administered activity arises mainly from considerations of the dose to the whole body and, in cases with diffuse pulmonary metastases, the lungs.

In therapy of hyperthyroidism high activities of the order of 10 mCi were traditionally administered (92). In recent years,however, much lower activities in the range 2-4 mCi are not uncommon (170-172), although high dose therapy still persists. To obtain a reasonable estimate of the absorbed dose in rads, the activity retained in the gland in μCi/g and the cumulated activity must be evaluated as outlined in II and III. In the absence of such measurements quoted doses represent, at best, mean values that in individual cases can be highly misleading (149). Subject to this qualification, administered activities in the 10 mCi range are associated with gland doses of 10,000-20,000 rads, and those in the 2-4 mCi range are associated with doses of 2,000 - 10,000 rads (Table 17).

Diagnostic investigations of the thyroid, such as uptake tests or scans using ^{131}I have traditionally had high radiation doses associated with them. For example it was not uncommon to use activities up to 30 μCi for uptake estimates and up to 200μCi for scans (175). The doses associated with these activities would be in the range 40 rads and 250 rads respectively (173 - 75). These doses are unacceptably high given the availability of more sensitive

	UPTAKE	ABSORBED DOSE : RADS/ mCi ADMINISTERED									
		$^{99}Tc^{m}$ +	^{123}I*	^{124}I*	^{125}I*	^{126}I*	^{129}Io	^{130}I*	^{131}I*	^{132}I*	^{133}Io
THYROID DOSE	5	0.13	2.4	180	140	320	700	22	260	2.3	51
	15		7.5	530	450	960	2100	68	800	7.4	161
	25		13.0	890	790	1600	3500	120	1300	13.0	281
WHOLE BODY DOSE	5	0.013	0.025	0.36	0.11	0.28		0.25	0.24	0.10	
	15		0.027	0.59	0.29	0.61		0.27	0.47	0.10	
	25		0.029	0.83	0.49	0.95		0.29	0.71	0.11	
RATIO THYROID DOSE/ WHOLE BODY DOSE	5	10	96	500	1270	1140		88	1080	22	
	15		280	900	1550	1570		250	1700	74	
	25		450	1070	1610	1680		410	1830	120	

* Values from MIRD Dose Extimate Report No. 5 (108)
\+ Values from MIRD Dose Extimate Report No. 8. Uptake values not relevant to $^{99}Tc^{m}$ (110)
o Approximate values calculated by author using MIRD scheme.

TABLE 16: Dose in rads to thyroid and whole body from injestion of 1 mCi of various radionuclides. Uptake values do not apply to $^{99}Tc^{m}$. Uptakes in percent of dose.

PROCEDURE	ACTIVITY ADMINISTERED AND NUCLIDE	ABSORBED DOSE RANGE
Thyroid Carcinoma Therapy	80 - 150 mCi of ^{131}I	10^3 to 10^5 rads
Hyperthyroidism Therapy	1-10 mCi of ^{131}I 5-50 mCi of ^{125}I	1,000 - 15,000 rads 1,000 - 30,000 rads
Thyroid Scan	2-3 mCi of $^{99}Tc^m$ 50-100 μCi of ^{131}I 50-100 μCi of ^{123}I	0.2 - 2.0 rads 30 - 300 rads 3 - 50 rads*
Thyroid Uptake	5-50 μCi of ^{131}I, 5-50 μCi of ^{123}I	3 - 150 rads 0.3 - 25 rads*

* including contributions from ^{124}I.

TABLE 17: Typical Dose Ranges for Medical Procedures. Extreme values are not accounted for.

equipment and alternative nuclides (173,174). Consequently,for many purposes these tests in their traditional forms can be regarded as hazardous and obsolete (174). With modern equipment,uptake tests may be performed using as little as a few μCi of ^{131}I, which substantially reduces the gland dose. A further reduction may be achieved by using ^{123}I if it is available, and its short half life does not interfere with the purpose of the test being performed. In making dose estimates for ^{123}I,it is well to remember that it is usually contaminated with ^{124}I. With commercially available material,this will approximately double the thyroid dose, and may give rise to some technical problems (173). Thyroid imaging using $^{99}Tc^{m}$ provides excellent scans with a greatly reduced thyroid dose although with the activities commonly used the whole body dose is comparable with that from a ^{131}I scan. As $^{99}Tc^{m}$ pertechnetate is not a perfect analogue for iodine, special cases exist where an iodine scan will still be required (151,175).Doses associated with typical diagnostic procedures are listed in Table 17.

Apart from the above situations,the thyroid may also be irradiated by being included in direct or scattered radiological beams from both therapeutic and diagnostic sources. The doses received vary in their size and consequences (6,72,176-178). The gland is also sometimes irradiated to quite high dose levels, during radionuclide investigations primarily aimed at other organs. These doses may be minimized by using effective thyroid blocking or discharge procedures (89,179).

Accidental or unintentional irradiation of the thyroid is most likely to occur through ingestion of nuclides of iodine or other materials with similar dosimetric properties. In practice such incidents are most likely to occur in those handling such nuclides for medical and/or biological applications, to persons working in the nuclear industry, or following uncontrolled release of fission products. The most widespread procedures that presently give rise to a serious risk of ingesting radioiodine are those associated with ^{125}I

protein iodination and those related to dispensing and administering therapeutic doses of ^{131}I. In many institutions, work of this nature is performed on a regular basis up to several times per month. Table 18 lists approximate thyroid doses that would result from ingesting small amounts of activity during such procedures. The amounts that would have to be ingested to reach the maximum permissable doses allowed by various regulatory agencies are also listed (168,180-182). From the table it is evident that there should be little practical difficulty in keeping the annual dose below 5 rads. Higher dose limits require sustained activities in the gland that approach those used for diagnostic purposes (173). One of the most useful devices for reducing ingestion is a well designed fume cupboard, which as illustrated in Fig. 19 is very effective in this regard.

In the aftermath of nuclear explosions or other incidents involving release of fission products, radionuclides of iodine may be relatively abundant. Since the circumstances of each incident are different no, general guidelines on the thyroid dose can be presented. However primary data on particular events are available and of interest (87). With regard to the release of small amounts of fission products into the environment, particular attention must be paid to ^{129}I. Because of its exceedingly long physical half life, once it is introduced into the environment it is difficult to eliminate. Consequently, its concentration in stable iodine must be monitored and kept low (156). Its dosimetry in the thyroid also needs further investigation, particularly in view of the existence of long term stagnant pools of iodine even in normal glands (163,167).

The figures presented above are intended to provide approximate rather than accurate estimates of the dose in individual cases. They apply only to human thyroids. Dose estimates for experimental animals would be quite different due to the gland mass considerations outlined in IV,A and due to substantial differences in iodine kinetics.

Radionuclide	Dose per year (rad)	Typical Incident(s) leading to dose
^{131}I	1.5	Ingestion once of ~1 µCi
	5.0	Ingestion 20 times of ~0.15 µCi
	30.0	Ingestion 20 times of ~1 µCi
	50.0	Ingestion 20 times of ~1.5 µCi
	150.0	Ingestion once per week of ~1.5 µCi
^{125}I	1.0	Ingestion once of ~1 µCi
	5.0	Ingestion 20 times of ~0.25 µCi
	30.0	Ingestion 20 times of ~1.5 µCi
	50.0	Ingestion 20 times of ~2.5 µCi
	150.0	Ingestion once per week of ~2.5 µCi

TABLE 18: Typical incidents leading to annual thyroid radiation doses in the range 1.0-150 rads

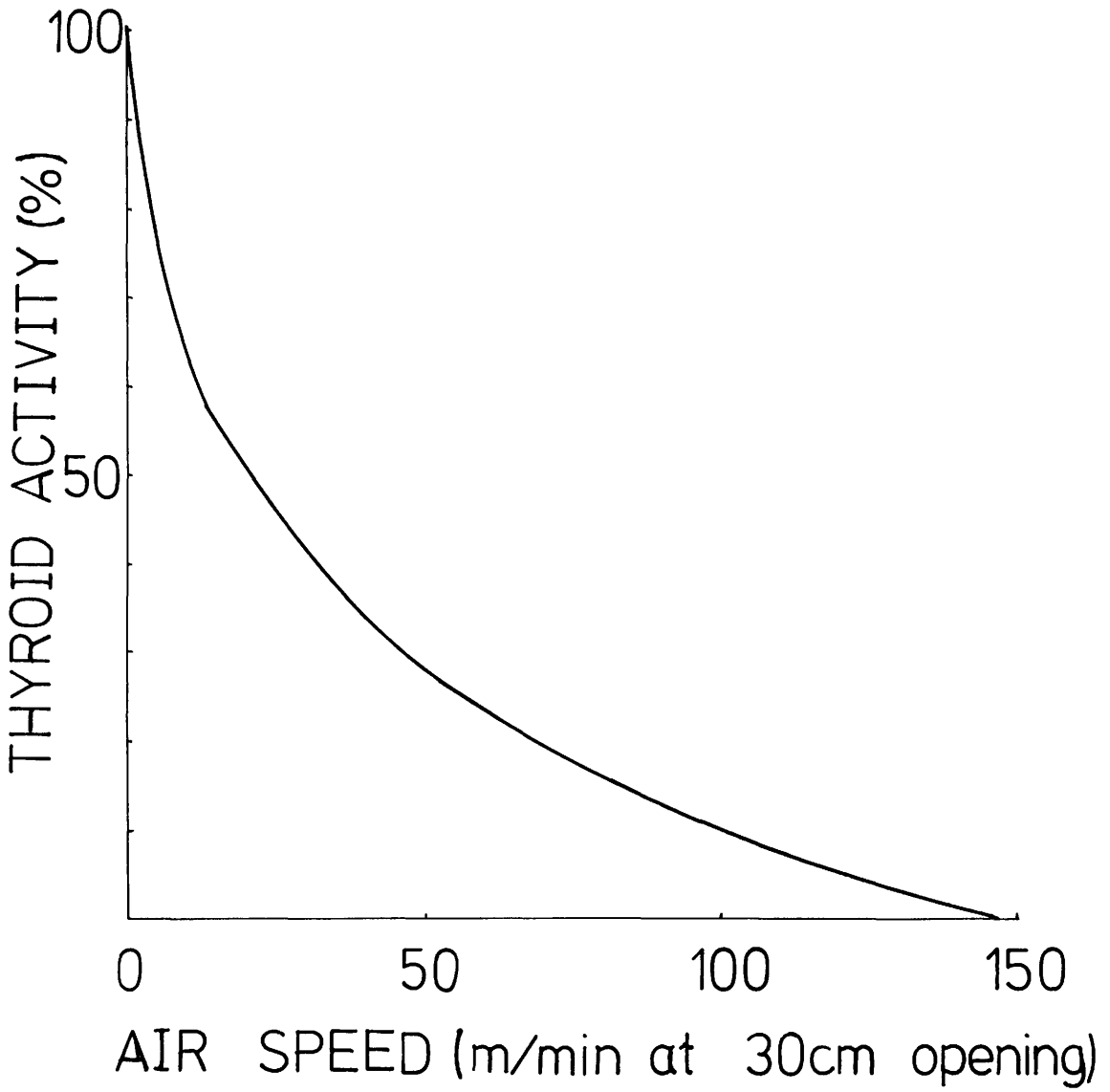


Fig. 19 : The relative ^{125}I activity present in the thyroid of workers performing protein iodinations as a function the air speed in a fume cupboard. Redrawn and adapted from an original by Birchall, (86).

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J.E. DUMONT

SECTION IV

CONTROL OF PHYSIOLOGICAL FUNCTION AND GROWTH IN THE UNIRRADIATED THYROID

I. Cellular Physiology of the Thyroid Follicular Cell

II. Control of Thyroid Metabolism
- A. The Action of TSH
- B. Intracellular Biochemical Regulatory Mechanisms
  - 1) The Cyclic AMP System
  - 2) Regulation by Iodide of Cyclic AMP System
  - 3) Role of Calcium
  - 4) The Cyclic GMP System
- C. Other Possible Physiological Controls Besides Thyrotropin
- D. Control of Human Thyroid
- E. Control of Thyroid as it affects Iodine Metabolism

III. Control of Thyroid Growth

IV. Thyroid Cell Kinetics
- A. The Normal Thyroid at Rest
- B. The Stimulation of Cell Proliferation

The thyroid has two main endocrine functions : secretion of thyroid hormones, thyroxin (T_4) and triiodothyronine (T_3), which is carried out by the follicular cells and the secretion of calcitonin by the C cells. Thyroid hormones are first synthesized as a prohormone, thyroglobulin (Tg), a large glycoprotein. This prohormone is released with thyroid hormone from the thyroid. In the present section, we shall review recent developments on the function and growth of the thyroid and on their control.

I. CELLULAR PHYSIOLOGY OF THE THYROID FOLLICULAR CELL

The role of the thyroid follicular cell is to trap iodide and to use it for the synthesis of the thyroid hormones. This metabolism proceeds by several well defined steps (Fig. 1) (221-230).

- the trapping of iodide by active transport at the base of the cell against an electrical gradient and its transport in the follicular lumen where it is concentrated (226,227).

- the oxidation of iodide by a peroxidase, presumably at the interface of the cell ant the lumen (i.e. on the microvilli), into an oxidized form of iodine and its incorporation in the tyrosyl groups of thyroglobulin, forming mono (MIT) and diiodotyrosine (DIT) residues in the protein. The H_2O_2 used by the peroxidase is supplied by an ill defined H_2O_2 generating system which uses $NADPH+H^+$ as coenzyme (221,223,229).

- the oxidative coupling in the thyroglobulin molecule of already formed iodotyrosines into iodothyronines T_4 and T_3 and very small amounts of rT_3. This oxidation seems to be catalyzed by the same peroxidase (rT_3 is 3-3'-5' triiodothyronine) (221,223,229).

- by diffusion and, in some species, by the stirring of ciliae, thyroglobulin slowly mixes in the colloid; iodination and oxidative coupling take place when the molecule encounters the apex of the cells; the rapidity of this process depends on the level of activity of the gland (231).

- secretion seems to require the internalization of thyroglobulin in colloid droplets for its digestion by lysosomal enzymes. Ingestion may be carried out by two processes : micropinocytosis (232) or pseudopod engulfment and macropinocytosis i.e.phagocytosis (222, 233). The latter

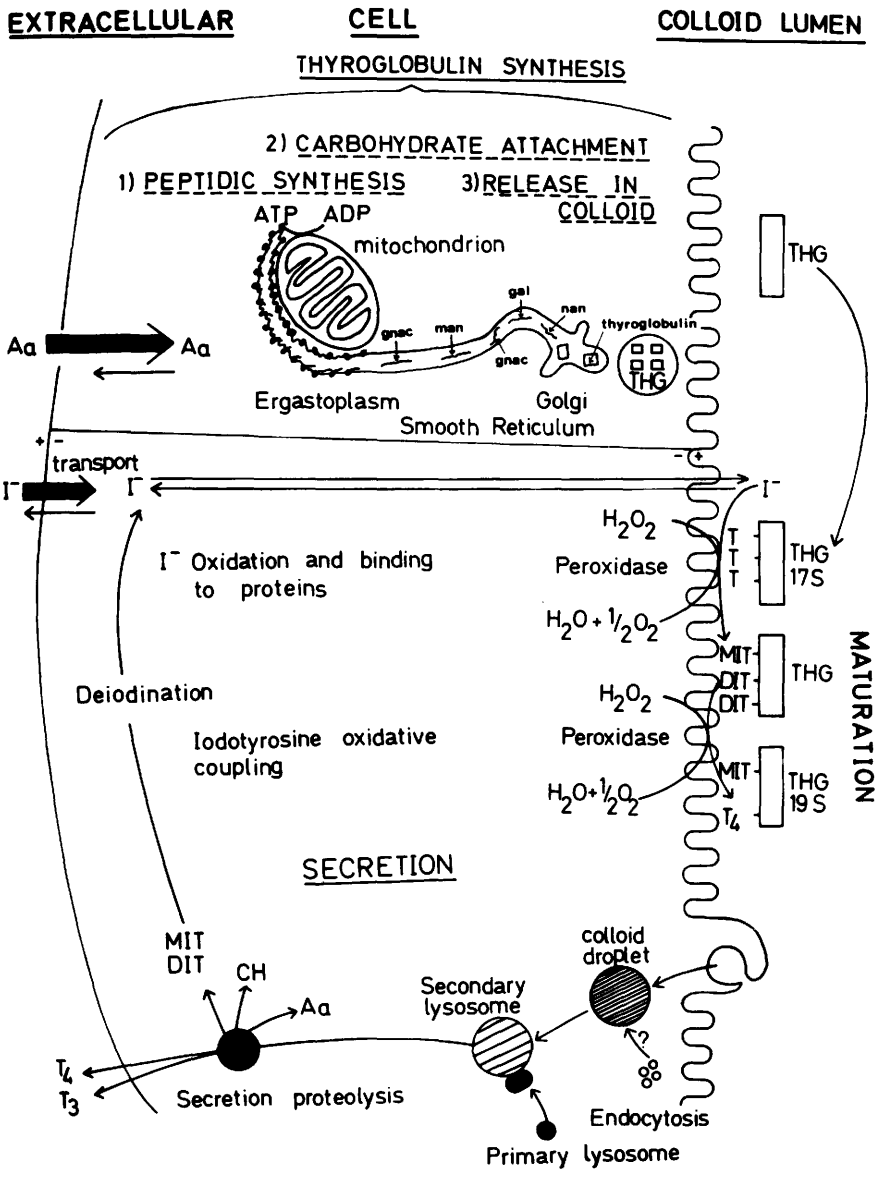


Fig. 1 : Cellular physiology of the thyroid gland

mechanism accounts for thyroid hormone secretion after acute TSH stimulation, but the role of the two processes in basal secretion is still debated.

- digestion of thyroglobulin is carried out in secondary lysosomes first by reduction of SS bonds by glutathione (GSH) and then by proteolysis (234).

- it is assumed that after proteolysis the iodothyronines diffuse from the secondary lysosomes in the cell and from the cell to the extracellular space (222, 224) but an exocytotic process is not excluded.

- iodotyrosines are deiodinated in the cell by a $NADPH+H^+$ dependent deiodinase and this iodide mixes with newly entered iodide. Released aminoacids and carbohydrates presumably mix with the cellular pools while the lysosomes recycle (222). There is evidence that some tyroxine is deiodinated to T_3 and rT_3 in the follicular cell, more so after TSH stimulation, which accounts for the fact that T_3 and rT_3 secretion are more important than their relative concentration in Tg would allow (235,236).

The metabolism of iodine in the thyroid is geared for efficient utilization of a scarce and highly discontinuous supply of iodide to the organism : the trapping of iodide can achieve a gradient of more than 100 to 1; I^- is concentrated in the follicular lumen where iodination takes place. For physiological concentrations, all the iodide taken up is immediately oxidized and bound to Tg; the Tg peroxidase system is able to synthesize iodothyronines with very few iodine atoms per Tg molecule (237). Thus the capacity of the thyroid to synthesize thyroid

hormone is mostly in excess of the regular requirements for these hormones, allowing it to use efficiently even transient supplies of iodine. The high storage capacity of Tg for iodine and of the colloid lumen for Tg allows a normal thyroid to sustain steady secretion of iodothyronine for a long time after a block of synthesis.

II. CONTROL OF THYROID METABOLISM

Until very recently, it was accepted that the activity and growth of thyroid tissue was controlled by one factor : the TSH plasma level. In such a scheme the gland responds only to a positive signal, TSH, which itself is controlled by a negative feedback at the level of hypophysis. As the only control is positive, the system may be called unidirectional (238). However, it was later shown that the iodine supply exerts a negative control on the gland. Moreover, several other factors have been shown to influence thyroid metabolism in vivo or in vitro : the thyroid hormones themselves, catecholamines and cholinergic agents. The physiological relevance of these factors remains to be demonstrated. TSH, the main regulatory agent, is secreted discontinuously by the hypophysis; its concentration exhibiting a nocturnal rise (239). It does not appear to be catabolized by its target organ (240).

A. The Action of TSH

TSH stimulates all facets of thyroid metabolism. On the basis of kinetics, two types of effects can be distinguished : rapid effects which correspond to a functional activation (e.g., activation of secretion, iodothyronine synthesis and of general metabolic pathways) (241) and delayed effects which correspond to growth or to an increased functional capacity of the tissue (increased syntheses and thus increased volume of cells, RNA and protein contents of cells and number of cells) (241-245).

The stimulation of secretion mainly bears on the first step of this process, i.e., phagocytosis. In dogs, pseudopod formation takes place within 2 min. after TSH addition to the incubation medium of thyroid slices (246), intracellular accumulation of colloid droplets follows (247, 248); thyroid hormone release is increased 10 min. after TSH injection (248,249). The amplitude and the length of this effect increase with the dosage of hormone. The kinetics of TSH action on iodide transport is clearly biphasic : it is depressed early (up to 1 to 2 hours) and greatly enhanced thereafter (249, 250). The former effect is due to an acute increase in iodide efflux rate from the follicular cells presumably reflecting a general increase in membrane permeability (251). The latter effect is caused by an enhanced unidirectional clearance of iodide by the cells presumably reflecting the induction of iodide carriers (252). The activation of iodide binding to proteins and of iodothyronine formation is also very rapid. Two enzymatic systems are involved in this process : the generation of H_2O_2 and the oxidation of I^- by a peroxidase (221,229,253,254). As no rapid effect of TSH on peroxidase activity has been observed (255) and as H_2O_2 mimics the action of the hormone it is probable that the H_2O_2 generating system is the target of activation (241,256).

The in vivo stimulation of thyroid blood flow is an early or a delayed effect depending on the species (248,257,258).

In general all the rapid effects of TSH are not inhibited by protein or RNA synthesis inhibitors while the delayed effects which have been studied in this regard are inhibited by such agents (252, 259, 260). In the latter case, it is therefore believed that the hormone acts at the transcription level (252). Chronic stimulation causes both types of effects, i.e., activation and hyperplasia. The hyperplasia is characterized

by an increase in the number and in the volume of thyroid cells and an increase in the concentration of ribosomes (241, 243, 245).

The effects of any hormone may be distinguished, from a physiological point of view, by at least two criteria : the delay of the action and the nature of the action (Table I). The delays vary from seconds to days. The effect may be to stimulate or inhibit an existing function, or to induce a new function (i.e., to differentiate) in the target cell. The induction of a new function obviously implies the formation of selective units, these units being enzymes, organelles, etc. The stimulation of a function may imply an increase in the number of units (growth) or an activation of existing units. The primary biochemical mechanisms involved in these actions may be very simple such as changes of permeability (eg. to Ca^{++}) or in membrane transport, or the formation, or the release of allosteric effectors (e.g., cyclic nucleotides). When new units are formed, the mechanisms may operate at the translation and/or at the transcription level; an induction, i.e., a differentiating action, would presumably require an effect at the level of transcription. A probable point of action of the signal in the cell may be proposed for each mechanism (e.g., plasma membrane for effect on permeability, nucleus for transcriptional events, etc.). It is obvious that an action which requires prior synthesis of RNA and of protein will require at least an hour and sometimes days whereas an effect on the membrane may be quasi immediate. Similarly effects which require RNA synthesis will be blocked by inhibitors of transcription (e.g., actinomycin) and translation (e.g. puromycin, cycloheximide, etc.). Thus,from rather simple considerations a useful classification of hormonal effects may be proposed (Table I). Effects at one level could cause effects at the subsequent levels, e.g., an activation of membrane transport could modify transcription. If an action at a given level causes one of the preceding types of effect, e.g., activation

EFFECTS OF TSH - MECHANISMS OF ACTION ?

	DELAY	INHIBITED BY ACTINOMYCIN	INHIBITED BY PUROMYCIN	POINT OF STRUCTURE	ACTION FUNCTION	PHYSIOLOGICAL SIGNIFICANCE	INCREASE	EXAMPLES	DEPENDENT EFFECTS OF TSH
A	+ SEC	0	0	MEMBRANES	TRANSPORT PERMEABILITY ⋮ (EX: Ca ++)	STIMULATION	ACTIVITY / UNIT	EPINEPHRINE∝ INSULIN ACETYLCHOLINE	↗UPTAKES (GLUCOSE Aa...) ↗PBI FORMATION
B	+ + MIN	0	0	MEMBRANE CYTOPLASM	FORMATION OF ALLOSTERIC EFFECTORS (EX: 3'-5' AMP)	STIMULATION	ACTIVITY / UNIT	ACTH EPINEPHRINE β GLUCAGON	↗PHAGOCYTOSIS ↓ ↗ENERGETIC METABOLISM
C	+ + + MIN	0	+	CYTOPLASM.	TRANSLATION (PROT. SYNTH.)	STIMULATION	N OF UNITS	INSULIN ACTH	?
D	+ + + + + + HOURS	+	+	NUCLEUS	TRANSCRIPTION (RNA SYNTH.)	STIMULATION	N OF UNITS	ALDOSTERON ANDROGENS ESTROGENS	↗IODIDE UPTAKE ↗ WEIGHT ↗ RIBOSOMES... ↗ MITOSES.....
E	+ + + + + + + + + + + + DAYS	+	+	NUCLEUS	TRANSCRIPTION (RNA SYNTH.)	DIFFERENTIATION	PRODUCTION OF SELECTIVE UNITS	ERYTHROPOIETIN ECDYSON	APPEARANCE OF Tg SYNTHESIS I^- UPTAKE I^- OXIDATION FOLLICULAR STRUCTURE

HORMONE → A → B → C → D

HORMONE → A

D C B

Table 1 : Mechanisms of actions of hormones

at the transcription level causing a change in membrane permeability, this effect acquires the characteristics of its cause (e.g., delay, sensitivity to inhibitors, etc.). However, it is conceivable that the signal may act independently at the different levels. In the case of TSH, one can find effects at all the levels. Whether they are all secondary to a unique primary biochemical event (e.g., the activation of adenylate cyclase) is doubtful.

A present working model of the regulation of thyroid cell metabolism is outlined in Fig. 2 .

B. Intracellular Biochemical Regulatory Mechanisms.

Three types of regulatory circuits have been demonstrated : a) the cAMP system; b) the cGMP-Ca^{++} system; c) the iodide feedback loop (XI). The cAMP and cGMP systems are located in follicular cells (261) as is presumably the iodide loop. In such a scheme continuous lines represent chemical reactions while interrupted lines represent negative (—) or positive (+) controls, i.e., inhibitions or activations. As can be seen, TSH acts on the thyroid cell mainly through activation of adenylate cyclase; cyclic 3'5'-AMP formed by adenylate cyclase is degraded by specific phosphodiesterases; it acts on the cell metabolism through activation of cAMP dependent protein kinases; phosphorylation of cellular proteins by the enzymes activate or inactivate these proteins thus eliciting the hormonal effects. This scheme is the direct application to TSH and thyroid of the general Sutherland concept of hormonal action (262, 263). In some species, adrenergic agents, by a β type of effect, also activate thyroid adenylate cyclase. The cyclic 3'5'-AMP system is negatively controlled by the iodide supply of the gland, this control being exerted by a postulated oxidized derivative XI. This action probably bears on adenylate cyclase. As in other tissues, intracyto-

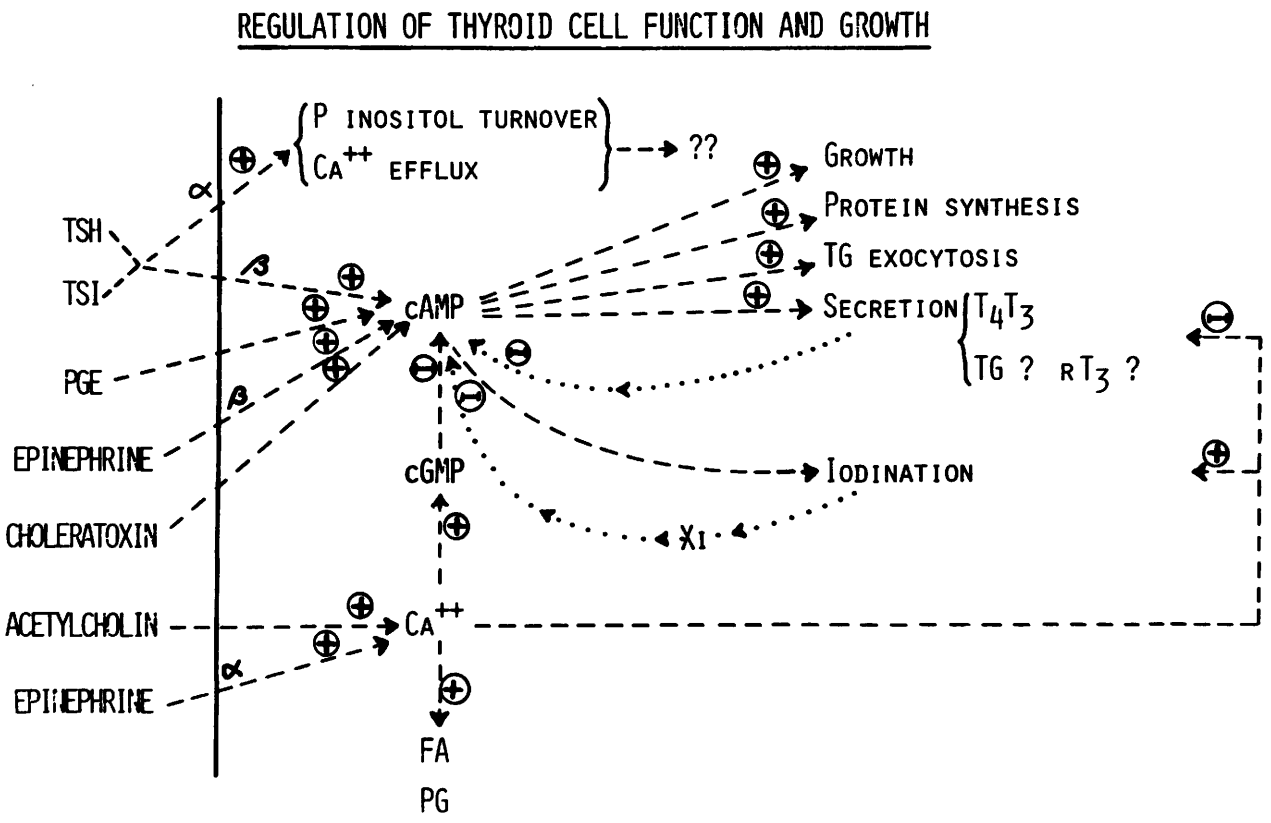


Fig. 2. : Control of Thyroid Metabolism

FA : Fatty Acids

PG : Prostaglandins

P Inositol : Phosphatidylinositol

plasmic Ca^{++} also plays a regulatory role. Its level presumably depends from the balance between passive influx through the plasma membrane, or from intracellular stores (e.g., mitochondria), and the active outflow by the plasma membrane and uptake by the mitochondria. This level is increased by acetylcholine. Ca^{++} mimics some effects of TSH (e.g., it activates protein iodination) but antagonizes some others (e.g., cAMP accumulation, secretion). The level of intracellular Ca^{++} regulates cGMP accumulation; but the role of cGMP is not known.

The scheme presented does not account for some TSH effects which are clearly not secondary to adenylate cyclase activation (such as the acceleration of phosphatidylinositol turnover) (264,265).

1) The Cyclic AMP System

It is now well accepted that most effects of TSH on the thyroid are secondary to the activation of thyroid adenylate cyclase by the hormone (241, 266). However, it should be pointed out that the criteria proposed by Sutherland to validate this hypothesis (262) have only been fully satisfied for dog thyroids in vitro and for some effects of TSH, namely the activation of secretion and of the binding of iodide to proteins.

Whether cyclic AMP is the secondary messenger of TSH growth promoting action is not yet proved. Cyclic AMP or its analogues mimic several TSH activations of biosyntheses in intact cells in vitro : of proteins synthesis (267, 268) of ornithine decarboxylase synthesis (269,270), of precursors incorporation into RNA (241,242,244,267) of RNA polymerase (267), the induction of an iodide trapping capacity in isolated cells (252), etc..., but the relation of these effects to growth is not proved. Cyclic AMP as well as cyclic GMP promotes thyroid growth and accelerates protein and RNA synthesis when injected in vivo (271,272). Inhibitors of phosphodiesterase such as the methylxanthines

potentiate goiter formation in vivo (273). However, they may raise cGMP as well as cAMP levels. Moreover, it is difficult to exclude absolutely indirect effects (e.g., on TSH secretion) in these in vivo experiments (241). The evidence therefore suggests that cyclic AMP, at least partly, mediates the growth promoting action of TSH. However, this is far from proved and this hypothesis remains doubtful for two reasons :

- the failure to induce true growth by cyclic AMP or an analogue in an in vitro intact cell system(274). This negative evidence itself is of doubtful value as the DBcAMP concentrations used were much less potent than the TSH concentrations which elicited cell multiplication (241).
- the prevailing hypothesis in the cyclic nucleotide field that cyclic AMP rise induces differentiation while cyclic GMP or/and Ca^{++} rise and cyclic AMP fall cause growth (224,238,275).

That TSH and cyclic AMP may induce differentiation is suggested by the fact that in thyroid cell culture both induce the formation of follicle like structure and the resumption of iodide uptake and binding to proteins, and thyroid hormone synthesis (276). Since differentiation of thyroid in the fetus in vivo occurs in decapitated embryos, it is not sure whether this action of TSH has a role in vivo (277).

2) Regulation by Iodide of the Cyclic AMP System

The scarcity of iodide in food and its irregular intake are compensated by a very efficient iodide trapping mechanism in the thyroid, by the availability of excess thyroglobulin in the follicular lumen to bind iodine and by storage of this iodine in the thyroglobulin. All the biochemistry of the thyroid is geared to retain and make the most efficient use of iodine. It is therefore to be expected that regulatory mechanisms should exist to shift

this pattern in case of excess iodine intake. Indeed, iodide at high concentrations inhibits its uptake (278) and its binding to proteins in thyroid (the Wolff-Chaikoff effect) and decreases secretion and blood flow in activated glands (278,279). Moreover, the iodide supply in the diet modulates the response of the thyroid to TSH, and iodine deficiency induces thyroid growth in hypophysectomized animals (280,281).

Iodide in vitro inhibits the TSH enhancement of cAMP accumulation. Several indirect arguments have suggested a model to explain this action. Iodide after its trapping by the follicular cell is oxidized by thyroid peroxidase and bound to thyroglobulin : part of the oxidized iodide is transformed in a compound XI which negatively controls cAMP accumulation by inhibiting adenylate cyclase, activating the phosphodiesterases or cAMP efflux from the cells (282). This model accounts for several data obtained with dog thyroids. XI may also affect directly some steps of iodine metabolism (such as trapping) (283) or the action of cyclic 3'5'-AMP (284). The identity of XI and its mechanism of action are unknown. The XI scheme does not account for all the inhibitory effects of iodide which are not relieved by perchlorate or peroxidase inhibitors. It is therefore probable that other mechanisms will have to be postulated to explain effects, such as the inhibition by iodide of secretion in hyperthyroid patients with antithyroid drugs. Moreover, results showing that iodothyronines inhibit directly thyroid function (285) suggest that thyroid hormones themselves may constitute negative feedback signals if not XI. The rapid kinetics of the action of methimazole bears against this hypothesis. However, independently of iodide, the interest of an intracellular negative control by thyroid hormone is obvious : the iodothyronine content of thyroglobulin would modulate the response of the cell to TSH, i.e., the amount of thyroglobulin taken up and hydrolyzed, i.e., the secretion of thyroid hormones.

3. Role of Calcium

Tissues can be divided in two categories. In unidirectional systems the tissue is only submitted to positive control, i.e., to the action of one stimulatory signal. In bidirectional systems, the tissue is regulated both by positive and negative control, i.e., by stimulatory and inhibitory signals (238,275). It has been proposed that in unidirectional systems cAMP on the one hand and cGMP and/or Ca^{++} on the other hand act in parallel, whereas in bidirectional systems both types of signals would be opposite (238,275).

The predominant role of Ca^{++} as a signal for muscle contraction in the excitation-contraction coupling and in the excitation-secretion coupling raises the question of a possible role of calcium in thyroid secretion or more generally in the regulation of thyroid metabolism (224,233,241). Extracellular Ca^{++} is not necessary for the primary effect of TSH on thyroid, the increase of cyclic 3'5'-AMP accumulation, nor for one of its consequences, secretion, but is required for two other metabolic effects induced by this primary action : the activation of iodide binding to proteins and of glucose oxidation (233). A rise of intracellular Ca^{++} per se in the thyroid stimulates very much these metabolisms (286); Ca^{++} is thus necessary and sufficient to elicit such activations. On the other hand, not only does Ca^{++} not increase cyclic 3'5'-AMP accumulation and secretion but it depresses these variables . Thus Ca^{++} appears to have both similar and opposite effects to TSH and cyclic 3'5'-AMP (286). TSH accelerates the release of intracellular calcium. Thus, TSH causes a translocation of Ca^{++} in thyroid tissue (287). This effect could correspond to an increased release of Ca^{++} from an intracellular sequestrating site to the cytosol, with a subsequent spill-over of this Ca^{++} out of the cells, but it could as well reflect an increase in the discharge of Ca^{++} from the cytosol to the extracellular space. This action could correspond to an increase or a decrease of cytosol

Ca^{++} level. The role of Ca^{++} in TSH action thus remains to be elucidated.

4) The Cyclic GMP System

Elements of the cGMP system have been identified in thyroid. This tissue contains cGMP (286,288) and a guanylate cyclase (289). In dog thyroid slices in vitro, cGMP levels are enhanced by carbamylcholine and acetylcholine (286 , 288). The action of carbamylcholine is inhibited by atropin (10^{-6}M); it corresponds to a muscarinic effect. Under various experimental conditions, TSH failed to enhance cGMP levels in thyroid.

In thyroid slices, whatever the stimulatory agent, no increase in cGMP level is observed in the absence of Ca^{++} in the medium. Thus Ca^{++} is required to increase cGMP level in thyroid cells. In the presence of ionophore A23187, calcium per se (10^{-3}M) markedly enhances cGMP concentration in dog thyroid slices. Thus calcium is necessary and sufficient to raise or even to maintain intracellular cGMP level (286). If we start to understand the regulation of cGMP concentration in thyroid, its role remains unclear. According to the Yin-Yang hypothesis (238), cGMP could be expected to antagonize cAMP action if the thyroid is a bidirectional system, or to mimic cAMP action if the thyroid is a monodirectional system. In fact, all agents which raise cGMP levels in thyroid cells activate, as TSH, the binding of iodide to proteins and the pentose phosphate pathway, but depress the stimulation of cAMP accumulation and of thyroid secretion induced by TSH. These effects are abolished in calcium depleted thyroid slices. Thus, the thyroid cell behaves neither as a unidirectional nor as a bidirectional system, but rather as a system with both types of properties (286).

The question may of course be raised whether in vivo the thyroid is a uni- or bi-directional system. Classically, until now, the thyroid as the adrenal has been considered as a typically unidirectional system, being regulated by one positive signal (TSH or ACTH). However, the existence of

cholinergic sensitive cGMP accumulation as well as of cholinergic nerve terminals in some thyroids are compatible with the hypothesis of a negative cholinergic regulation, i.e., with the concept of a bidirectional control of this tissue. It should be pointed out however that, in vivo, stimulatory rather than inhibitory effects of acetylcholine on thyroid secretion have been found (290).

All the agents which increase cGMP concentration in the thyroid tissue thus also elicit certain metabolic effects : activation of the binding of iodide to proteins, of the pentose phosphate pathway, inhibition of cAMP accumulation and of secretion. There is good evidence that these effects are secondary to a rise of Ca^{++} in the cytosol. It is however not clear whether they are caused by Ca^{++} or by the rise in cGMP which is consequent to enhanced calcium concentrations; the question remains whether the increased cGMP accumulation is a necessary link between agents such as acetylcholine and their effects or is a mere by product of this main action. The mechanism by which Ca^{++} or cGMP negatively modulates cAMP accumulation is not clear.

C. Other Possible Physiological Controls besides Thyrotropin

A neural control of thyroid metabolism has been postulated for a long time. Cannon (291) already showed indirectly that cervical sympathetic stimulation could induce thyroid secretion. However because of the demonstration of the central role of the hypophysis in the regulation of thyroid function, and of a normal physiological regulation operating in enervated or transplanted glands these observations were forgotten. Old and recent work suggests that the sympathetic and parasympathetic innervation may modulate thyroid metabolism and its response to TSH (257,292) as in the case of other endocrine glands (293).

The existence of an adrenergic control of thyroid metabolism has been demonstrated in some species but not in others (e.g., the dog) (257,292). In sensitive species, adrenergic terminals, some of them ending up close to follicles, have been observed. The number of these terminals may decrease with age (292). Catecholamines stimulate thyroid secretion in vivo and/or in vitro and when this has been investigated adenylate cyclase of such thyroids responds to these effectors (294,295). The stimulatory effect appears to be cyclic AMP mediated and of the β_2 type. However, some effects inhibited by α type inhibitors have been reported (292). The evidence in favor of a cholinergic control is much less strong at the present time. It consists mainly in the fact that acetylcholine in vitro has a definite action on thyroid metabolism (vide supra) and that it may influence secretion in vivo (290). Prostaglandins seem to play an important role in thyroid metabolism but the nature of this role is still unclear. The thyroid appears to contain prostaglandins of the various types and metabolic studies suggest that it synthesizes them. Prostaglandins of the E type activate adenylate cyclase, raise cyclic AMP levels in thyroid slices and mimic several of the cyclic AMP dependent TSH effects (233, 241, 266, 296). Proteins binding specifically prostaglandins of the E type have been identified (297). It has been reported that TSH increases prostaglandin formation in thyroids in vitro (298) and several mechanisms have been proposed for this action, however in our hands no such effect has been found. The probably important role of prostaglandins in the TSH action and in the regulation of thyroid metabolism remains an open field.

The thyroid is undoubtedly also regulated by other unspecific hormones. Insulin and glucocorticoids are often necessary for the survival or growth of follicular cells in culture (299, 300). Moreover, goiter formation, i.e., growth in vivo is enhanced or requires a secretion of growth hormone

(301) and/or insulin (302), and/or glucocorticoids (303).

D. Control of Human Thyroid

Although the metabolism of human thyroids and its regulation has been much less studied than in animal, the main regulatory circuits described here seem to apply to this tissue. Human thyroid tissue contains a TSH sensitive adenylate cyclase and cyclic nucleotide phosphodiesterases and, when intact, responds by an impressive rise of cyclic AMP to TSH (304, 305). TSH enhances several parameters of thyroid metabolism in vivo and these effects are mimicked by dibutyryl cyclic 3'5'-AMP and by prostaglandin E_1 (306,307). Catecholamines by a β type of effect,also enhance cyclic AMP levels in the thyroid and mimic some TSH effects (305). Adrenergic innervation of the follicles has been demonstrated (308). Carbamylcholine by a muscarinic type of effect raises cyclic GMP levels in the tissue and affects thyroid metabolism. Prostaglandins stimulate thyroid secretion in vivo (309).

E. Control of Thyroid as it affects Iodine Metabolism

Thyrotropin in vivo and in vitro acutely enhances protein iodination, iodothyronines synthesis and thyroglobulin endocytosis with a consequent release of thyroid hormone. Its effect on iodide trapping is biphasic, with decrease during the first two hours, followed by a progressive increase. Thus an acute injection of TSH induces an immediate release of thyroid iodine, followed by a delayed increase of uptake of exterior iodide (241).
Under conditions of chronic stimulation, all the steps of iodine metabolism are accelerated : iodide trapping, binding to proteins as well as its release as iodothyronine. The net result of these effects is to increase the immediate uptake of iodine, but to accelerate very much its release. In chronically stimulated thyroids, the uptake of iodine is high but its thyroid half life is considerably shortened. This situation applies in clinical

thyroidology to hyperthyroidism (Graves' disease or Basedow's disease) and certain types of endemic goiters. Similarly under conditions of chronic local activation (eg. in chronic thyroiditis or toxic adenomas) the release of iodine is generally rapid even though the total iodine uptake may not be increased.

The adaptation to iodine deficiency classically consists in greatly increased iodide trapping in the thyroid. Whereas this may be accompanied by a faster release of iodine, in the established cases of endemic goiter, as well as in many cases of sporadic goiter, iodine turnover in the hyperplastic gland is slow.

In chronically understimulated thyroids, eg. under thyroid hormone therapy, all the steps of iodine metabolism are slowed down; the uptake of iodide is low and its half life is prolonged (310).

III. CONTROL OF THYROID GROWTH

The best known and studied mechanism controlling thyroid growth is the tonic regulation by thyrotropin and the pituitary thyrotrophs. However, as reviewed by Doniach (311), other processes exist.

Any treatment that decreases thyroid secretion induces, by relieving the feedback exerted on the pituitary, a secretion of thyrotropin which itself enhances thyroid growth. That such a mechanism applies may be proved by demonstrating a decrease in thyroid hormone level, an increase in TSH level and the suppression of growth by thyroid hormone administration or hypophysectomy. This has been shown to be the case for compensatory hypertrophy (i.e. after removal of one lobe of the thyroid) or in goiters obtained with an iodine free diet or after administration of goitrogens (i.e. drugs which inhibit iodide trapping or oxidation). The fact that, even in hypophysecto-

mized rats, thyroid size remains larger under condition of iodine free diet suggests that intracellular factors (eg. the postulated XI)(282) may also play a role in this type of growth.

After successfull grafting, surviving thyroid follicles exhibit mitotic proliferation and formation of new follicles. A similar phenomenon may be observed in areas of the human thyroid flanking hemorrage or inflammation. This type of hyperplasia, called "reparative growth" is essentially self limited and independent of TSH, as it is not inhibited by thyroxine or hypophysectomy. Whether this process corresponds to a relief of local inhibition or to the release of local activators, such as prostaglandins,by tissue injury is unknown. There is no doubt that tissue injury induces a release of prostaglandins, that prostaglandins enhance cAMP accumulation in thyroid cells and that cAMP appears to be a possible mediator of thyroid cell multiplication (see below). It has been suggested that infantile thyroid growth is similarly independent of TSH,as the glands of rats given daily injections of thyroxine from birth, grow from a birth weight of 1 mg to an adult weight of 17 mg at the age of 4 months (312). However, this evidence should be reexamined by more modern methods (i.e., with serum TSH measurements).

The biochemical mechanisms of cell growth control are still in general poorly understood. The best data available concern mostly fibroblasts in culture. In such systems, there is a negative correlation between cAMP levels and growth,and cAMP itself and its analogues inhibit growth. However, even in fibroblasts, there are cases in which cAMP rises are not accompanied by decreased growth (313) and there is evidence that Ca^{++} may be a positive signal of growth (275). In other types of cells, (eg. the lymphocytes) cGMP has been proposed as a positive signal of growth (314). In the thyroid TSH stimulates cell growth and multiplication in vivo and in culture. On the basis

of experiments in which TSH, but not DBcAMP, enhanced thyroid cell multiplication in culture it has been suggested that this TSH effect is not mediated by cAMP (274). However, the concentrations of TSH and DBcAMP used were not equivalent, the DBcAMP concentration being in other system equipotent with 1/100 of the TSH concentration used (241). Moreover, there are now several arguments supporting concept that in the thyroid cAMP may be one of the positive signals of growth :

1) cAMP as TSH enhances protein synthesis in vitro and increases, presumably by an action at the transcription level, iodide transport (241,252)

2) cAMP as TSH enhances ornithine decarboxylase synthesis which is a concomitant of cell growth is most eucaryotic systems (269,270)

3) cAMP as TSH injected in vivo induces thyroid growth (271)

4) cholera toxin, the only known action of which is to activate adenylate cyclase, enhances, as TSH, the growth of dog thyroid cells in culture (217)

Although there are alternative explanations for all these results, we think that they strongly suggest that cAMP may be a the mediator of growth in follicular cells.

At the present time, nothing is known on the other possible regulators of thyroid growth outside (e.g. prostaglandins, acetylcholine, growth hormone, insulin, etc) or inside (Ca^{++}, cGMP, etc.) the cell.

IV. THYROID CELL KINETICS

A. The Normal Thyroid at Rest

All the functions of the thyroid in iodine metabolism and iodothyronine secretion are carried out in the functional units of the gland, the follicles, whose elements, the follicular cells, enclose the colloid lumen. Beside these

cells, the thyroid also contains from 20 to 30 % stromal cells, mainly fibroblasts and endothelial cells, and scarce C cells (the calcitonin secreting cells)(245,315). The thyroid cells normally undergo little mitotic activity, but they can be induced to do so under direct or indirect stimulation (goitrogen diets, TSH)

Whatever the species in which it has been measured, the renewal rate of adult thyroid follicular cells is very slow (Fig. 3). In young mice the ^{3}H thymidine labelling index (percent of S cells in the population, at any time) is about 0.19 % (316) and in adult rat about 0.14 % (6). As gland weight and cell number are relatively constant, the proliferative activities indicated by the index simply reflect cell renewal. In mice, the length of the S phase (as measured by double labelling) is about 5.2h (316), which is very similar to S-phase duration in most tissues of the mouse and rat. In the rat thyroid it has been assumed to be at least 6 h (6). Knowing the S-phase duration (t_S) and the labeling index (L.I. = percent of ^{3}H thymidine pulse - labeled cells) the turnover time (t_0) in a tissue can be calculated using the formula : $t_0 = t_S : L.I. \times 100$. This represents the time for the replacement of a number of cells equal to that present in the considered population. The equation assumes homogeneous (rectangular) age distributions of cells along the cell cycle (as in steady state populations with cell loss occurring randomly). If growth fraction (G.F.) is unity (that is there is no quiescent compartment) $t_0 = T_c$ (cell cycle time). The turnover time can therefore be estimated at $5.2 \times 100/0.19 = 2736$ h, i.e. more than 100 days, in the rat. Assuming a cell cycle of 50 hrs (6) with ts = 6 h, 12 % of the cells should be labeled if all cells were in the mitotic cycles. As the labeling index is of 0.14 %, GF should be of the order of $\frac{0.14\ \%}{12\ \%} = 1.16\ \%$, i.e. in the thyroid there would be at any given time 1% of the cell population progressing through the cell cycle.

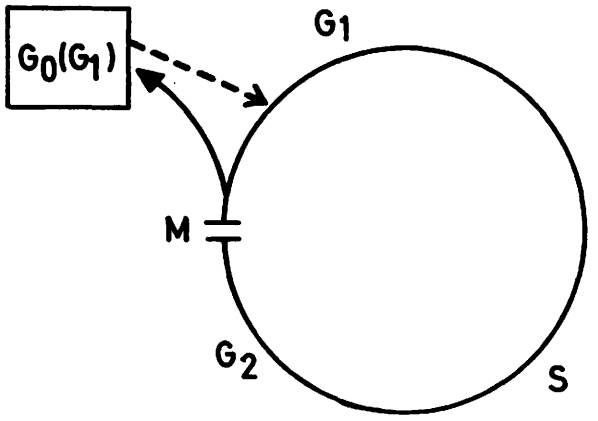


Fig. 3 : The mitotic cycle in eukaryotic cells.

M : Mitosis

S : Phase of DNA synthesis

G_0 : Phase of cells not currently engaged in the mitotic cycle

It should be pointed out that without knowing the growth fraction, such measurements do not allow to establish whether the thyroid is a Go system (i.e. a system in which a few cells would constitute a germinating pool and most of the cells would not participate in the proliferation pool (GF low)) or a G1 system in which most of the cells would participate in the proliferation albeit with very long G1 phases (GF = 1) or an intermediary system. In PTU treated rat Sheline has estimated GF to at least 0.2 (317).

Data on labeling index, S-phase and renewal rate are not yet available in man, although the double labeling in vitro with thymidine could provide such data. The validity of this technique for various tissues has been demonstrated (318). It is known that, even during growth, cell multiplication must be slow in human thyroid. Mitoses are only very rarely seen in the follicular cells. Moreover, Doniach has calculated that the human thyroid weighing 1 g at birth and 20 g by 20 years, without much change in the proportion of follicular cells vs colloid or other cells, the cells must undergo about 5 mitoses in 20 years (319), i.e. about 1 every 3 or 4 years, more if there are cell deaths. Doniach suggests that there may be almost no division in the adult. In our laboratory, preliminary experiments by Galand show very low but definite labeling index in the follicular cell population (of the order of 1/10.000) and somewhat higher proliferative activities in interfollicular cells (Fig. 4).

B. The Stimulation of Cell Proliferation

Acute administration of TSH induces in the thyroid a wave of DNA synthesis and mitoses (241,320). Chronic stimulation by the hormone induces intense cell proliferation, resulting in tissue growth. Such a response can be obtained by direct administration of the hormone or by indirect stimulation of the pituitary by any goitrogenic agent. Such agents by

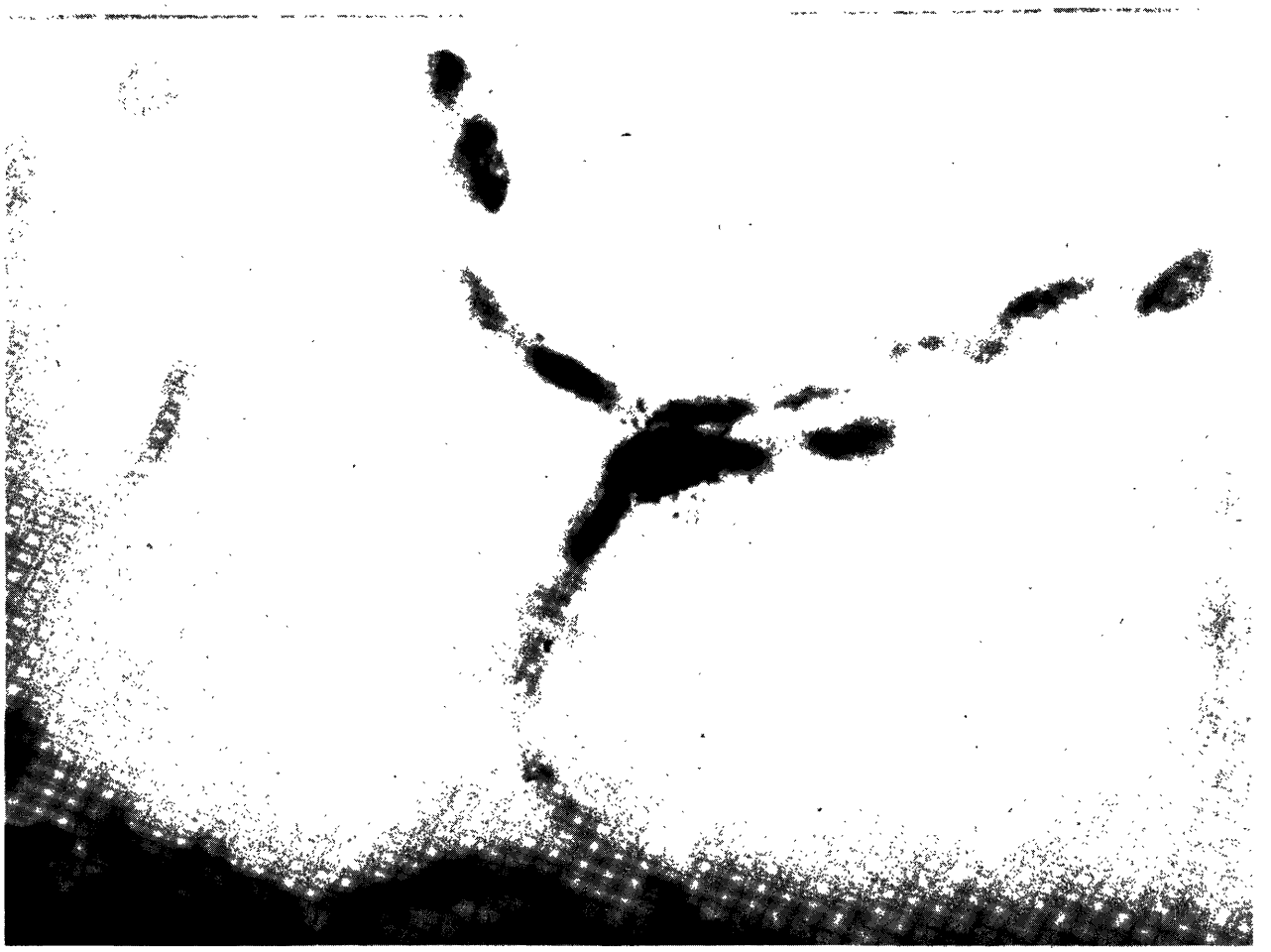


Fig. 4. - Radioautograph from human thyroid gland, following in vitro incubation in the presence of ^{3}H-thymidine (10 uCi/ml) for 15 min. Note a heavily labelled follicular cell, having incorporated the DNA precursor, thus indicating that the cell is engaged into proliferative activity.

- Slices ± 1 mm thick were incubated at 37°C in Eagle Basal Medium (diploid) supplemented with 10 % fetal bovine serum, and gassed with carbogen.

decreasing thyroid hormones synthesis and thus its secretion relieve the pituitary thyrotrophs from the tonic inhibition exerted by these hormones and consequently activate TSH synthesis and secretion.

The kinetics of rat thyroid growth under chronic goitrogenic stimulation follows a classical sigmoidal curve in log weight vs time coordinates : it consists of a lag phase, followed by logarithmic growth and a plateau (6, 204, 321). It mainly reflects cell multiplication as the number of cells per light microscopy field does not change and as total weight and DNA increase in parallel (6, 204). The cell multiplication involves both stromal and follicular cells, the former earlier and more so than the latter (321). The increase in thyroid cell number under chronic stimulation could be due to increased multiplication of a germ cells pool, to expansion of this pool or (if GF = 1) to acceleration of cell division in the whole cell population. The fact that early growth is accompanied by a dramatic increase in the DNA labeling index has been taken as argument in favor of the latter hypothesis (6). Whatever its mechanism, the induced cell multiplication is similar in young and adult rats (317).

It is of interest that removal of the stimulant induces a rapid decrease in the number of cells followed by a plateau at a level higher than the starting level as if 2 populations of cells would exist one stable, the other dying under resting conditions (245).

Several arguments support the concept that the thyroid cells have a small but definite lifespan, i.e. that they can undergo only a limited number of divisions :

a) the growth curves reach a plateau even though the same stimulus remains present (4 to 5 doublings) (6,204).However, if the labeling index decreases it does not fall back to its previous value (321) which suggests

a cell turnover at a higher level.

b) after thyroid weight has reached a plateau, removal of one thyroid lobe does not induce further growth in the remaining lobe (319).

c) assuming that the rate of cell multiplication remains as high in the adult as during growth, with a renewal time of 4 years, the number of thyroid cell divisions in man would be about 15 to 20, in the mice (renewal time 100 days) 12 to 16, during whole life.

d) in culture our dog thyroid cells reach a plateau in their growth (5 to 6 doublings) much before they reach confluence (217).

Such a conclusion has obvious implications in the interpretation of human thyroid pathology and therapy (eg. to interpret the latency of I^{131} treatment of hyperthyroidism). However, it needs to be further substantiated.

RADIATION INDUCED DAMAGE

J.E. DUMONT and

J.F. MALONE

SECTION V

INDUCTION OF THYROID CANCERS BY EXPERIMENTAL IRRADIATION

I. Chemical Effects of Ionizing Radiation and O_2 Metabolism in the Thyroid

II. Effects of Radiation on the Thyroid

III. Induction of Thyroid Cancer by Radiation in Animals and Man

A) Carcinogenesis in Experimental Animals in the Absence of Radiation

B) Radiation Induced Carcinogenesis in Experimental Animals

C) Radiation Induced Carcinogenesis in Man and its Relation to Present Dose Limits.

IV. Present Concepts in Tumorigenesis as Applied to Radiation Induced Thyroid Cancers

V. Biochemical Regulatory Systems in Irradiation Induced Thyroid Cancers.

I. CHEMICAL EFFECTS OF IONIZING RADIATION AND O_2 METABOLISM IN THE THYROID

A detailed analysis of the chemical effects of ionizing radiation in cells is out of place in this monograph. Excellent reviews on the subject have been published (322-334). However, the effects of radiation involve the generation of free radicals, O_2^- and H_2O_2, whereas the thyroid, as the leukocyte, is the site of a very active oxidative metabolism in which H_2O_2 and possibly O_2^- are involved and processed. It is therefore of some interest to review this little considered subject briefly to show how the particular metabolism of the thyroid may affect its response to radiation and to point out areas which deserve to be investigated.

Much of the energy absorbed by irradiated cells goes into producing excited molecules. It appears, however, that most of this energy does not produce chemical reactions and is eventually dissipated as heat. It is ionizations that lead to most of the immediate relevant changes and these changes are subsequently transferred through a chain of chemical reactions, finally producing irreversible damage to critical molecules of biologic importance to the cell. Chemical damage may be repaired before it is irreversible by radical recombination, or other mechanisms, and the energy dissipated as fluorescence, phosphorescence or vibrational energy.

The time required for this entire chain of physical and chemical events, from the initial interaction of the ionizing wave or particle until the initial biologic change, is of the order of milliseconds or less. The subsequent development of biochemical and visible physiologic changes, however, may take hours to days or even longer.

RADIATION AND FREE RADICALS

(after Pryor)

INITIATION

$$H_2O \xrightarrow{Rad} H_2O^+ + e^-$$

$$H_2O^+ \longrightarrow H^+ + OH\bullet$$

$$e^- + H_2O \longrightarrow OH^- + H\bullet$$

PROPAGATION

$$H\bullet + O_2 \longrightarrow HO_2^\bullet \rightleftharpoons H^+ + O_2^- \quad \text{presence of } O_2$$

$$O_2^- + H_2O_2 \longrightarrow OH^- + OH\bullet + O_2 \quad \text{(Haber \& Weiss reaction)}$$

$$H\bullet + RH \longrightarrow R\bullet + H_2$$

$$RH + HO_2^\bullet \longrightarrow R\bullet + H_2O_2$$

$$OH\bullet + RH \longrightarrow R\bullet + H_2O$$

$$R\bullet + RH + O_2 \longrightarrow R\bullet + ROOH \quad \text{presence of } O_2$$

TERMINATION

$$H\bullet + H\bullet \longrightarrow H_2$$

$$OH\bullet + HO_2^\bullet \longrightarrow H_2O + O_2$$

$$H\bullet + HO_2^\bullet \longrightarrow H_2O_2$$

$$OH\bullet + OH\bullet \longrightarrow H_2O_2$$

$$H\bullet + OH\bullet \longrightarrow H_2O$$

$$H\bullet + R\bullet \longrightarrow RH$$

$$OH\bullet + R\bullet \longrightarrow ROH$$

$$HO_2^\bullet + HO_2^\bullet \longrightarrow H_2O_2 + O_2$$

TABLE 1 : Radiation and free radicals (324).

• : symbol of free radical.

The radiosensitive target or critical macromolecule in the cell may be inactivated by direct action, which would, of course, be the only mechanism operative in molecules or viruses irradiated in the dry state. Since roughly 80 per cent of the mammalian cell is water, however, it is probable that most cellular radiation damage is mediated by aqueous-free radicals. Moreover, most of the products from water react with organic compounds to give organic free radicals similar to those formed directly by absorption of radiation (323).

In its simplest form, the ejection of an electron and resultant ionization of water by radiation leads to the formation of hydrogen ($H^{\bullet}$) and hydroxyl ($OH^{\bullet}$) free radicals. Free radicals are atoms or molecules containing unpaired electrons. Such entities are usually highly unstable and therefore very reactive. The free radicals produced by the radiolysis of water generally have a lifetime of the order of a microsecond or less before recombination or reaction with another molecule occurs. Current evidence indicates that under anoxic conditions the $OH^{\bullet}$ radical is the major oxidizing species, whereas $H^{\bullet}$ is the reducing species at the pH of cells. In the presence of oxygen, $HO^{\bullet}_2$ and H_2O_2 become important oxidizing products. The free radicals formed in cellular water may lead to a wide variety of chemical reactions in organic molecules in the cell, eventually terminating in damage to critical macromolecules. The energy may subsequently be transferred within the macromolecule, causing rupture of a bond or other damage quite distant from the initial site of attack. The radiation chemistry of water is schematized in Table I.

Cells irradiated in the presence of oxygen are considerably more susceptible to the development of damage than those irradiated anoxically. It appears that oxygen reacts strongly during the chemical stages of fixation of radiation damage in a number of ways (336). The first is in the

aqueous medium of the cell, where the presence of oxygen leads to the formation of O_2^- and $HO_2^\bullet$ radicals as well as H_2O_2, of which particularly $HO_2^\bullet$ is much more reactive than the radicals produced in the absence of oxygen. In addition, when oxygen is present it may attack organic molecules directly. It does so by combining rapidly with the organic free radicals produced by radiation leading to the formation of peroxy radicals and thus irreversible damage ($R^\bullet + O_2 \longrightarrow RO_2^\bullet$), preventing normal repair reactions ($R^\bullet + H^\bullet \longrightarrow RH$). When the relative radiosensitivity of cells is studied as a function of the oxygen content of the surrounding medium, it is found that sensitivity rises rapidly from the anoxic state and becomes maximal at an oxygen tension (pO_2) of about 20 to 30 mm of mercury. Most normal tissues in vivo, therefore, are maximally radiosensitive, though hypoxic areas of reduced sensitivity may occur deep within tumors, where the vascular supply is poor. Apart from the above effects of oxygen, a number of others have been described and are implicated in physiological aspects of the repair and recovery from radiation damage (436-438).

Free radicals will attack all available organic molecules, the most important targets in cells being proteins and their SH groups, lipids and nucleic acids. Alterations of the latter may imply genetic changes. The principal lesions observed in DNA irradiated in aqueous media have been shown to be hydrogen bond breaks, single or double strandbreaks, and degradation of purine or pyrimidic bases (eg. apurination, apyrimidination, i.e. release of degraded purines and pyrimidines leaving unsubstituted deoxyribose residues in the DNA chain) (323).

Oxygen radicals are also produced naturally in aerobic cells. O_2^- is generated by mitochondria (326), by the autooxidations of intermediates of the electron transport chain (eg. flavins) of hemoglobin, by oxidases (eg. xanthine oxidase), etc. Leukocytes and macrophages generate O_2^- during phagocytosis. O_2^- in the presence of H_2O_2 and trace metals generate highly reactive and

SPONTANEOUS PRODUCTION OF OXYGEN RADICALS IN CELLS

(after Fridovich (329)

Reduced cytochrome P_{450}, flavine , NADPH $\longrightarrow$ e^-

$$O_2 + e^- \longrightarrow O_2^-$$

$$O_2^- + e^- + 2H^+ \longrightarrow H_2O_2$$

$$O_2^- + H_2O_2 \longrightarrow OH^- + OH\bullet + O_2 \quad \text{(Haber and Weiss reaction)}$$

$$H_2O_2 + e^- + H^+ \longrightarrow H_2O + OH\bullet$$

$$OH\bullet + e^- + H^+ \longrightarrow H_2O$$

ENZYMATIC DEFENSES AGAINST O_2 DERIVATIVES

Superoxide dismutases	O_2^-	+	O_2^-	+	$2H^+$	$\longrightarrow H_2O_2 + O_2$
Catalases	H_2O_2	+	H_2O_2			$\longrightarrow 2H_2O + O_2$
Peroxidases	H_2O_2	+	RH_2			$\longrightarrow 2H_2O + R$

(notably GSH peroxidase which generates GSSG)

Ascorbate

$NAD(P)H_2$ Semidehydroascorbate reductase

• symbol of free radical

TABLE 2

toxic OH• (327-330). Several mechanisms have evolved to protect the cell against these free radicals (Table II). The electron transport chain reduces O_2 to H_2O with little release of other intermediates. Mitochondria and cytosol contain superoxide dismutases (329) and there is compelling evidence that these enzymes are the main defense system against O_2 toxicity in bacterial and eukaryotic cells. Catalases and peroxidases also efficiently dispose of H_2O_2, thus further decreasing the probability of OH• formation. If O_2^- toxicity were also due to electronically excited singlet oxygen formation in the Haber Weiss reactions (331) the same mechanism of defense would operate. Ascorbate is also an effective scavenger of free radicals and notably of the superoxide O_2^- radical (332). Semidehydroascorbate is reduced in cells by a still ill defined semidehydroascorbate reductase with $NADH_2$ or $NADPH_2$ as coenzyme. Tissues which contain much ascorbate (adrenal, leukocyte, thyroid) are also tissues with a very active non mitochondrial respiration. This ascorbate system could therefore constitute another defense mechanism against O_2 free radicals.

Systems which protect against O_2 toxicity may decrease radiation damage. It is clear from Table 1 that in the radiochemical decomposition of H_2O the reactions which require O_2 involve $HO_2^•$ and O_2^-. The removal of $HO_2^•$ and its conjugated base O_2^- would obviously decrease OH• and R• generation. Indeed, it has been shown that superoxide dismutase decreases radiation damage in cells in culture and even whole animals (329,333). Similarly, radiosensitive tissues accumulate the semidehydroascorbate radical during exposure to ionizing radiation (334); ant it has been suggested that the higher resistance to radiation of leukocytes in comparison with lymphocytes, is due in part to their higher capacity to reduce semidehydroascorbate (336). While ascorbate itself was formerly considered to have no radioprotective ability in vivo (336), it has recently been shown that ascorbic acid exercises a radioprotective effect on mammalian cell cultures in vitro and on rats subjected to whole body irradiation in vivo (431-433).

In the leukocyte and other macrophages O_2^- generation appears to be an important mechanism for the killing of bacteria (328, 337). These cells themselves are protected against the toxic effects of their products by their enzyme defense mechanisms. Indeed, they contain superoxide dismutase, catalases, GSH peroxidase, GSSG reductase ($NADPH_2$), semidehydroascorbate reductase ($NADPH_2$) and high concentrations of ascorbate. The intracellular O_2^- is transformed to H_2O_2 by superoxide dismutase, and H_2O_2 is reduced by glutathione peroxidase and catalases. The reduction of GSSG formed is carried out by GSSG reductase ($NADPH_2$) and the pentose phosphate pathway with $NADPH_2$ as intermediate, which explains the close coupling of the activation of O_2^- generation and of the pentose phosphate pathway in the leukocyte. Leukocytes and macrophages are also highly radioresistant (335, 337).

Little is known about O_2 metabolism in thyroid. Iodide is oxidized by a peroxidase using presumably H_2O_2 as substrate (228,338). The possibility that lipid peroxides could be used as the oxidizing agent has not been explored. The system which generates H_2O_2 has not been identified; it is known to use $NADPH_2$ as coenzyme (221,339). It could quite possibly be similar to the leukocyte system in which O_2^- is generated by reduction of O_2 by a $NADPH_2$ linked enzyme, O_2^- itself being transformed in H_2O_2 by superoxide dismutase. In fact xanthine oxidase, which generates O_2^-, has been identified in thyroid, and has been proposed as an important source of H_2O_2 in the gland (340). Hᵃti and Degroot have also suggested a role for O_2^- in the generation of H_2O_2 in thyroid (339).

Nothing is known about the existence of defense mechanisms against O_2 free radicals in thyroid, i.e. superoxide dismutase, catalases, GSH peroxidase, GSSG reductase, semidehydroascorbate reductase, etc., although the high concentration of ascorbate and the linkage between activation of iodination

and activation of the pentose phosphate pathway suggest that such mechanisms exist. Knowledge about these defense mechanisms and their regulation would not only be of academic interest in the interpretation of the relative radioresistance of thyroid cells (Section V,II) but it might open new avenues of prevention and protection by the physiological or pharmacological control of these mechanisms. The successfull radioprotection offered by superoxide dismutase in vivo (333) is certainly hopeful in this regard. It is therefore interesting that Murad et al. have proposed the general hypothesis that guanylate cyclase could function as a monitor of O_2 free radicals in the cell and through cyclic GMP regulate their disposal (341). The thyroid contains guanylate cyclase and cyclic GMP and their role in this tissue is now actively studied in our laboratory.

II. EFFECTS OF RADIATION ON THE THYROID

The biological consequences of thyroid irradiation have been subject to investigation for many years, particularly since the introduction of radionuclides of iodine led to its widespread irradiation during medical procedures (6). Among mammalian systems, the gland is unique in that it is one of the few highly differentiated tissues for which it is necessary to develop a complete radiobiology. The knowledge that is required ranges from information on mutagenic and carcinogenic events, through data on cell survival and its relationship with the integrity of the gland as a whole, to the results of studies on the effect of radiation on hormone output, cell function and degree of cellular differentiation.

Despite the need for extensive radiobiological data on the thyroid, the subject has not developed as well as might have been expected, with the possible exception of studies on radiation induced neoplasia (5,6,41,183,184,212).

The reasons for this are mainfold and include, in relation to cell survival and associated studies, the absence, until relatively recently of a method that might be used to quantitatively measure effects in this area. Studies on the effects of radiation on gland function have been equally hampered by the absence of suitable methodology and by the absence of a good tradition of radiobiological measurements of cell function. The in vivo data that are available are difficult to interpret, with the exception of those on extreme effects, such as destruction of the gland. Information on less drastic consequences of thyroid irradiation obtained in vivo is confused by the presence of body pools of hormone and the response of the gland to stimulation via the hypothalamic-pituitary-thyroid axis. Many of these problems may be reduced by the development of suitable tissue culture methods for study of the glands response (96, 186, 211).

The effects of radiation on the thyroid have been reviewed recently by Doniach and Malone (6, 183), and the problems of dosimetry are reviewed in Section III. As indicated there internal irradiation is not easily standardized because of heterogeneity of isotope distribution and differences in dose rate due to differences in uptakes and effective half life. Consequently in many radiobiological studies the dosimetry has been either nonexistant or very approximate in character (6). Although exceptions to this statement exist (99, 160) it is prudent to start by having serious reservations about the validity of all absorbed dose estimates in in vivo radiobiological studies of the thyroid employing nuclides of iodine. Hence we have used, in this section, results which for the greater part were obtained using external X or gamma radiations. Qualitatively similar conclusions may be drawn from internal irradiation data.

If the doses are large enough, acute irradiation may inhibit many pathways of thyroid metabolism. Increasing levels of external gamma ray irradiation will, within a few hours, inhibit purine biosynthesis (50% inhibition for 3500 rads), protein synthesis (75000 rads) and the trapping (300.000 rads) and organification (200.000 rads) of iodine but not O_2 consumption in sheep and calf thyroid slices in vitro. Such rapid effects obviously

involve direct damage to enzymes and membranes. The most sensitive parameters (purine biosynthesis) is only affected by very high doses comparable to large in vivo radiotherapy doses (342,343).

In vivo high exposures to X irradiation (750 to 4500 rads) of sheep induce, after nine weeks, obvious histologic lesions (fibrosis, necrosis, vascular damage, inflammation) without much apparent change in thyroid function (344). Interphase cell death as evidenced by a disappearance of thymidine H^3 labeled DNA from irradiated thyroids also takes place at such levels (194, 208, 345). Other delayed direct effects of radiation at lower levels (250 to 1500 rads) are the appearance of chromosomal abnormalities (190, 346) and decreased growth response to goitrogens, although the DNA content per cell may be increased (203-205, 208, 347- 349). As the major part of this growth response is a direct result of cellular proliferation, this effect reflects inhibition of cell division which may result in mitotic death. This effect not due to artefactual irradiation of the hypophysis as doses of the same order applied to the hypophysis have no such effect (350). A more sensitive sign of radiation damage is observed within 24 hours after irradiation, i.e. the leakage of thyroglobulin from the gland. This effect is demonstrated in rat already after a 5 rads treatment by an increase in plasma PBI (351). Such a leakage might lead to the autoimmune response later observed in I^{131} treated patients (352). As evaluated by electron microscopy, the organelle which appears to be the most sensitive to radiation by moderate doses of I^{131} in the thyroid is the apical plasma membrane (353) which may explain thyroglobulin leakage.

The main consequence of normally encountered heavy in vivo irradiation of the thyroid therefore appears to be the failure of thyroid cells to replicate

and cell death.Xray irradiation induces a latent cell damage which is expressed later as a decreased thyroid growth response under goitrogenic stimulation. In rat, it reduces the plateau level of thyroid weight but not the rate of growth (6). As cell density remains approximately constant under these conditions, the reduction in thyroid weight reflects a reduction in cell number.As it is known that goitrogenic stimulation after irradiation is followed by increases in cell DNA by a factor of two or more, the defect appears to be on the mitotic process. At 2000 rads the block is complete. Qualitatively similar results have been obtained for other tissues : in the weanling mice for instance, 1500 to 2000 rads Xray irradiation block compensatory renal growth completely and permanently (354), and approximately 1800 rads of X-rays is regarded as the tolerance dose of many normal tissues (439).

If the capacity of the cell to undergo mitosis is taken as an index of cell survival, then survival can be estimated from the plateau growth of the thyroid under goitrogenic stimulation using a number of assumptions (6). Measurement of cell survival after irradiation in the thyroid is important

from many points of view. For example, it is thought to be one of the critical parameters in determining the final outcome of radioiodine therapy (6,93,169,201,2 It is also relevant to treatment of thyroid carcinoma and to determining whether or not the carcinogenic action of radiation in the gland can be expressed (187). However, cell survival measurements have been difficult to achieve in the gland, because this parameter is usually defined in radiobiology with reference to the presence or absence of capacity for cell proliferation (6). Other indices such as trypan blue exclusion or interphase death are not sufficiently sensitive, at the relevant dose levels,to be of value (213). As the thyroid is highly differentiated and under normal circumstances does not undertake much cell proliferation in vivo, it was difficult to find a means of applying the concept of cell survival to it in anything other than qualitative form. Even in circumstances where growth in the size of the gland could be induced by goitrogenic stimulation it was not clear until relatively recently what proportion of the growth was due to hyperplasia (6,203-205).

In 1948 Skanse reported that large doses of ^{131}I inhibited the growth response of chicken thyroid to goitrogenic stimulation (206). This effect was widely used by several groups to investigate the radiation response of the gland in a number of species (6). Studies performed in the late 1960's in the rat and mouse thyroid indicated the proportion of gland growth that was due to cell proliferation and the influence of radiation on this component (203,204,208). This finally allowed a number of indices approximating closely to cell survival to be developed (6,99,205-208). In Fig. 1 results from one of these methods is presented indicating, on the left side , the radiation induced inhibition of goitrogenic weight increase. The same data is presented on the right side, after processing, so that it is representative of an index of cell survival. The index is not in fact the one normally quoted by radiobiologists, that is the proportion of cells capable of proliferating. Instead the closely related property of total increase in the cell number in the gland is used (6, 99). The parameters for the available thyroid cell survival curves obtained using this method are listed in Table 3 . They

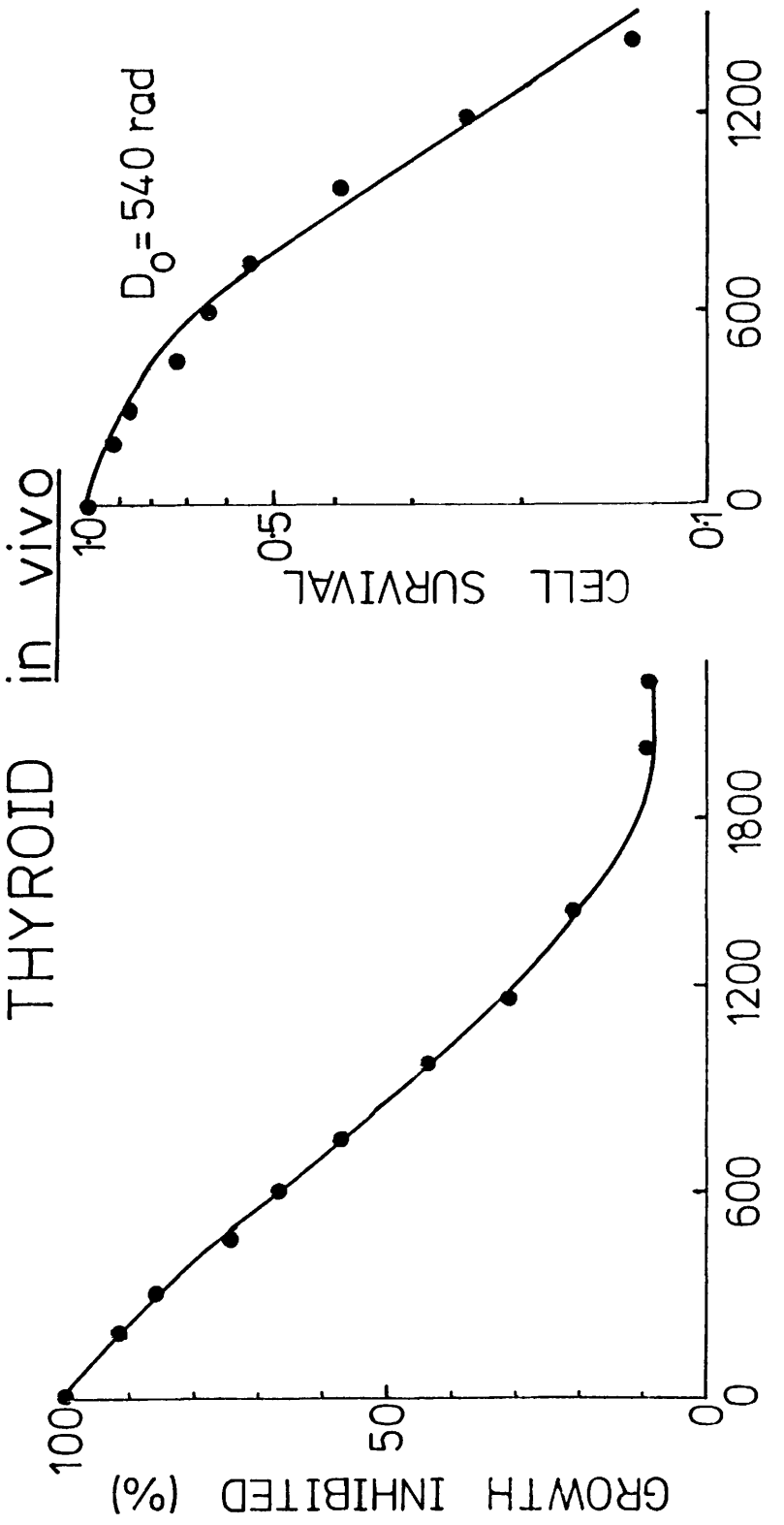


Fig. 1 : Left : The inhibition of goitrogen induced weight increase in the rat thyroid by a single dose of X-rays. Right : The same data reprocessed and expressed as cell survival.

IN VIVO SURVIVAL PARAMETERS			
Radiation Type	D_o (rad)	Extrapolation No. "n"	Ref.
X-Rays	450	1.7	99
γ-Rays	540	2.0	209
γ-Rays	410	3.5	209
γ-Rays	405	2.8	210
X-Rays	~490*	~1.7*	207,6
X-Rays	~530*	~1.8*	207,6
SPECIAL IN VIVO SURVIVAL PARAMETERS			
Radiation Type	D_o (rad)	Extrapolation No. "n"	Ref.
^{131}I	5,500	1	99
^{125}I	9,400	1	99
IN VITRO SURVIVAL PARAMETERS.			
Radiaiton/Type and Culture Age	D_o (rad)	Extrapolation No. "n"	Ref.
X-Ray; 3 day differentiated	410	1.14	96
X-Ray; 10 day differentiated	424	1.18	96
X-Ray; 10 day differentiated	439	1.04	96

* Values calculated by author from data presented for other purposes.

TABLE 3 : Parameters of various thyroid cell survival curves using in vivo and in vitro assay systems.

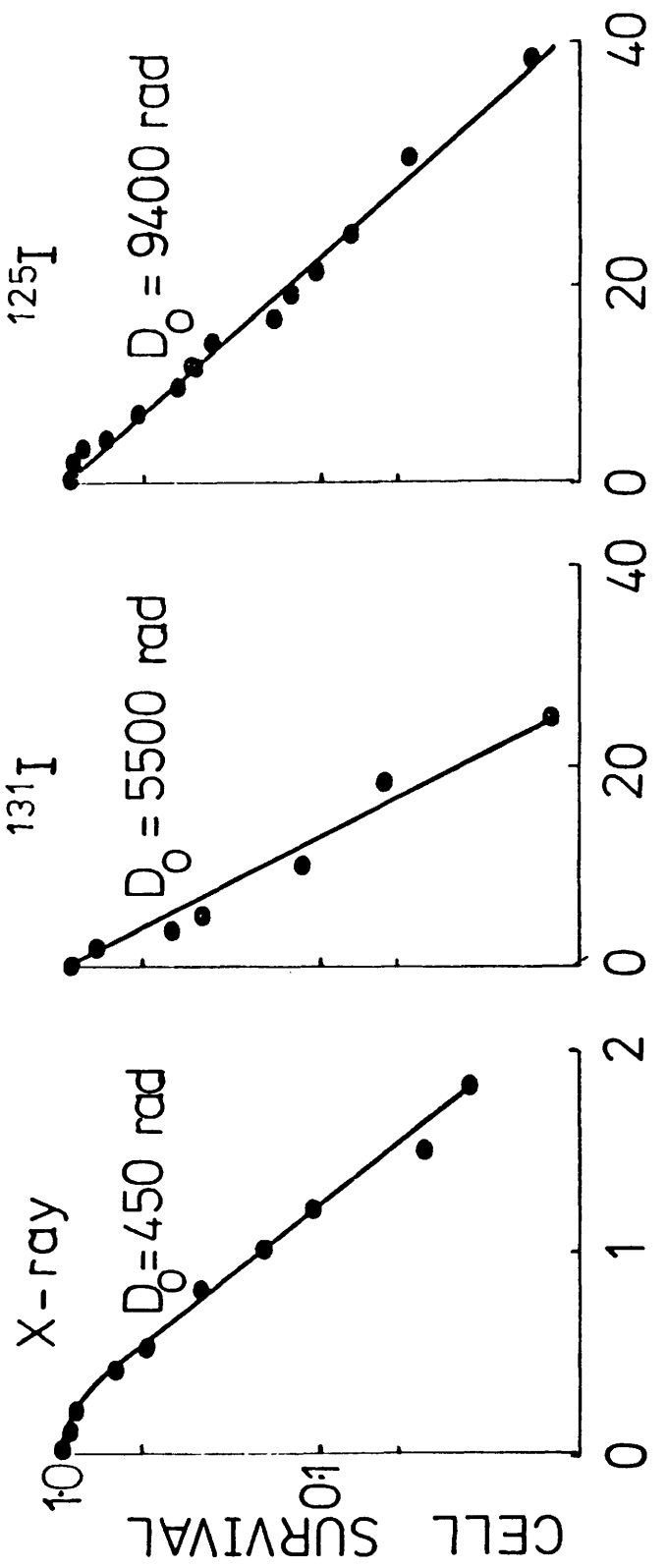


Fig. 2 : Survival of rat thyroid cells assessed in vivo after irradiation with X-rays, ^{131}I and ^{125}I. From Greig et al., with the permission of author and publisher, (99).

consistently demonstrate an extrapolation number ("n") of about 2, which is normal for mammalian cells. The mean lethal dose ("D_0") is in the region of 400 - 550 rads. This value is very high for mammalian cells, which generally have a D_0 in the range 80 - 200 rads. (209 - 214), and consequently indicates that with respect to cell survival the thyroid appears radioresistant (6). Antithyroid drugs that inhibit thyroid peroxidase (methylthiouracil, aminotriazole), but not perchlorate which inhibits iodide uptake, protect the thyroid (349). This effect has been attributed to a decrease, by peroxidase inhibition by the drug, of the yield of active free radicals. It is not clear how peroxidase by reducing H_2O_2 could enhance the radiation effects. However, it has been reported that H_2O_2 decreases radiation sensitivity in bacteria (355).

This method of measuring cell survival has been used to demonstrate that the gland has many conventional radiobiological properties. For example, split dose experiments show that recovery from sublethal radiation damage takes place in the thyroid although the recovery factor is smaller in the thyroid than in tissue culture cell lines and some in vivo systems. Nevertheless, it can be estimated that "about 4650 rads of X radiation, delivered in daily fractions of 218 rads, would be needed to produce an effect equal to that of a 1800 rads single dose" (209, 210). At the reduced dose rates experienced during ^{131}I or ^{125}I irradiation much less damage is caused. This is illustrated in Fig. 2 which demonstrates an approximately 10- fold increase in the D_0 value for ^{131}I compared with high dose rate X-rays (99). The curve for ^{125}I has an even larger D_0 and this may be accounted for by the fact that dose to the cell nucleus is much less than the mean gland dose with this nuclide (Section III). While the major part of the above effects may be accounted for by dose rate considerations, it is possible that dosimetry errors could be responsible for a minor portion (6).

Recent work has led to the development of a system that allows long term retention of follicular structure in cultured sheep thyroid cells in vitro (96, 186, 215 - 217). This system allows conventional radiobiological assays to be

applied to the gland. Cell survival assessed by cloning in this system also suggests that the thyroid is highly radioresistant as is indicated by the data in Fig. 3 and Table 3. Furthermore, the system suggests that in the absence of induced cell proliferation radiation damage develops very slowly in the gland, and that in the short term it is refractory to very high doses (96).

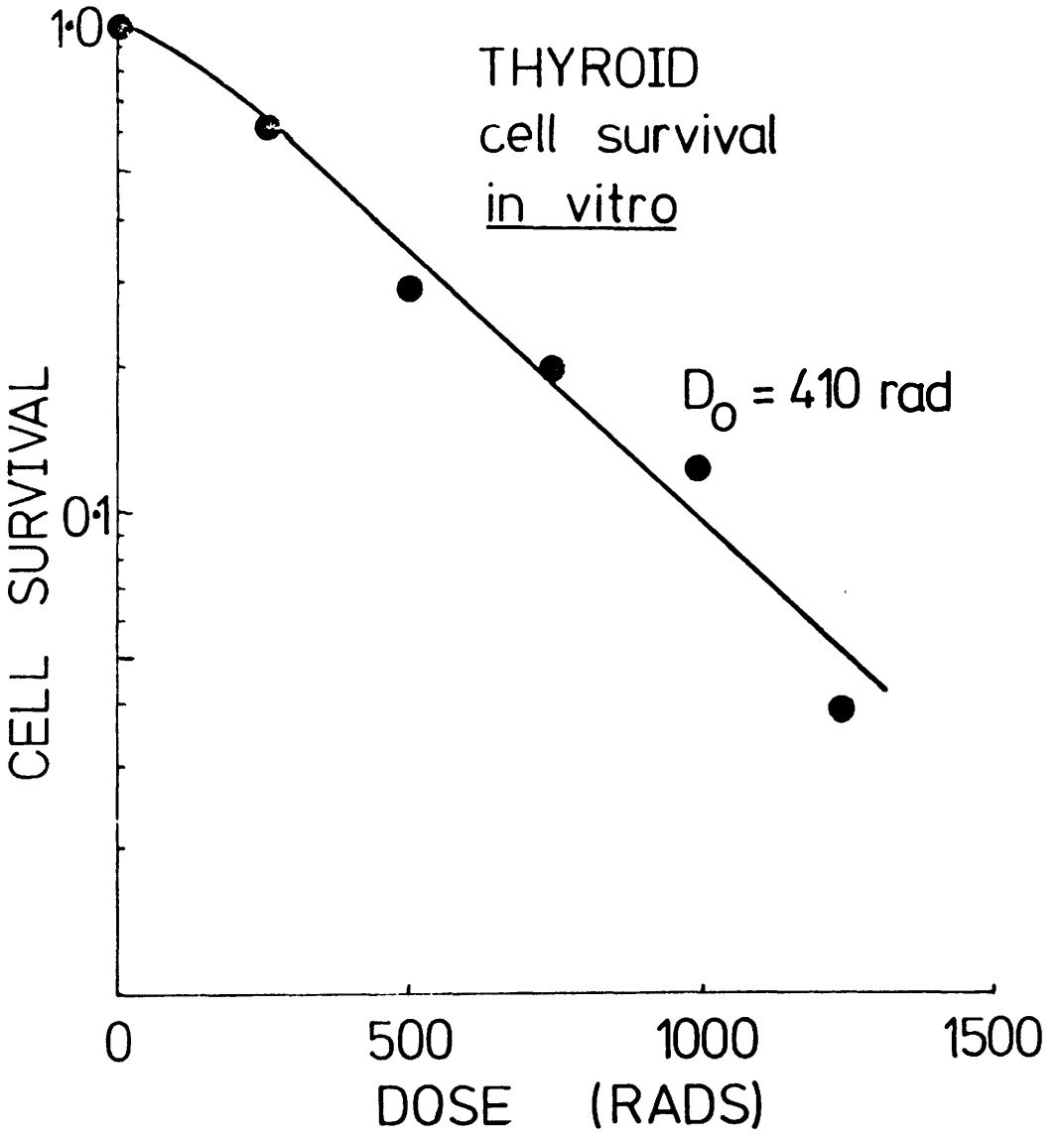


Fig. 3 : Survival of sheep thyroid cells assessed in vitro. Irradiation was performed three days after explantation.

The late consequences of the failure to divide and mitotic and interphase cell death is atrophy and hypofunction of a thyroid which is characterized by its low response to administred TSH (356). The latter phenomenon and such features as increased iodide content, high T_3/T_4 ratio,may be due to increased TSH levels in response to thyroid insufficiency, as they are accompanied by increased TSH levels and suppressed by thyroid hormone treatment (357). Thyroid irradiation is a convenient way to induce thyrotropic adenomas in rats (358).

A later consequence of the irradiation and the TSH response is the appearance of cell hypertrophy, nuclear changes (359) and of a striking focal epithelial hyperplasia presumably involving the cells which are still able to respond to TSH by multiplication. Such foci are probably the starting points of adenomas and thyroid cancers (360,361). The optimal carcinogenic dose of X ray is between 1000 and 2000 rads, i.e. at the level at which a great part of the thyroid is no longer able to respond by growth to goitrogenic stimulation.

In this area there is a general paralell between the effects of X-ray and ^{131}I irradiation in the thyroid. However, as pointed out in Section III the different properties of ^{131}I and ^{125}I radiations lead one to expect quantitatively different results with the two isotopes. Much of the soft radiation from the ^{125}I must be absorbed in the colloid and the apical part of the follicular cells, whereas the nuclei must receive less radiation from the luminal ^{131}I. Indeed 17 months after radioiodine administration, ^{131}I treated rats (25 μCi) displayed evidence of hypothyroidism (reduction of iodine uptake and high TSH plasma levels), but no such effect could be detected with ^{125}I even with high doses (125 μCi) (362).

Very large doses of ^{131}I or ^{125}I administered to the normal or hyperthyroid human gland cause loss of gland function and possible total ablation of the tissue (6,87,91 ,92,105).This may even occur in foetal glands when the mother ingests radioiodine(218-220)Moderate doses used in therapy of thyrotoxicosis cause a reduction in the gland's function which in the short term may or may not be complete. Such doses reduce cell survival so that in the long term the capacity of the gland to renew itself is limited. Consequently failure of the gland, or radiation induced hypothyroidism, is possible
The time lapse between radiation and failure is probably a function of the level to which cell survival is reduced and the humoral pressures on the gland.

Formerly it was thought that radiation induced hypothyroidism did not have a well defined relationship with radiation dose. This impression is probably in part attributable to the poor quality of the dosimetry associated with radioiodine therapy (149,214). However, recent work has demonstrated that the incidence of hypothyroidism appears to be a two step process, one of which is dose related(41,93 ,219). The early incidence, two years after therapy is, as illustrated in Fig. 4 , a linear function of dose for both ^{131}I and ^{125}I (41,93,94). Therefore, the mechanisms underlying it must be closely associated with the amount of radiation damage developed in the gland. The rate of incidence,that is the additional increment of hypothyroidism per year, from two years onwards,is relatively dose independent, indicating it is not strongly associated with primary radiation damage. It is more likely to be determined by a fundamental biological process involving the gland itself and may be initiated by the radiation insult (93). However, small differences in the rate of late incidence have been noted and may be important in the long-term (35,94,171).

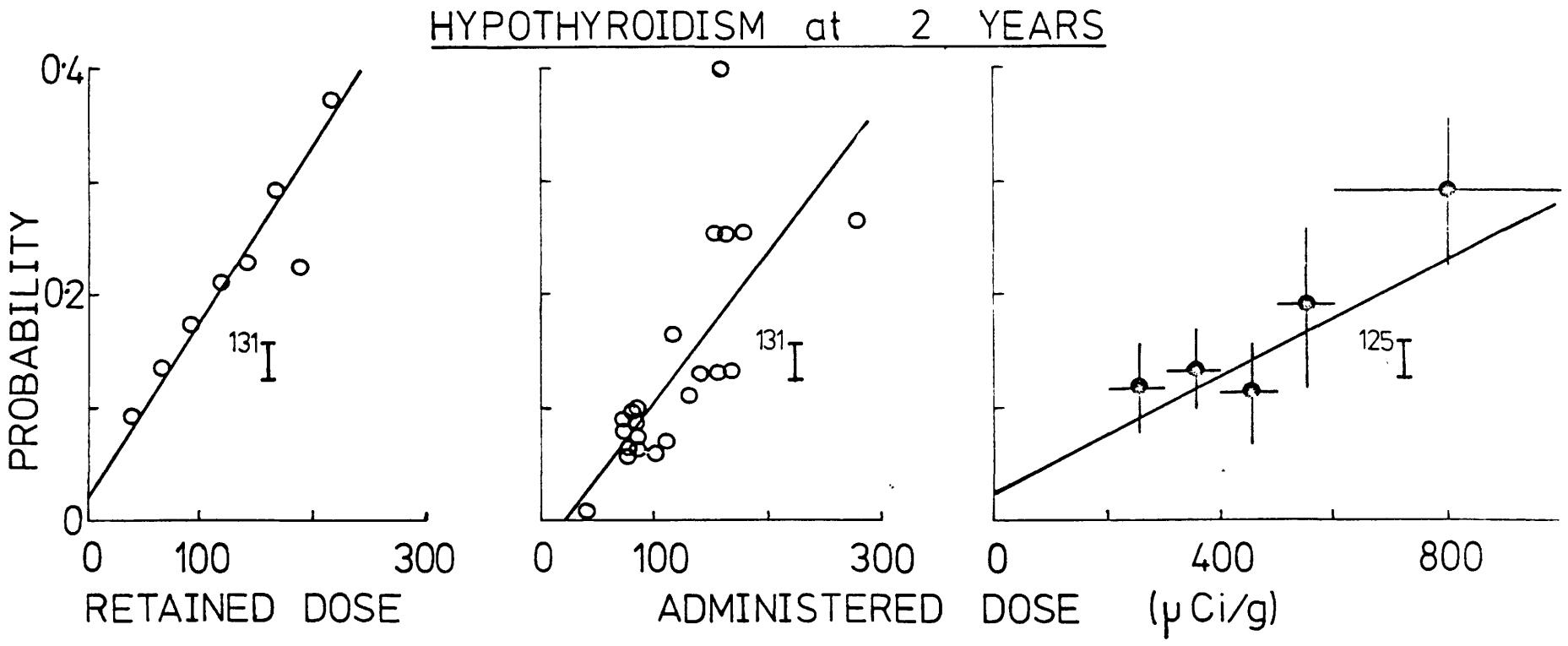


Fig. 4 : Probability of hypothyroidism 2 years after radioiodine therapy as a function of dose. The left panel, for ^{131}I is based on data produced by the Cooperative Thyroxicosis Follow Up Study in the U.S.A., Ref:35 The centre panel, for ^{131}I is based on results presented by numerous authors during the last 20 years. The right panel for ^{125}I, is based on results presented by McDougal et al., and Malone et al., (48,94).

These data indicate clearly that, in humans, aspects of thyroid function have a well defined dose-response relationship. However, they represent a very severe end point, that is total loss of gland function. Study of less dramatic end points is rendered difficult *in vivo* by the existence of interchangeable body pools of hormone, and by the autoregulating mechanisms of the pituitary-thyroid axis (6,105). The advent of tissue culture methods, in which differentiation and function can be preserved for long periods of time, will reduce many of these problems (96,216,217). Consequently it should now be possible to obtain a relatively clear picture of the radiation response of gland function without the inevitable complications encountered in *in vivo* experimental models. This should, when coupled with good dosimetry, allow a better understanding to be evolved for the inter-relationships between cell survival, gland function, the integrity of the gland as a whole, response to humeral pressures and carcinogenesis which will be discussed in the next section.

III. INDUCTION OF THYROID CANCER BY RADIATION IN ANIMALS AND MAN

A) Carcinogenesis in Experimental Animals in the Absence of Radiation

Tumors appear spontaneously in animal thyroids and their incidence, which is greater in some strains than in others (i.e. depends on genetic factors), increases with ageing. The incidence of thyroid tumors may be greatly increased by any treatment which leads to chronic stimulation of the gland : TSH secreting pituitary tumors, severe iodine deficiency, treatment with goitrogens which block at one step or another thyroid hormone secretion, partial thyroidectomy, intrasplenic transplantation, etc. Combinations of these treatments further enhance the incidence of tumors. Irradiation by external or internal radiation may by itself increase the incidence of tumors; this effect is greatly enhanced if irradiation is followed by any type of chronic stimulation. Similarly, chemical carcinogenesis accelerates the formation of tumors in chronically stimulated glands. This subject has been reviewed by Christov and Raichev (7).

Except in some inbred strains, thyroid tumors are infrequent in mice (0,2 ‰). In rats, spontaneous tumors are frequent. They are carcinomas, mostly of the lobular type, composed of light parafollicular cells. Their frequency varies much from one strain of inbred animals to another (0 % to 40 % at 24 months age) which clearly suggests a genetic influence (363).

The transplantation in mice of autonomous thyrotropin producing tumors of the hypophysis induces in thyroid transplants hyperplasia, then adenomas. Serial passages of such adenomas result in the progressive emergence of autonomous carcinomas which metastasize (364). Subtotal thyroidectomy also increases tumor incidence, but to a much lower extent, unless treatment with I^{131} or with a groitrogen is coupled (365).

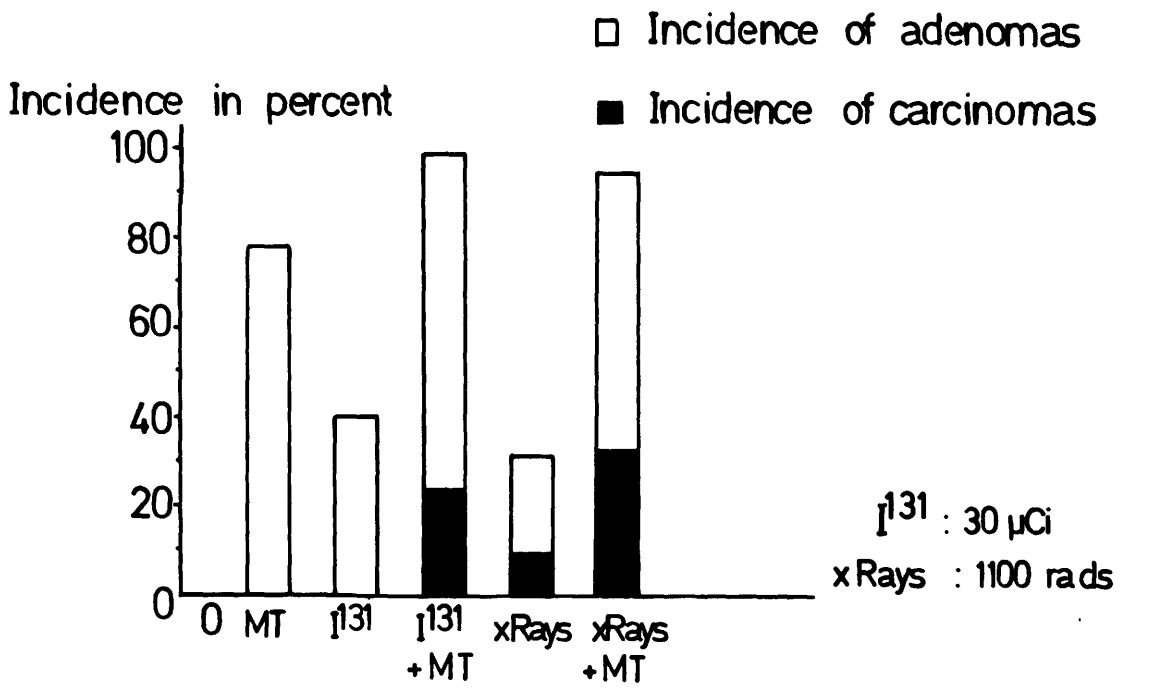


Fig. 5. : From data of Doniach (387).

Similarly, transplantation of thyroid tissue in the spleen of thyroidectomized animals leads to thyroxine degradation in the liver, marked stimulation of pituitary thyrotrophs, hyperplasia of the thyroid and the appearance of adenomas (366). There is therefore no doubt that chronic thyrotropin stimulation per se may induce thyroid tumours in experimental animals.

Feeding a very low iodine diet to rats or mice causes a lowering of plasma levels of thyroid hormones, increased levels of TSH, then diffuse hyperplasia of thyroid epithelium, followed after 12 months by the appearance of adenomas and carcinomas (367-370). The latter tumours show infiltrative growth and develop metastases (367, 371). The appearance of chromosomal abnormalities (chromatid deletions, hyperdiploidy, etc.) precedes nodule formation (369,372). In this case also, it appears that chronic stimulation per se is sufficient to induce tumorigenesis. However, the relative roles of thyrotropin stimulation and relief of iodine intrathyroidal inhibition have not been investigated. As could be expected, administration of iodine at an early stage decreases the size of adenomas, if not their number, but light parafollicular cell nodules seem strongly stimulated (368

The best studied example of thyroid carcinogenesis in chronically stimulated tissue is the induction of tumours by goitrogenic agents in rats, mice and hamsters (Fig. 5). The most commonly used drugs are thiouracil, propylthiouracil and methylthiouracil. Iodization of thiouracil in the 5 position eliminates both its goitrogenic and carcinogenic effects, which suggests that both effects are linked. Three stages can be distinguished in the genesis of the tumours after the beginning of the treatment : diffuse hyperplasia (until 6 to 8 months), nodular proliferation of epithelial cells with formation of adenomas (until the 16th to 18th month), malignant

tumour growth (after 18 months). Extending the treatment period increases both the number of animals with tumours and the number of tumours per gland. However, the age at which the treatment is applied does not play a significant role. Increasing the dosage of the goitrogen will, above a certain level, depress thyroid growth. As in the case of spontaneous tumours, the incidence of adenomas in goitrogen treated rats varies much from one inbred strain to another (7,373-376). Although there is no doubt that tumorigenesis by goitrogens is secondary to chronic stimulation, a supplementary direct role of these agents on thyroid enzyme systems (6,321) and for instance on the iodine intrathyroidal autoregulatory mechanisms (282) is not excluded. Serial passage of goitrogen induced tumours leads to progressive dedifferentiation and TSH independence (374). In goitrogen treated animals the incidence and the rate of appearance of thyroid tumours are increased by previous administration of chemical carcinogens.

The functional characteristics of induced thyroid tumours vary from a fully differentiated to the undifferentiated stage. Although, there is no strict relation between structure and function, in general, follicular variants express the most differentiated functional activity. The main aspects of dedifferentiation are greatly increased thyroglobulin secretion, formation of large amounts of iodoproteins (eg. albumin) other than thyroglobulin, impaired iodothyronine synthesis and protein iodination, and loss of response to thyrotropin.

While spontaneous thyroid tumours in rats are mostly of the parafollicular cell type, induced tumours resemble much more human spontaneous and induced tumours and thus represent good experimental models. As in man, adenomas, papillary and follicular carcinomas are found, although there are less mixed variants and few anaplastic carcinomas. As in man, their iodine

metabolism varies from a complete cycle to truncated sequences to the absence of any specific metabolism.

In general, experimentally induced tumours remain very dependent on TSH. When serial passages of the tumours are carried out, the first passages must be in thyroidectomized animals, i.e. under TSH stimulation; later passages can be performed in euthyroid animals. During successive passages, the characteristics of normal thyroid tissue tend to dissapear. For example follicular structure, polarized secretory aspects of the cell, karyotype, iodide trapping, thyroglobulin synthesis, protein iodination, iodothyronine synthesis and secretion, and functional and growth responses to TSH are all reduced. However there is no precise sequence or linkage between markers in this dedifferentiation. Thus different tumour cell lines with different characteristics may be evolved (370,372,374,377). Such a pattern of almost random loss of morphological and biochemical markers is similar to the pattern observed in spontaneous and induced animal and spontaneous human thyroid tumours (378-381).

B) Radiation Induced Carcinogenesis in Experimental Animals.

Irradiation whether by external X-rays or internal emissions from various radioisotopes induces thyroid tumours. The similar action of different radiations is in keeping with data in other systems and suggests a common mechanism (382-383).

Administration of radioiodine alone induces the formation of tumours. In one typical experiment on 15 rats, 25 μCi of I^{131} induced 9 adenomas and 3 carcinomas within 2 years. Similarly administration of X-rays (1000 rads) induced adenomas in 54 % and carcinomas in 22 % of the irradiated rats after 2 years while the incidence of alveolar carcinomas did not increase (363) (Fig. 5).

Carcinomas appear even after administration of a single dose of 1 μCi

i.e. in cases where no evidence of TSH stimulation is found (365,375). Tumours may even develop in the presence of reduced TSH levels (319). However, even with the additional stimulus of a low iodine diet, no tumours develop in hypophysectomized animals (384). Of course, as seen above, radiation by its late depressing effect on thyroid function may induce TSH secretion (192,194). Thus radiation by itself without increased TSH activation induces thyroid tumours but it will not do so in the absence of TSH.

The pattern of histological development of these tumours has been described by Lindsay (360,363). This pattern is very similar to the pattern observed in tumorigenesis induced by iodine deficiency or goitrogens (360).

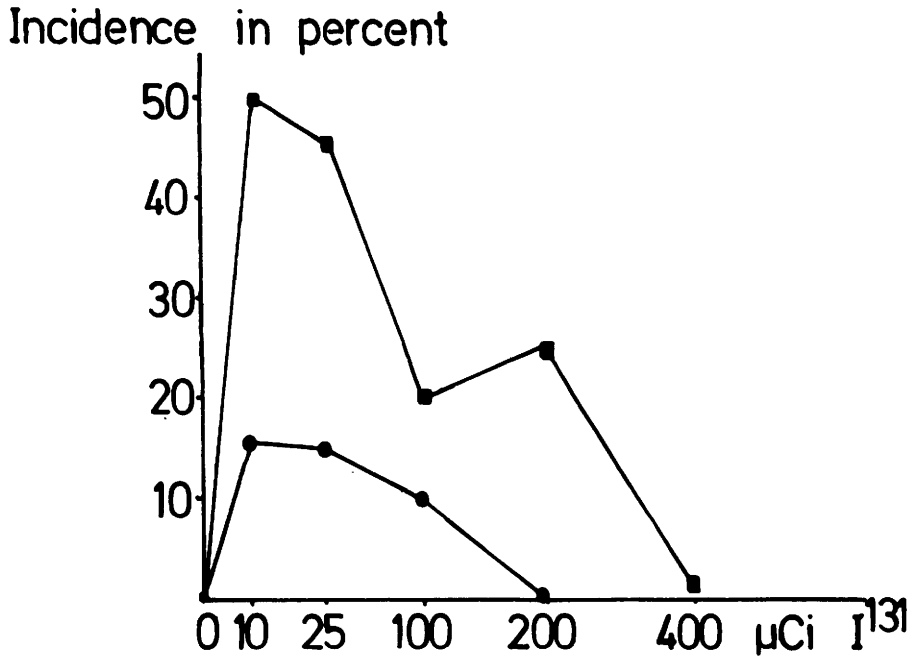
"The smallest and earliest lesions observed consisted of a group of enlarged thyroid follicles that appeared to arise in a segment of a thyroid lobule. The enlarged follicles were lined by cuboidal epithelium, and contained pale, vacuolated colloid. In larger nodules, epithelial hyperplasia with papillary infolding was observed. Further enlargement seemed to result from epithelial growth by follicular budding, leading to the development of macrofollicular or microfollicular patterns. As a rule the smaller follicles contained little colloid, whereas the macrofollicles generally were well filled with this substance.

As the nodules enlarged, they tended to compress the surrounding parenchyma from which they were sharply demarcated by intact fibrous capsules. These adenomas occurred singly, but in many instances were multiple in one or both lobes. In some cases, these enlarging macrofollicular nodules had entirely replaced the original thyroid parenchyma and thus caused enlargement and distension of an entire lobe.

Some macrofollicular nodules were designated as papillary adenomas. These were cystic and encapsulated, and were composed of large follicles lined by thyroid epithelium that displayed many delicate papillary folds or fronds" (363).

Carcinomas were either papillary or follicular. This is the description of a nodule containing a papillary carcinoma: "The neoplasm consisted of follicles of varying size (normal to microfollicular) which were composed of mildly pleomorphic, cuboidal or flattened epithelial cells. The pattern of this portion of the nodule was identical with those of the benign follicular adenomas observed in many of the animals. Approximately one-third of the large nodule was occupied by malignant neoplastic tissue that had a distinctly different histologic and cytologic pattern. The follicular and papillary structures were composed of moderately pleomorphic cells with pale, vesicular opaque nuclei, characteristic of those of papillary carcinoma. The cytoplasm was sparse; a few mitoses were present. This papillary and follicular neoplastic tissue had infiltrated the benign nodule in which it appeared to have arisen and had penetrated the narrow rim of residual parenchyma to the thyroid capsule." In such carcinomas, often the neoplasm had infiltrated widely and extended through the thyroid capsule. Many extraglandular satellite nodules were found, and invasion between tracheal cartilages had occurred. Several veins in the peripheral portion of the neoplasm were invaded by neoplastic thyroid epithelium (363).

A typical follicular carcinoma is also described by Lindsay (363). "The neoplasm had locally infiltrated the adjacent parenchyma and had invaded the lumen of a large thyroid vein. The pattern of this tumour was mainly microfollicular, but a few larger follicles, some containing fresh blood, were present. Many of the follicles contained pale, vacuolated colloid. The cells were mildly pleomorphic, with oval or round vesicular nuclei and



INCIDENCE OF ADENOMAS (■) AND CARCINOMAS (●)
18 TO 29 MONTHS AFTER I^{131} ADMINISTRATION TO RATS
(DATA FROM LINDSAY, 1968)

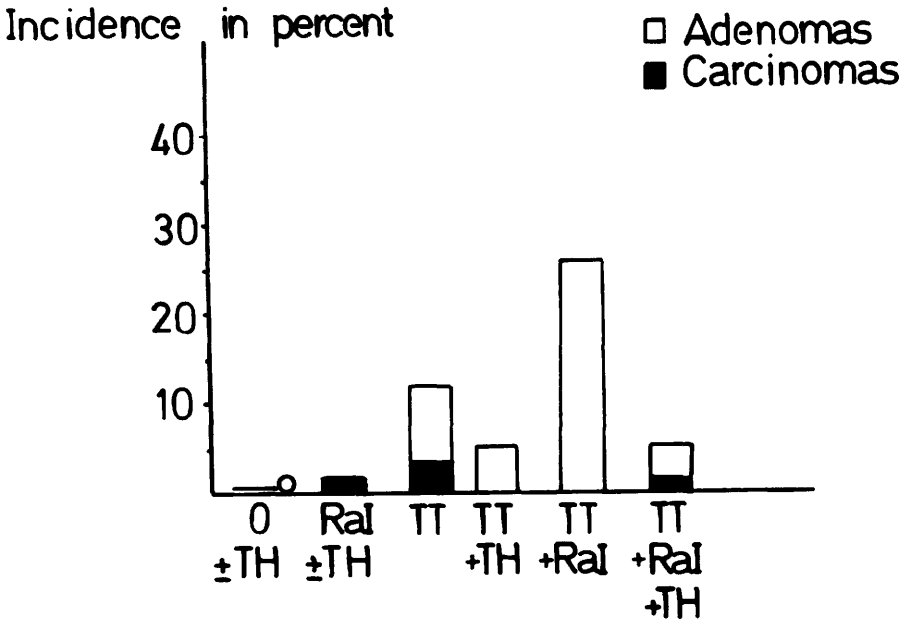
Fig. 6.: From data of Lindsay (363).

abundant vacuolated cytoplasm. Few mitoses were present."

The finding of carcinomas developing in adenomas, as well as the similarity of the pattern (papillary and follicular) of adenomas and carcinomas suggest that malignant cells originate from previously benign nodules. Similar induction of thyroid neoplasms and carcinomas by I^{131} treatment alone has been observed in mice, sheep and dogs (7,360,385).

The dose response for I^{131}, as well as for Xray irradiation, clearly exhibits a maximum (Fig. 6). This is true for I^{131} in rats (where the optimal dose was 30 µCi) as well as for Xray (where the optimal dose was 1100 rads) (363,386,387). Tumour induction by radiation obviously requires a balance between the inductory effect and the lethal effects on thyroid cells (183). There is some suggestion that in mice the curve of frequency of adenomas, may be biphasic, the slope being lower for low doses (194) but the data do not allow any firm conclusion. That the dose rate is important in carcinogenesis is shown by the great differences observed between results of comparable Xray and I^{131} irradiations (more than 10.000 rads of I^{131} giving less response than 1100 rads of Xray). In the case of I^{131} the irradiation is delivered in several days whereas it is delivered in a few minutes for the Xrays. On the other hand, administration of I^{131} in 2 doses separated by 4 to 6 months did not decrease the incidence of tumours in rats (183,319). Experimental data do not throw more light than clinical data on the subject.

Susceptibility to cancer is clearly different from one strain to another, which suggests a genetic component in susceptibility (7). This has its counterpart in man, with the higher susceptibility of Jewish patients (388). Whereas spontaneous thyroid cancers (lobular and carcinomas) appear twice more often in females rats after irradiation, their spontaneous frequency is higher in males (389). Because follicular cells are taller in males, it has beer



EFFECT, AFTER 2 YEARS, OF PARTIAL THYROIDECTOMY (TT), RADIOIODINE ADMINISTRATION (1 µCi), AND DESSICATED THYROID HORMONE POWDER IN THE FOOD ON THE INCIDENCE OF TUMORS IN THE RAT (FROM DATA OF GOLDBERG).

Fig. 7 : TH indicates administration of thyroid extract (365).

suggested that this is due to higher TSH levels or responsivity in males (183,319,387). In humans the incidence of radiation induced and spontaneous tumours is higher in females (87,388).

The types of neoplasms induced by radiation in the rat are mostly the follicular and papillary carcinomas. This is different from the most common spontaneous tumours in these animals (lobular carcinomas) but similar to human spontaneous and radiation induced tumours (360,363). In man and in sheep (385), radiation induced and spontaneous carcinomas are of similar type (360). The data in rat however suggest that radiation induces a certain number of tumours rather than increasing their spontaneous incidence. As with tumours induced by chronic stimulation alone, radiation induced thyroid tumours are often initially TSH dependent, but subsequently loose this dependence (384). The latency of induced cancers is long compared to the life span of the species : 8 months in the rat, 10 years in sheep (385), and 10 to 20 years in man which is of the same order as for various types of leukaemias (390).

TSH as well as any treatment stimulating the gland (e.g. goitrogens) greatly enhances the frequency of radiation induced cancers and combination of these treatments further multiply this frequency (321,360,386) (Fig. 5,7). The converse effect is obtained by thyroid hormone administration (Fig.7). Among such goitrogens, some are chemicals used for various purposes (e.g. aminotriazole as an herbicide) (376). Goitrogens also reduce the delay between irradiation and the appearance of tumours (to 5-6 months from 24 months).

Even though the formation of tumours is greatly accelerated by TSH, in the presence of goitrogens thyroid extract in small quantities may potentiate goitrogenesis and the appearance of adenomas and carcinomas. Thus tumorigenesis and goitrogenesis are favored by the presence of a minimum of thyroid hormone. It is probable that this is due to the fact that such a minimum is required to maintain the level of growth factors, such as growth hormone (373,375). It has also been reported that stress by faradization increases the frequency and decreased the latency of thyroid cancers in rats treated with I^{131} and methylthiouracil (392).

In the induction of thyroid tumours, the proliferation state of the thyroid at the time of irradiation is crucial. 300 rads of Xrays given to a non proliferating rat thyroid gland induced tumour growth in 25 % of the animals 18 months after irradiation. The same dose, applied to a proliferating thyroid of a goitrogen treated animal increased the tumour incidence to 30 % when administered in the lag phase, to 75 % when administered at the peak of the proliferating phase, and to 62,5 % when given at the plateau phase. Moreover, most malignant tumours appear in the animals irradiated at the top of the proliferative wave. Similarly, when animals are treated with a carcinogen AAF (2 acetylaminofluorene) instead of irradiation, during the different phases of the thyroid proliferating wave, most tumours appear when the carcinogen is given at the top of the proliferating wave (321). A similar phenomenon has been observed for liver and kidney.

C. Radiation induced carcinogenesis in man and its relation to present dose limits.

The known carcinogenic action of ionizing radiations has led to concern that their widespread use in the thyroid may lead to development of unwanted and potentially dangerous neoplasia (41,80,187,188 Section II). The criteria by which a relationship can be established between irradiation and subsequent neoplastic development in human subjects are demanding and have been outlined by Saenger and co-workers (188). In particular the hypothesis claiming to establish an association must be formulated in a fashion that it could be proven to be untrue. Thus selection of appropriate control groups when surveys on radiation induced disease are being conducted is particularly important. For example, comparison of the radiated group with the public at large will frequently not provide an adequate control. This is because radiation will often have been administered as a medical procedure for a condition that may predispose the subject to acquire the disease being investigated (188). Therefore, finding valid control groups is difficult, although in the case of the thyroid it has been achieved (41,178,188). Once acceptable controls have been established; it is also desirable to demonstrate a dose-effect relationship when an association between radiation and disease is being evaluated.

Some reports associating head and neck irradiation during childhood with

thyroid neoplasia in later life did not have controls satisfying the above criteria (61). The uncertainty resulting from this position has been resolved, and the epidemiological evidence linking neoplastic development in the gland with childhood irradiation is now indisputable (41,178,188). It is based on a wide variety of experience including irradiation consequent on nuclear explosions as well as diagnostic and therapeutic medical procedures (6,41,61,72,87,178,183,184,188,189) (see Section II). Furthermore, the data demonstrate a dose-effect relationship that is continuous down to 6.5 rads. Data on induction of cancer in the thyroid were critically reviewed by the BEIR Committee and more recently have been summarized by Conard (87,178). Additional data (above and beyond those discussed in these reports) is available, and has been subject to some analytical comment (41,72,80,176,189,212). The risk estimates for malignant and benign neoplastic developments from these reports are summarized in Table 4. For calculation purposes a value of 3×10^{-6} per man-rad per year will be taken for induction of malignancies. The rate at which benign adenomas occur is greater, but more uncertain and appears to range from twice to fifty times the rate for carcinomas. However, for calculation purposes it is not unreasonable to use a value of 5 (41,87,187).

The epidemiological investigations cited above have been performed to a large extent in children and are supported by the extensive experimental work in animals noted in V,III,B. These investigations confirm the sensitivity of the thyroid to low doses (190), and clearly identify irradiation as a significant factor in the tumour induction process (80,183,187, 191-193). This process requires that some time after irradiation the thyroid is subjected to a stress such as TSH stimulation, which will lead to cell division. The fact that the gland comes under such pressures naturally during adolescence is thought to explain the high tumour incidence in young adults whose thyroids were irradiated while they were children. It is also likely that similar mechanisms operate in adults whose thyroid is subject to hormonal pressures arising naturally for example from

RISKS ASSOCIATED WITH THYROID IRRADIATION

Dose each year for 40 years (rems)	Percentage Chance over 30 years*		
	Malignancy	Benign	Fatality (ICRP, 1977) (181)
150	54	270	3
50	18	90	1
30	11	54	0.6
15	5	27	0.3
5	2	9	0.1

*For effect of MPD received once divide by 30.

TABLE 4 : Risks associated with thyroid irradiation (168)

pregnancy, through disease or through dietary factors. Consequently while these risk estimates are for a great part based on the results from populations irradiated during childhood, they may not be ignored for the adult population. This is supported by the fact that radiation induced neoplasia have been noted in adult populations in studies of both animals and man (87,177,184,192,194,434) and a recent investigation noted a similar cancer incidence in those irradiated as children or adults (41). Furthermore, the risk of death from a thyroid cancer induced after adult irradiation may be greater, since thyroid cancers in older people tend to follow a more malignant course (178). This may be associated with a more prolonged period of stress arising from abnormal thyroid status, than the limited time scale of stress during adolesence.

Table 5 lists the consequences of these risk estimates for workers receiving various annual doses during a 40 year working life with an average follow up period of 30 years. These figures suggest that the risk of malignancy for a worker receiving 50 rads/year to the thyroid would be 18 % and that of a benign adenoma would be 90 %. The adenoma risk appears somewhat high compared with some values quoted in the literature but is in keeping with recent estimates (Table 5) (41,178,195). The risks of fatality in Table 5 are calculated from estimates in the recent recommendations of ICRP (181).

While the risks quoted above do not imply a fatal outcome, except those of ICRP, they are relatively high when considered in relation to the maximum permissible thyroid dose levels allowed by various agencies (180,181). Because of the high ratio of thyroid to whole body dose when nuclides of iodine are ingested, the maximum permissible dose to the gland is quite large if it is calculated according to the new ICRP weighting factor system (181). In many

Risk per 10^6 man rads per year		Reference
Malignant	Benign	
1.6 - 9.3	75% of those receiving 1000 rads	178
3.4+	49+	87
*Approx 10	-	72,189
4.2	12.3	41

+ Mean values from 10 groups

* Approximate value

TABLE 5 : Risk of benign and malignant neoplasia in thyroid after irradiation. Adapted from Malone, 1978 (168)

cases it is so high that it is constrained by the 50 rad limit whose main purpose is to prevent non stochastic effects (168,181). Therefore, within the present dose limits it may be possible for subgroups of the population to be at substantial risk of nonfatal harm from thyroid irradiation. It could be worth further constraining dose limits or introducing new forms of medical surveillance to reduce these risks pending a clearer evaluation of the above data, and an assessment of the acceptability of nonfatal harm to radiation workers (168,434,435).

At higher dose levels, for example after radioiodine therapy of hyperthyroidis it has been established that there is no excess of thyroid carcinoma in radiation treated patients when they are compared with a surgically treated control group (39). This is thought to be a consequence of radiation sterilization of the cells which renders them refractory to TSH pressure to undertake mitosis, and thereby makes tumour formation difficult. Strong support for this view is available from experimental work in animals noted in B above (6,41,196,212). The data on incidence of thyroid cancer after radioiodine therapy has been obtained from studying groups who,by todays standards,received relatively high doses. With low dose therapy and the use of ^{125}I there is a possibility that the cells in the gland may not be as effectively sterilized as with larger doses. Hence the question of radiation induced neoplasia must be reexamined for patients who have been treated in this manner (6,184).

Similar surveys have established that there is no excess of leukaemia after radioiodine therapy for hyperthyroidism (197), although there may be in those given very large doses for thyroid carcinoma (198). The likelihood of abnormalities in reproductive history after these forms of treatment is regarded small provided sufficient time is allowed to lapse between therapy and conception (6,199,200,220).

IV. PRESENT CONCEPTS IN TUMORIGENESIS AS APPLIED TO RADIATION INDUCED THYROID CANCERS

Our present concepts on the induction of tumours are derived from the now classical induction of skin neoplasia by the successive application of benzopyrene and croton oil (393). The induction of a tumour would result from 2 independent actions referred to as "initiation" and "promotion" (11,393-395). The former would be a fast irreversible process acting on a normal cell and conferring upon it tumorous characteristics; the induced cell might remain indefinitely in a dormant state without further division. When followed by the slowly acting process of promotion, initiation would result in tumour growth.

Initiators are compounds which usually behave as mutagens and can be given under conditions where no tumours form. Promoters, which are not mutagens, and do not by themselves cause tumours, can cause the expression of tumours in animals pretreated with initiators. In contrast to the one hit effect of initiators, promoters must be continuously applied to first cause tumours such as papillomas; these disappear when promoter is removed; only after prolonged application of promoters do tumours appear (396). The actions of initiation and promotion are thus resolved in time but also in quality. The final yields of tumours is generally a function of the initiators dose, while the rate of appearance depends upon the time of action and dose of the promoter. It is considered in general (11) that radiation is a very special carcinogenic agent, shares the properties of initiator and promotor and cannot be considered as a pure initiator or promoter.

Initiation and promotion may involve several discrete steps. A model which apparently accounts for existing data has been proposed for the induction of osteosarcomas by internal emitters; it involves 3 successive stages,

2 of initiation followed by one of promotion (390). With human carcinomas, a log-log plot of incidence versus age gives a straight line of slope 4-6 which suggests 4 to 6 stages in the progression of normal to cancer cell (396,397). In inherited medullary thyroid carcinomas, the presence in the same individuals of different monoclonal tumours suggests that the inherited defect is an initial mutation producing multiple clones of defective cells; each tumour would then arise as a final mutation in one clone of these cells (398).

In the systems studied so far, there has been a relation between promotion and enhancement of cellular proliferation; the latter is clearly necessary for tumour progression. However, so far, there is no unequivocal evidence that the induction of proliferation in cells is a key event in radiation carcinogenesis (11). Most promoters stimulate cell division but many non promoting chemicals also stimulate cell proliferation.

It is widely believed that initiation involves an alteration in the cell's DNA. This is supported by the fact that a single low dose of initiator is sufficient to produce permanent changes. Tumours develop in the mouse skin, for example, even if a year is allowed to elapse between application of the initiator and treatment with the promoter. The cells appear to have a memory for the initiator, a result implying that initiation involves a genetic change that can be passed from one generation of cells to the next. The fact that initiating agents are or can be converted to compounds that attack DNA also supports this concept (399).

The most prevalent concept about the nature of initiator attack is that they induce somatic mutations. The proposal that the induction of malignancy is associated with somatic mutation has been and still is supported by many arguments including :

1) Most chemical carcinogens in eukaryotic cells are mutagens in bacteria , provided the chemicals are treated with liver endoplasmic reticulum, as an in vitro substitute of in vivo metabolic transformations. There is a rough parallelism between the two properties (400,401). Indeed, a test of the mutagenic capacity of environmental chemicals is now used to predict potential carcinogenic actions.

2) A common feature of very different chemical carcinogens and a variety of radiations which are also carcinogenic,is that all damage DNA (383,400,402).

3) Metabolic defects of DNA repair mechanisms (eg. in xeroderma pigmentosum ataxia telangiectasia, Fanconi's anaemia) are accompanied by a high incidence of malignant lesions and high susceptibility to UV induced lesions (403-405). Although for each disease, some strains of cells have been shown to be repair deficient for ionizing radiation damage (405,406), we know of no study on the possible X ray induction of malignant neoplasms in such patients.

4) The elegant cell hybridization experiments of Harris have shown that hybrid cells formed by fusing malignant and non malignant mouse cells are in general non malignant. The hybrids become malignant when some definite chromosomes are lost. This clearly suggests that the factor which controls the expression of malignancy behaves as recessive genetic character (407).

5) The simulation of equations describing a model in which transformations would be caused by a specific DNA alteration,according to Harris model, reproduces experimental transformation versus dose curves (408).

There is therefore now strong support for the concept that in a cell carrying the recessive malignant genotype, the expression of malignancy could result from a mutation or aberration removing the suppressive action of a specific gene(400).

Initiation may require cell proliferation. This concept is supported by the fact that several carcinogens are carcinogenic in liver if injected after partial hepatectomy, but not in intact animals (409). Recently, in a more precise analysis, Cayama et al. (410) have shown that foci of phenotypically altered hepatocytes (the precursors of tumours) only appear if the carcinogen is given after hepatectomy at a time of rapid cell proliferation. Several carcinogens, which induce foci of altered hepatocytes without exogenously induced cell proliferation (eg. by hepatectomy) are necrogenic and induce per se compensatory liver cell proliferation. Although the mechanism of this effect is not known, it clearly suggests that replication of carcinogen damaged DNA before repair would fix this damage by increasing the chances of altered nucleotide sequences in the newly made DNA. Indeed such carcinogen damaged DNA replicates in vivo. Transformation of cell cultures with DNA viruses and Xrays also requires at least one cycle of cell proliferation (411) .

Recent observations on the action of promoters reveal important facts. Phorbol esters induce in cultured cells changes (eg. in cell morphology, increase in plasminogen activator synthesis, in deoxyglucose uptake, and loss of large external transformation sensitive proteins, etc.), which resemble those seen on transformation by chemical carcinogens or tumour viruses, and further enhance the expression of these transformations' specific phenotypic features in already transformed cells. These effects are not entirely a consequence of growth stimulation since they occur in chicken fibroblasts under conditions where growth stimulation does not occur (412). The second important action of phorbol esters on cell biology is to inhibit terminal differentiation. Such an effect has been demonstrated in several systems. This has an important consequence in systems where tissue growth is sustained by a stable pool of stem cells achieving asymmetric division, i.e. with one

daughter cell remaining a stem cell, while the other is terminally committed to differentiate and to stop dividing. Both of these phorbol esters' actions enhance cell multiplication and may favour the multiplication of initiated cells. However, such hypotheses are still highly speculative (412).

The biochemical changes induced by promoters have been intensively investigated. Two such changes are the increases in the enzymes ornithine decarboxylase (ODC) and plasminogen activator. ODC is greatly increased within 2 hours after exposure of mouse skin or cultured cells to the most effective promoter TPA (12-O-tetradecanoylphorbol-13 acetate) and,for various derivatives, there is a close correlation between the degree of promotion and increased ODC activity. Thus far, all promoters tested have been found to increase ODC activity, but some non promoters also do so. The enzyme ODC is needed for the synthesis of polyamines which are involved in cell multiplication. Thus enhanced production of ODC could lead to greater cell proliferation. Promoters transitorily induce ODC production in normal cells,but in initiated cells high production of the enzyme eventually becomes permanent. This has suggested to Boutwell et al. (413) that initiation would involve the loss of a gene that would normally control induction of ODC. A number of agents which inhibit ODC induction by promoters also inhibit promotion (eg.putrescine, retinoids, inhibitors of prostaglandin synthesis, etc...). Thus,there is strong support for the hypothesis that ODC activity is a prerequisite for tumour promotion (413).

In cultured cells, a specific protease, plasminogen activator is also increased by treatment with phorbol esters (412,414). It has been proposed that this protease would turn on genes by destroying the proteins that normally block their expression. Although, this hypothesis looks attractive many promoters unrelated to the phorbol compounds have no effect on the production of plasminogen activator.

There is some evidence that promotion involves a series of steps. In the mouse skin the first tumours formed are benign papillomas. Most of these regress if exposure to the promoter ceases, but some of them grow autonomously. Carcinomas develop more frequently in such papillomas. Moreover, papillomas appear much more rapidly in skin in which papillomas had formed and regressed than in normal skin. Thus, cells previously submitted to promoters retain some permanent characteristics. This concept of multistep promotion suggests that by removing a promoting agent or by using inhibitors of promotion one might stop the progression towards cancer (394). This would be even more so in cases in which the various steps would not be irreversible and redifferentiation could take place (395).

The concept of multistep progression from the normal to the fully invasive cancer cell (397) also appears to apply to the formation of metastasizing cells. Indeed, clones derived in vitro from parent cultures of malignant melanoma cells vary greatly in their ability to produce metastatic colonies. This suggests that the parent tumour is heterogeneous with regard to this property and that highly metastatic tumour cell variants preexist in the parental population, i.e. that the acquisition of this property is another discrete genetic step in the process of transformation(415).

It is perhaps in the framework of the concept of tumour promotion that the very challenging hypothesis of tumour production of ectopic growth factors and their autostimulation by these factors should be introduced. It is well known that many types of tumours secrete proteins, such as hormones or growth factors that the normal parental cells do not synthesize (eg. somatomedins, ACTH, etc.). These factors are necessary for the growth of some normal cells. It is also well known that tumour cells may have receptors for hormones other than the hormone controlling the normal parental cells. Secreting factors which would interact with them and stimulate their

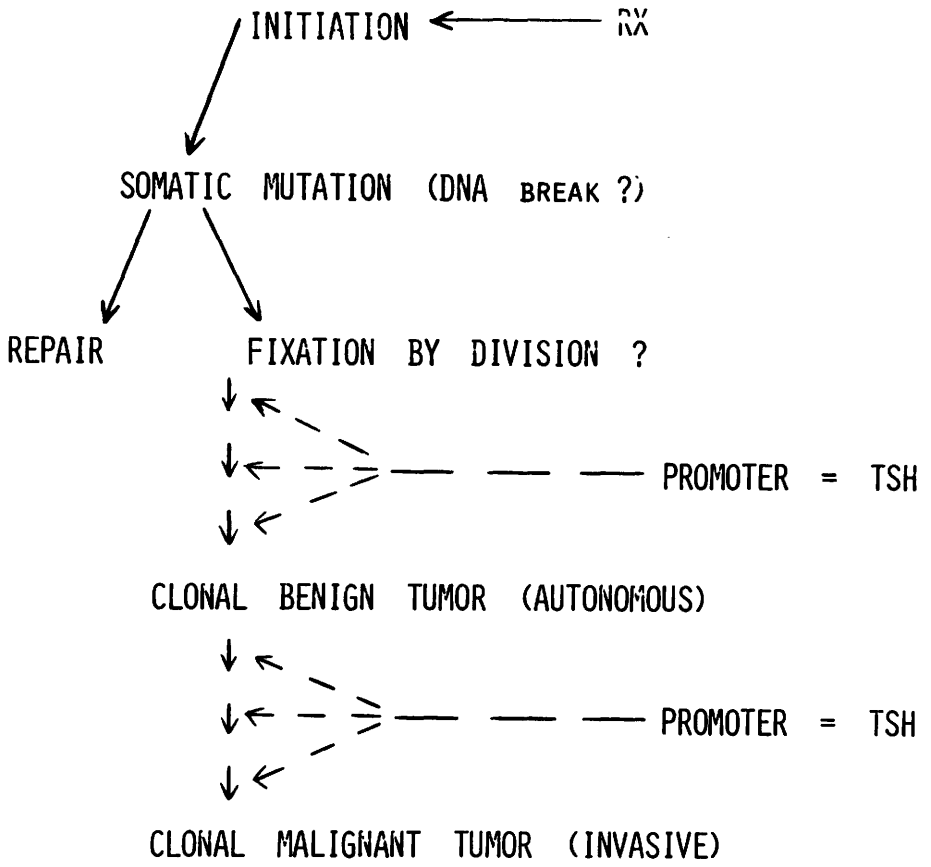


Fig. 8 . : Present working hypotheses on the mechanism of thyroid cancer induction by irradiation.

own growth would therefore confer a great advantage to tumour cells. Although the evidence that such a scheme would apply is tenuous, it would give a role to two until now puzzling phenomena : ectopic protein synthesis and ectopic receptor appearance (416). Prostaglandins which are secreted in greater amounts by some tumours and act as promoters in skin epithelium (417) may be another example of such a mechanism.

The parallels between the generation of thyroid tumours and the concepts developed above, with irradiation as the initiator and TSH or growth stimulation as promoter, as proposed by Doniach and Christov (7,183)are striking (Fig. 8). There are several arguments suggesting that irradiation fulfills the criteria for an initiator :

1) Radiation is considered as an initiator in other systems.
2) Tumours appear when irradiation precedes stimulation.
3) One hit irradiation is sufficient.
4) The frequency of experimental tumours is a function of the radiation dose.
5) The carcinogenic effect of radiation in rat reflects an induction of new cancers rather than an increase in spontaneous incidence.
6) Irradiation is a more effective carcinogenic agent with proliferative thyroid cells, just as irradiation, viral transformation and other carcinogens are in other cells (411).

The known mutagenic action of irradiation, the appearance of chromosomal abnormalities in thyroid irradiated at carcinogenetic levels and the fact that long lasting irradiation (by internal radioisotopes) induces less tumours than equal radiation applied in a short time, i.e. that repair phenomena take place, are compatible with the concept that initiation is caused by a somatic mutation. Moreover, a very good argument in favor of the application of this theory would be the demonstration of a clonal origin of the tumour cells. The inactivation of one X chromosome in each

somatic cell of mammalian females, with the expression of one allele for any X linked enzyme in each cell, gives the means to test this hypothesis. Fialkov et al. (418) have shown that, in thyroid tumours of women, only one allele of the X linked glucose 6 phosphate dehydrogenase is expressed. However, such a compelling evidence has, as yet, not been looked for in irradiation caused thyroid tumours whether human or experimental.

The concept that TSH acts as a promoter in irradiation induced thyroid tumours is suggested by the fact that all experimental procedures which increase TSH stimulation increase the frequency of tumours and/or decrease their latency. Moreover suppression of the continuous stimulation by TSH leads to a decrease or suppression of tumour appearance. That promotion may also be achieved by alteration of intracellular iodine metabolism is suggested by the fact that goitrogens, i.e., inhibitors of iodide oxidation, are the most efficient promoters, while iodide decreases tumour frequency in irradiated glands. However, this concept is still debatable.

It is therefore clear that the concept of radiation as initiator and TSH as promoter of thyroid tumour formation is compatible with most of the existing data. However, this concept should be refined. Radiation alone, with no increased TSH stimulation but not in the absence of TSH, can induce tumours. In this case, normal thyroid growth alone could act as the promoter. On the other hand, prolonged thyroid stimulation alone also leads to tumour formation. TSH could thus promote spontaneously initiated cells.

It is obvious that the action of TSH should be related to its growth promoting rather than to its function activating effects. This is supported by the parallel between the goitrogenic and carcinogenic properties of antithyroid drugs and in keeping with the possible role of cellular proliferation in the promotion of tumours. The precise mechanism of promotion by

TSH is unknown, but it is interesting to note that TSH like other promoters in other systems activates the synthesis of ornithine decarboxylase and that human tumours contain increased amounts of polyamines (419). Nothing is known about the synthesis of plasminogen activator by normal or tumour thyroid cells.

Prostaglandins which like TSH enhance the accumulation of cyclic AMP and the consequent ornithine decarboxylase induction in thyroid cells act as typical promoters on skin epithelial (417) and thyroid cells. In the skin the effect of promoters on the induction of ornithine decarboxylase is blocked by inhibitors of prostaglandin synthesis such as indomethacin, but relieved by prostaglandins of the E type (413,420). The role of prostaglandin like compounds in TSH promotion action or as an independent promoter certainly deserves further study.

The long latency period of induced thyroid tumours can be explained in part by the time required for a transformed cell to multiply into a clone of detectable size. However, experimental evidence implies that the evolution of many neoplasms involves a series of qualitative changes that give rise to successive populations of increasingly autonomous cells. There is good evidence that this concept applies to radiation induced thyroid cancers

1) In experimental tumour induction, hyperplasia, adenoma, carcinoma, follow a clear sequence. Generation of carcinomas requires stronger tumorigenic stimuli.

2) In any given animal, carcinomas are of the same type as the adenomas (papillary vs. follicular).

3) There are good demonstrations of carcinomas developing in previously existing adenomas.

4) The loss of biochemical markers of differentiation and of follicular

characteristics is independent, stepwise and progressive. This is also true for the appearance of TSH independance in human carcinomas as in serially transplanted experimental tumours. However, the demonstrated discrepancies between incidence of radiation induced thyroid adenomas and carcinomas (eg. rats treated with I^{131} alone, greater incidence of nodules but not carcinomas in female patients, etc.) suggest that the sequence between the observed discrete changes may not be straightforward.

V. REGULATORY SYSTEMS IN IRRADIATION INDUCED THYROID CANCERS

The biochemistry of spontaneous and induced thyroid tumours, though not specially of irradiation induced tumours, has been much studied with regard to iodine and specialized metabolism (379). To summarize shortly this important literature, isolated or combined defects of all the metabolic steps in thyroid hormone synthesis or secretion have been described : defects in iodide trapping, in protein iodination at the level of H_2O_2 generation or peroxidase, defective synthesis or sialidation of thyroglobulin, preferential accumulation of iodalbumin in the colloid lumen, defective coupling of iodotyrosyls in iodothyronines, abnormal secretion of thyroglobulin or of iodoalbumin, etc. (374,379). There seems to be no clear-cut relationship between the histological appearance of cancers and their specialized metabolism. When they are irreversible, such defects have a great importance in therapy as the most efficient treatment for irradiation of thyroid tumours and their metastases is their destruction by administered and sequestrated I^{131}.

From the therapeutic view point the most interesting area in the biochemistry of normal and tumour thyroid is the regulation of growth and differentiation. Which are the intracellular signals involved and how are they controlled ? Could their modulation in tumours stop growth and induce redifferentiation ?

Pastan and his group (421) have shown that cyclic AMP and its derivatives inhibit the growth of normal and transformed fibroblasts. The cells lost most of their transformation characteristics and appeared to redifferentiate. Moreover, in such cells an inverse correlation was demonstrated between cyclic AMP levels and rate of growth, transformed cells containing less cyclic AMP than the parent strain from which they were derived. The cause of the decrease was related to decreased adenylate cyclase or to increased cyclic nucleotide phosphodiesterase activity. Based on such data, Pastan et al. proposed the general hypothesis that cyclic AMP is a negative signal of growth and a positive signal for differentiation and that this signal is the regulator of the expression of transformation, vs differentiation (421). However, later studies in other cells (314,422,423) showed that cyclic GMP analogs stimulated them to initiate DNA synthesis and increase in cyclic GMP occurred when they were stimulated to divide (238,314). Thus there is some evidence that cyclic GMP could be a positive signal for growth. Rates of cell multiplication in culture have also been related to the ratio cyclic GMP/cyclic AMP (423). Berridge has made a strong case in favor of the hypothesis that Ca^{++} could be the positive signal for growth and cell multiplication (275). In his scheme, cyclic nucleotides would mostly be involved in the regulation of calcium levels. Despite the apparent contradictions between these theories, a unifying scheme is slowly emerging. First of all, although the intracellular signals may modulate the rate of growth and cell multiplication, they do not appear to be required for any fundamental aspect of these processes. For example, cells devoid of cyclic AMP or mutants lacking responsive cyclic AMP dependent protein kinase grow and divide normally. Second, it is more and more apparent that different types of cells respond differently to the same intracellular signal. Cyclic AMP may be an inhibitor of fibroblasts growth, but it

enhances the proliferation of follicular thyroid cells (Section IV). Although there may be a final common mechanism or trigger of cell multiplication in various types of cells, this mechanism may be modulated differently by intracellular signals or by general metabolism depending on the cell type (423).

Within this framework, it would be of great interest to define the alterations of the various control mechanisms and actions of extracellular and intracellular signals at the various stages of thyroid tumour induction. According to Pastan's hypothesis, cyclic AMP concentration or action should be depressed in thyroid tumours. No data are available on human or animal radiation induced thyroid tumours. Some information may however be obtained from other radiation induced tumours or non radiation induced thyroid tumours. X irradiation induced rat small bowel adenocarcinoma contains significantly reduced intracellular quantities of cyclic AMP compared to normal intestinal tissue. This decrease has been related to elevated cyclic nucleotide phosphodiesterases activities (424). Radiation induced thyroid tumours in animals are similar to other experimentally induced tumours (V, III,B) and there is no apparent difference between spontaneous and radiation induced thyroid tumours in man (SectionII). Evidence on animal experimental tumours and human spontaneous cancers will therefore be examined. Cyclic AMP levels are higher in incubated human carcinomatous tissue than in the adjacent normal thyroid tissue. Similarly, basal adenylate cyclase activity is higher in the carcinomatous tissue (425). Orgiazzi et al. have shown that the latter conclusion only applies to differentiated carcinomas (426). Stimulation of adenylate cyclase by TSH is on the average normal in differentiated but abolished in anaplastic carcinomas (425-427). However, this apparent similarity reflects the existence of some higly responsive and many poorly responsive carcinomas. In slices, the enhancement of cyclic AMP

accumulation by TSH is much reduced. Generally similar results have been obtained in rat experimentally induced tumours (379,428). In such tumours, the decreased response to TSH is accompanied by a reduction of TSH binding to plasma membranes (428). Thus, the general pattern seems clear in the differentiated thyroid tumours. Cyclic AMP levels and adenylate cyclase activity are high while the response of the tumour to TSH is decreased by an alteration at the level of the TSH receptor. Such a conclusion is in keeping with findings in other types of epithelial tumours (422). It clearly suggests that in thyroid tumours cyclic AMP is no more the negative signal of transformation and the positive signal of differentiation than it is the negative signal of growth in normal thyroid cells.

Nothing is known about a final common pathway for induction of growth and dedifferentiation. Tantalizing clues about such a mechanism exist and suggest a role of ornithine decarboxylase and the polyamines synthesized by this pathway. TSH through a cyclic AMP dependent mechanism greatly enhances ornithine decarboxylase synthesis and accumulation (Section IV). Ornithine decarboxylase synthesis precedes growth in all vertebrate tissues. The role for this enzyme in tumour promotion has been discussed above. Human thyroid adenocarcinomas contain much higher levels of polyamines (mostly putrescine) than the normal tissue (419). It is obviously impossible at this stage to propose mechanisms, but on the basis of this evidence further investigations are certainly warranted.

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CONCLUSION

The relation between irradiation and thyroid disease, particularly cancer is well demonstrated in humans (Section II) as well as in experimental animals (Section V). With the use of human epidemiological and clinical data (Section II), of animal experiments, and of the huge information provided by studies on experimental carcinogenesis in other systems (Section V) a fairly clear picture of the pathogenesis of this cancer can now be proposed. The implications with regard to prevention and treatment are generally accepted (Section II). However, as has been shown all through this book, many questions remain open and as conclusion we should like to point out the most obvious.

From the clinical and epidemiological point of view, the most vexing question remains, in the thyroid as in other organs, the dose effect relationship particularly in the range of clinical interest. In the thyroid this problem has a number of unusual aspects, in that the doses received accidentally and in diagnostic medical work, have frequently been large, i.e. in the range of several rads to several hundred rads, compared with those received by other organs. Notwithstanding these large doses it has still been difficult to define dose effect relationships because the dosimetry in most cases has not been exact and the dose rates involved have generally been low. In defining dose-effect relationships the possible existence of tresholds is always of interest as is the level at which they occur. While no treshold is known to exist for carcinogenesis the investigation of the low dose region must remain important. On the other hand, at much higher doses where hypothyroidism is induced, the existence of a treshold is possible on theoretical grounds. If such a treshold exists it would be of interest to characterize it with respect to dose and the dependence, if any, of the dose on the age and clinical standing of subjects.

Fruitful epidemiological studies could perhaps be performed on the numerous patients who in the early days of ^{131}I use received diagnostic doses of up to 200 μCi, although the exact rad dose to the thyroid of such subjects would be difficult to determine retrospectively. An advantage of studying such a population is the fact that their clinical and biochemical status would probably be very well defined. Patients who were hypothyroid at the time of investigation, i.e. whose thyroid was under intense stimulation, would presumably have been particularly sensitive to carcinogenesis, if their glands have not subsequently been ablated by large doses of ^{131}I. Epidemiological investigations might also be profitably be undertaken on populations of areas with high natural radioactivity such as Kerala in India, Gabon, Shaba, etc. Within this context it would be valuable to check if the human thyroid concentrates radium as has been suggested for cattle (429). In these studies and in contemporary accidental exposures it is worth attempting to obtain more exact dosimetric information. This should be facilitated in many cases by the thermoluminescent technique which should render it more practical to determine the cumulated activity in many circumstances.

An index allowing prediction of the likelihood that an individual patient will develop nodules or cancer when due account has been taken of the clinical, biochemical and dose considerations involved, would clearly be useful in the clinical care of irradiated patients. In this regard the systematic use of serum thyroglobulin measurements in the follow up of irradiated subjects could yield valuable results. Obviously, the dose level at which it is appropriate to begin to follow up patients needs consideration, since it is not practical to follow up, for example, every patient receiving a $^{99}Tc^{m}$ thyroid scan, although it may be worthwile considering including those who receive more than, for example, 100 μCi of ^{131}I. Likewise in the case

of occupational exposure it is obviously not necessary or desirable to follow up every minor incident. However, the ICRP Maximum Permissable Doses are set so high that to use them as guidelines to acceptable levels of exposure would be misleading and would probably misinterpret the significance that ICRP attaches to the dose limits. In view of the data in Section V even those receiving a fraction of the maximum permissible dose annually should be followed up. In this context it is worth noting that the level of non fatal harm consequent on thyroid irradiation is high and in this respect it may be unusual.

Apart from the fact that they should be protected from any irradiation, medical or otherwise, patients with genetic defects either in DNA repair (Fanconi's anemia, Xeroderma pigmentosum, Ataxia telengiectasia) or in O_2 metabolism (acatalasemia, glucose 6 phosphate dehydrogenase deficiency, chronic granulomatous disease, etc ...) could provide cells or tissue samples of great interest for radiobiological studies. The possibility of identifying heterozygotes (430) could also allow epidemiological studies.

With regard to the biochemistry of human thyroid cancers, spontaneous or radiation induced, we have seen that little is definitely known but

much could be learned by available methodology. Their monoclonal character, their synthesis of and sensitivity to other hormones than thyroxin and thyrotropin, including prostaglandins, the possibility to redifferentiate them by pharmacological agents as well as their intracellular control mechanisms (cyclic nucleotides) should be assessed.

The carcinogenetic process itself would be much better understood if more was known about the cellular physiology and the radiobiology of the thyroid cell itself. It is striking that we know so little of oxygen metabolism in the follicular cell and how the enzymes involved in this metabolism may influence its sensitivity to radiation. There are indications that the thyroid cell may be more radioresistant than other tissues (Section V), and this could be studied now, in vitro, using new systems of growing thyroid cells cultures, with relatively exact dosimetry and uncomplicated biological end points. In vivo studies in similar areas could also now be undertaken with more confidence in vue of the more reliable dosimetric methods available. The comparison of effects of UV vs X-ray irradiation of the cultured cells could have a very general impact on the understanding of the above problems.

Finally, an insight in two very fundamental problems could have very direct clinical implications. First,we do not know with certainty if human differentiated thyroid follicular cells have a finite life span, i.e., can only sustaina limited number of divisions, or even,if after maturity, they normally divide all. The answer to this question would bear directly on the problem of carcinogenesis and on the use of radioiodine therapy. Second, we know little of the control of cell growth and differentiation in thyroid,both at the intercellular level (interaction between follicular, endothelial cells and fibroblasts), and at the intracellular level (role of cyclic nucleotides, of polyamines, of prostaglandins, of iodine, etc.) although such knowledge could provide the tools to modify tumor promotion at several stages and thus to treat our patients.

Thus, as stated at the beginning of this section,in the field of irradiation and thyroid cancer, although the general picture is beginning to appear, much of the precise knowledge which allows to predict, to prevent and to treat,is still lacking. We cannot yet provide many answers but we can now begin to ask very good questions.

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Thyroid cancer caused by irradiation is an important public health problem because of the many possible causes of external and internal exposure: accidental, diagnostic and therapeutic. Three aspects are considered. Data in the literature are analysed to define the quantitative relation in man between irradiation and thyroid disease: thyroid insufficiency and neoplasia. The clinical characteristics of nodules and cancers of this origin, the prognosis and the therapeutic attitude are discussed. Next the radiobiology and the dosimetry of the thyroid are described and the necessary relation between the study of both is emphasized. The relative radioresistance of the gland is demonstrated. The characteristics of thyroid growth regulations is then discussed in relation with current concepts of carcinogenesis. The possible application of experimental *in vivo* and *in vitro* data and these current concepts to the case of irradiation-induced thyroid cancer is considered. New lines of research are suggested.

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