A Plan for Analysis of the Biologic Factors Involved in Experimental Carcinogenesis of the Thyroid by means of Radioactive Isotopes*

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IN studies by Hertz, Roberts *et al.*[1-7] the radioactive isotopes of iodine were utilized in studies of thyroid physiology, biochemistry, and pathologic physiology of both animals and man. In that series of experiments the isotopes I 128, I 130, and I 131 were found to give data in tracer experiments which led to a successful therapeutic application in Graves' disease.[7]

At the outset of the above experiments in 1937, it was thought that there might be equally promising therapeutic possibilities in the treatment of carcinoma of the thyroid. Preliminary tests on two patients with cancer of the thyroid were reported in 1942 in a John and Mary R. Markle Fund report.[12] Tracer studies in these two patients indicated that in the types of cancer of the thyroid which were present, adeno-carcinoma, there was no increased uptake of Ra-I over that of adjacent normal thyroid tissue. It was also demonstrated that metastases in the adjacent nodes were not receptive to the Ra-I. We pointed out, therefore, that the cancer cells were biologically quite different from the normal and hyperplastic thyroid cells with respect to their iodide metabolism. We postulated that there might be an enzyme system in the normal and hyperplastic thyroid which had the function of conversion of inorganic iodides to organic iodides in the preliminary steps of bio-synthesis of thyro-globulin, and that enzyme system ("iodase") might be either absent or deficient in the cancer tissue.

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*This paper is prepared in order to place on record an experimental approach to cancer of the thyroid. This approach impresses the author as of sufficient interest and importance to workers in the field of cancer to warrant publication of this article at the inception of a program of research being undertaken at the Massachusetts Institute of Technology and Beth Israel Hospital, Boston, Massachusetts. It is published in the hope that others will find in it a stimulus to adopt portions of the problem for analysis according to the available techniques in their particular laboratories so that the program may go ahead as rapidly as possible through a community of interest and division of labor.

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KNOWN FACTS. Experimental animals with cyanate goiter and hyperplastic glands induced by thyrotropic hormone were demonstrated to have an increased capacity to take up Ra-I.[3] The glands of these animals were comparable with the hyperplastic thyroid glands of patients with Graves' disease and cyanate goiter.[4]

On the other hand, patients treated with thiourea at Beth Israel Hospital in 1943 by Dr. Hermann L. Blumgart were demonstrated to have a decreased thyroid Ra-I uptake as were animals which had been treated with sulfathiazole in preliminary experiments at Massachusetts Institute of Technology.

Since hyperplasia induced by thyrotropic hormone was associated with increased basal metabolic rates, and both thiourea and thiocyanate goiter in man and animals were more characteristically associated with a lowering of the BMR's, we expressed the opinion that herein lay an important biologic set of evidence to indicate that the types of hyperplasia were distinct and of different mechanisms of production.[13] The literature already contains abundant evidence that the above opinion is correct from several other points of view.

The following table summarizes briefly some of the known facts.

TABLE 1*

Carcinogenesis	Type of Goiter	Prevented by Iodides		RA-I Uptake	BMR
?	Cyanate	Yes	*	+	—
Yes	Thiourea	No	*	—	—
?	Thyrotropic Hormones	Yes	*	+	+
?	Iodide Deficiency	Yes	*	+	O
?	Sulfa-Compounds	Yes	*	—	—

* The existence of the postulated enzyme system for each type of hyperplasia must be determined quantitatively by in vitro and in vivo techniques.

Thyroid Carcinogenesis. Carcinogenesis of the thyroid has been demonstrated to take place when 2-aceto-amino-fluorene is administered to animals which have been previously prepared with thiourea compounds.[8] Thiourea compounds, per

thiourea therapy should be especially careful in the use of such insecticide powders,[12] particularly when thiourea is being used in a prolonged fashion as a non-operative treatment of Graves' disease.

SUMMARY

On the basis of experience to date, in the study of normal and pathologic thyroid physiology, chemistry, and therapeutics by means of radioactive isotopes of iodine, a plan is presented for the analysis of experimental carcinogenesis in animals. Certain facts which have already been established by means of tracer use of radioactive iodine in clinical cases of cancer of the thyroid and in patients treated by means of thiourea are stressed as a starting basis for clinical applications and thinking.

The existence of an "iodase" enzyme system in the thyroid is formulated; and a table which may be useful in guiding a concerted program for the study of the variables involved in this type of carcinogenesis is offered as a working basis for such studies. The importance of available isotopes of radioactive iodine, sulphur, antimony, cyanate, and fluorine to such an analytic study is emphasized. From this projected program it is hoped that a logical theory of carcinogenesis and an understanding of important preventive and therapeutic factors may be developed.

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