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

SAUL HERTZ, M.D.**

BOSTON, MASSACHUSETTS

INTRODUCTION

THE radioactive isotopes of iodine were utilized by Hertz, Roberts, et al.,[1-7] 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 given in a John and Mary R. Markle Fund report in 1942. Tracer studies in these two patients indicated that in the types of cancer of the thyroid which were present (adenocarcinoma), 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 iodine 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 biosynthesis of thyroglobulin; and that enzyme system ("iodase") might be either absent or deficient in the cancer tissue.

KNOWN FACTS

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

On the other hand patients treated with thioureau 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.[12]

Since thyrotropic hormone-induced hyperplasia was associated with increased basal metabolic rates (B.M.R.'s), and both thiourea and thiocyanate goiter in man and animals were more characteristically associated with a lowering of the B.M.R.'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.[12]

The literature already contains abundant evidence that the above opinion is correct from several other points of view.

Table I summarizes briefly some of the known and unknown facts in this regard.

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 se, do not produce

*This paper is prepared in order to place on record an experimental approach to cancer of the thyroid which impresses the author as being of sufficient interest and importance to workers in the field of cancer to warrant its publication at the inception of a program of research which is 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 technics in their particular laboratories, to the end that the program may go ahead as rapidly as possible by virtue of such a community of interest and division of labor.

This material was presented as part of a Dry Clinic, conducted by invitation of the American Association for the Study of Goiter at its annual session held at Chicago, Illinois, June 22, 1946.

**Formerly in charge of the Thyroid Clinic of the Massachusetts General Hospital, Boston, Massachusetts, Research Associate, Harvard Medical School and Massachusetts Institute of Technology, and Commander (MC) USNR.

carcinogenesis, nor does 2-A-A-F produce thyroid carcinogenesis in animals which have not been prepared with thiourea, but 2-A-A-F does produce carcinogenesis in organs other than the thyroid when used alone.[9]

It is not, as yet, known whether carcinogenisis takes place following cyanate, thyrotropic hormone, iodide deficiency or sulfathiazole-induced types of hyperplasia when 2-A-A-F is added to the system.

in such an experimental program might prove of considerable interest both to the clinician and the biologist.

The known genetic, species variation and parabiotic technics for the study of carcinogenesis, should receive special controlled study.

The important nutritional and endocrine relationships of significance to growth and cellular metabolism should receive due attention in the proposed analytic plan by the employment of full controls of these factors.

Table I

Carcinogenesis	Type of Goiter	Prevented by Iodides	(Enzyme)	RA-I Uptake	B.M.R.
?	Cyanate	YES	*	+	—
Yes	Thiourea	NO	*	—	—
?	Thyrotropic Hormone	YES	*	+	+
?	Iodide Deficiency	YES	*	+	— (SL)
?	Sulpha-Compounds	YES	*	—	—

*The existence of the postulated enzyme system for each type of hyperplasia needs to be determined and quantitated by in vitro and in vivo technics

FACTS TO BE DETERMINED

It occurs to us that an important set of data would be derived from filling the "?" and "*" in Table I. Having established these facts, it should then be possible to proceed with a large scale study of the variables involved and to further the analysis of the mechanisms thereof.

A differential study of the metabolism of iodides, sulphur, fluorene and cyanate compounds in the normal, hyperplastic and carcinomatous thyroid cells could then be applied for the closer analysis of this type of carcinogenesis. Certain other isotopes, that is, ekiodine (element 85), carbon and antimony, would be of interest in furthering this analysis. By tracer methods which are already available, it should be possible to obtain data at various stages between normal, hyperplasia and carcinoma to enable the construction of a theory of carcinogenesis which may have far-reaching significance to the laboratory investigation of cancer in general, and possibly, to its ultimate treatment.

Since 2-A-A-F is productive of leukemia, and thiourea has a depressant effect on the leukocytic elements of the bone-marrow, it is important to study the hematopoietic systems of the experimental animals in a controlled manner. Certain other by-products

CLINICAL DATA AND ORIENTATION

The findings of Hertz and Roberts with respect to the cancer cell's inability to take up Ra-I has been confirmed by Hamilton and Soley (by radio-autographic studies). Others have applied the tracer technic to cases of cancer of the thyroid with suggestive results which indicate that certain tumor types do have a limited capacity for retaining Ra-I. These iodide retaining types are the exception, and it would seem that in only such cases, in which one can demonstrate such a favorable uptake by tracer studies, is the hope of radiotherapeutic dosage to be entertained. Since, even then, the radioactivities required in such a form of treatment are, of necessity, very large (to compare with external high voltage x-ray therapy), it is unlikely that this method of treatment will ever be of great clinical application in cancer of the thyroid.

It appears to us that the field of radioactive investigation in relation to thyroid cancer is most likely to bear fruit along the lines of further extensions of the tracer method to analyses of the type outlined above. This will remain so until a chemical

compound which is selectively concentrated by the cancer cell is found, one which can be produced with a high specific radioactivity. Of this we feel certain; it is not radioactive iodine or any of its presently known combinations in the great majority of thyroid cancer cases reported to date.

The tracer method, however, may prove to be quite useful in a diagnostic way, particularly in the location of hidden thyroid metastases which are not demonstrable by x-ray technics.

The implications of this new method of carcinogenesis of the thyroid for clinical medicine are important. Close clinical analysis of cancer of the thyroid should be made from the standpoint of possible ingestion of hyperplasia-producing factors and substances such as 2-aceto-amino-fluorene. A search for other compounds with similar types of carcinogenic properties would also be instructive.

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 if offered as a working basis for such studies. The importance of available isotopes of radioactive iodine, sulphur, antimony and carbon 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.

REFERENCES

1. Hertz, S.; Roberts, A. and Evans, R. D.: Proc. Soc. Exper. Biol. and Med., 38:510, 1938.
2. Hertz, S.; Roberts, A.; Means, J. H. and Evans, R. D.: Trans. Amer. Assn. for the Study of Goiter. 1939, pp. 260-276. Also: Am. J. Physiol., 128: 555-567, February, 1940.
3. Hertz, Saul: J. Roentgenol., 46:467-468, October, 1941.
4. Hertz, S.; Roberts, A. and Salter, W. T.: J. Clin. Invest., 21:25-32, 1942.
5. Hertz, S. and Roberts, A.: J. Clin. Invest., 21: 33-37, 1942.
6. Hertz, S. and Roberts, A.: J. Clin. Invest., 21:624, (Sect.) 1942.
7. Hertz, S. and Roberts, A.: J.A.M.A., June, 1946.
8. Bielschowsky, F.: Brit. J. Exper. Path., 25:90, June, 1946.
9. Wilson, R. H.; Deeds, F. and Cox, A. J: Cancer Research, 1:595, August, 1941.
10. Bielschowsky, F.: Brit. J. Exper. Path., 25:1, February, 1944.
11. J.A.M.A.: Editorial, 127:278-279, February 3, 1945.
12. Unpublished data of author.

Reprinted from The Western Journal of Surgery, Obstetrics and Gynecology

Vol. 54, pp. 487-489, December, 1946