FIFTY YEARS OF THYROIDOLOGY

Presidential Address. The American Thyroid Association, 50th Anniversary Meeting, Seattle, Wash., September 12-15 inc.,1973.

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This year our Association is celebrating its 50th Anniversary. It is particularly meaningful to me to deliver the Presidential address on this anniversary since I have spent almost as many years of my own life in the thyroid field. I would like to take this opportunity to thank personally all those who helped make this meeting in Seattle the special event that it is.

Last year at the Council meeting, the Council magnanimously suggested that a review of the past 50 years of thyroidology was obviously the subject for my talk. In a moment of unbelievable lack of foresight, I agreed. First, it has meant very hard work. The volume of contributions in this interval is formidable and the problem of selection has been worse. Moreover, the experience has been very humbling. The humbling has to come from being faced with the vast wealth of intellect, imagination, and skill which underlies most of these achievements. Finally, a once hour's talk has had to be considerably compressed to make up for tomorrow's shortened session. So, alas, much has had to be omitted. It was Pindar who said in 518 B.C. - "Every noble deed dieth, if suppressed in silence." Thus, for those who must, access to the original unabridged version can be arranged. The once symphony, now sinfonietta, has 3 movements. 1st movement: Leitmotif.

A Personal Note

My own interest in the thyroid began in the fall of 1932 when, having completed my internship, and before my residency

was to begin, I was accepted as a fellow with Philip E. Smith, then Professor of Anatomy. I wanted to work with the new Endocrinology. When I arrived ready to begin the great research, Dr. Smith shunted me to the library to learn something about the field; I stayed there for three solid months before I was released.

I think I would have been there still had it not been that among my readings, I encountered several articles on antihormones to pituitary hormones, including thyrotropin. I became persuaded that this represented merely antibody formation to a foreign protein and not the proposed physiologic antihormone designed to maintain homeostasis. This time when I told Dr. Smith about a conclusion of mine, a work bench and one guinea pig developed. I almost followed the guinea pig three weeks later when I found it lying dead in the cage and had to ask for another. Some 2 years later, I was able to restimulate with a flavianic acid preparation the thyroid of a guinea pig which had developed antihormones to an ammonium sulfate preparation, as well as maintain chronic thyroid hyperfunction ( ). It thus seemed that thyrotropin was indeed an antigen, the antibody to which neutralized its physiological effect ( ). The interest in the thyroid and in the immune area thus aroused has been one of the main threads running through my career.

The American Thyroid Association

According to Yung, a Charter Member, the earliest stirrings

of our Association took place in Bloomington, Illinois, in 1921 when the Illinois Clinic Club was formed under the leadership of Dr. E. P. Sloan. At that time, quote, "it was noted that some centers otherwise highly informed, were rather deficient in their knowledge of goiter." Unqoote. This led Dr. Sloan in the fall of 1923 to organize The American Association for the Study of Goiter. The first meeting was held in Bloomington, December 1923, with the founder as President. He reminded Dr. Yung, quote, "of Lincoln".

In 1930, an anonymous cash prize award of $300.00 was established for the best essay on "Goiter - especially its basic cause." This became the Van Meter Prize Award when Dr. Van Meter died - he had been the donor. The first award went to William F. Rienhoff, Jr. of Johns Hopkins. He reported that removal of nine-tenths of the toxic diffuse gland rendered 90 per cent of patients euthyroid; and also observed that ink injected into the thyroid reached the cervical lymphatics.

In 1948, we became The American Goiter Association, and in 1960, the American Thyroid Association ( ).

Presently, the Association has been engaged in reappraising its goals. Should we have a role, apart from our scientific meeting, in education of the profession at large and of service to the public? How far can we go in helping to identify and publicize risks to the population at large, such as from iodine want or excess; to patients whose thyroids were exposed to

radiation in infancy; in screening the newborn for hypothyroidism? Ad Hoc committees were formed this year to study two of these three suggestions and the third is under discussion. If yes, should these be funded, and who would do the work? Finally, will changes in research support affect the composition and productivity of our membership and how active can we be in defense of our field?

Research Funding. With the shift in 1947 from private financing of research by medical schools, private foundations, and individuals, to governmental sources, there came, as a few did foresee, the vulnerability to political pressure and personal bias which marks today. Surprisingly, many of our members have alternative sources of funding besides the NIH. Some have and will have little problem with obtaining grants or fellows. But for most, support may be harder to come by; and fellows could go where the money is, in cancer and heart disease, rather than into thyroidology, as a consequence. Just the day before yesterday, Congress failed to back the promised relaxation of the ban on fellowship support. 2nd Movement: Recitative.

A HALF CENTURY OF THYROIDOLOGY

Half of the remaining presentation was originally designed to acknowledge the contributions of as many as possible in more fundamental areas of work; the other half, more clinical in

nature, to present more of a point of view. Well-reviewed areas will receive only token mention.

My intensive readings for this paper lead me to quote from Shaw's "The Doctor's Dilemma". The conversation takes place between Sir Colenso Ridgeon, age 50, just knighted for a medical discovery, and Sir Patrick Cullen, a distinguished physician aged well over 70:

Ridgeon:	You keep up your interest in science, do you?
Sir Patrick:	Lord yes. Modern science is a wonderful thing. Look at your discovery.
Ridgeon:	Well, there's nothing like progress, is there?
Sir Patrick:	Don't misunderstand me, my boy. I'm not belittling your discovery. Most discoveries are made regularly every 15 years; and it's fully a hundred and fifty years since yours was last made.

The era opened most auspiciously, even without funding from the NIH. Prophylactic use of iodized salt was successfully reducing the incidence of endemic goiter ( ). Plummer reported in 1923 that he had administered Lugol's solution for 10 days following operation for toxic diffuse goiter and had had no mortality ( ). It should be mentioned, however, that in 1920, Neisser in Germany had treated 8 thyrotoxic patients with iodine with good results ( ); and shortly thereafter, success was described in 12 more similarly treated by Lowwe and Zondek ( ). P. E. Smith had learned by 1926-7 to perform hypophysectomy in

in the rat transsphenoidally, without injury to the overlying hypothalamus ( ). About the same time, Harriginton recognized the constitution of, and synthesized, thyroxine ( ).

Fundamental Investigation

Since most of the present advances in thyroid research followed the introduction of radioiodine, let me begin with this area.

Fermi was one of 3 great non-thyroidal thyroidologists. In 1934, he discovered radioactive iodine. Hevesy was the second. In 1923, he introduced the tracer as a biological tool when he used natural lead to study plant physiology. Last was Schoenheimer. In 1935, he administered deuterium to man and animals and declared that the "body does not discriminate between isotopes of the same element, radioactive or stable."

In 1936, Means, who started the weekly Thyroid rounds which became the first Thyroid Clinic in the early 20's ( ), heard Compton lecture about Fermi's work and mobilized Robley Evans of M.I.T. to apply this finding to human thyroid research ( ). Progress was facilitated by Livingood and Seaborg who added, in 1938, several radioisotopes of iodine including 131-I to the armamentarium. Shortly thereafter, the M.G.H. group administered 130-I ( ) and, Hamilton in California 131-I ( ), both to animals.

The next year, Hamilton and Soley used 131-I in humans and

recorded thyroidal uptake, urinary and fecal excretion. In 1940, they studied hyper- and hypothyroid patients. Papers by others followed ( ), including establishment of the 24 hour 131-I uptake as a simple diagnostic tool ( ). The first radioautograph was made in 1940 ( ), and was followed by the recognition of "cold" nodules in 1946 ( ), and of "hot" as well as "cold" nodules in 1948 ( ).

The Hypothalamus. Smith's hypophysectomy results seemed to exclude the hypothalamus from consideration. Nevertheless, in 1929, hypothalamic lesioning was claimed to cause lowering of the BMR ( ); and 10 years later, stalk section to prevent thyroid cell hypertrophy in response to cold ( ). In 1951, a ventromedial lesion in the rat prevented thyroid hypertrophy from antithyroid drug administration ( ), and electrical stimulation of the anterior median eminence, in adrenalectomized rabbits only, increased thyroid activity ( ). Extraction of an active principle ( ) and resolution of the structure of TRH and its synthesis ( ) are classic. In view of the numerous present studies with TRH, I shall mention only several; the prolactin releasing effect; the tertiary or hypothalamic hypothyroidism ( ) and, 1 patient, hyperthyroidism; the inhibitory effects of somatostatin; and finally the identification of 2 binding sites on the cell membranes of the thyrotrope ( ).

Thyrotropin (TSH). In 1926, Foster and P.E.Smith observed

in the rat that the BMR was decreased by hypophysectomy ( ); was restored by daily implants of rat hypophysis; and increased by injection of pituitary extracts, though not after thyroidectomy ( ).

A reciprocal pituitary thyroid relation, Salter's quote, "axis" unquote ( ), was first suggested by the work of Aron in 1930 ( ). He found an excess of TSH in the urine in hypo- and undetectable amounts in hyperthyroidism ( ); and prevented post-thyroidectomy hypertrophy of the rat anterior pituitary by feeding thyroid ( ). Pituitary hypertrophy after 131-I ablation in the guinea pig led to chromophobe tumor formation ( ), and such tumors in the rat were found to be thyrotropin secreting ( ) and dependent or autonomous to thyroid feeding ( ).

Purification of thyrotropin received its real impetus when the cation exchange resin IRC-50 was used in 1956 ( ). Further progress occurred mostly in 3 laboratories ( ). Correspondingly, biological assay for TSH burgeoned. Among the most used were the statis tadpole ( ), chick thyroid weight ( ), and the thyroid suppressed 131-I labelled mouse ( ) methods.

Purification of TSH made possible the establishment of the antigenicity of thyrotropin proper ( ), and the subsequent development of radioimmunoassay for the human hormone ( ). Radioimmunoassays, like the parent one for insulin ( ), utilize Ekins' principle of competitive protein binding displacement ( ).

In 1966, TSH binding to the thyroid cell surface was evidenced ( ). Six years before this TSH activation of adenyl cyclase within

the thyroid cell was indicated ( ), and 2 years after Sutherland's second requirement was fulfilled, namely, accumulation of cyclic AMP ( ). By 1970, similar findings were made for LATS ( ). Additionally, the abrupt rise of circulating TSH in the human fetus at birth, probably due to cooling ( ) can be mentioned; and the discovery of trophoblastic thyrotropin ( ) and hyperthyroidism therefrom ( ).

Experimental exophthalmos was first produced with pituitary extracts given to the baby duck ( ). The proposal that EPS is distinct from TSH ( ), has been clouded in doubt since. Recently, a small peptide fraction of TSH, possibly β subunit, was claimed to have only EPS properties ( ). Radioimmunoassay for β subunit, however, was negative in patients with Graves' disease eye changes ( ).

TSH as a clinical test was introduced in 1950 by two laboratories ( ). Suppression of the pituitary thyroid axis with exogenous thyroid hormone was employed in 1952 to investigate the pathogenesis of Graves' disease ( ), and was later exploited diagnostically by four groups ( ). Suppression as a therapy will be considered later.

<u>Thyroglobulin.</u> The mol. wt. of thyroglobulin (TGB), was first determined in 1937 at 675,000 Daltons ( ) but upon further purification ( ) was fixed at 660,000 with a sedimentation constant of 19S ( ). This latter center also studied the

proteolysis and physical chemistry of TGB ( ). Elsewhere, the synthesis stepwise to a 19S molecule, then iodinated, was elaborated ( ). Amino acid analysis followed in 1961 ( ), and identification of two different polysaccharide chains in the TGB molecule in 1965 ( ). A workable radioimmunoassay devised that year ( ) showed TGB to be present in about 65 per cent of normal human plasmas ( ). In 1968, study of the ultrastructure of TGB revealed a flexible helix with 2 turns ( ). Abnormal release of TGB ( ) and an abnormal TGB ( ) have been found in congenital goiter.

Thyroid Hormones and Thyroid Binding Proteins. Twenty-five years after the synthesis of T4, T3 was discovered, an accomplishment concurrently made from plasma by one laboratory ( ) from the thyroid by another ( ). The elaboration of the thyroxine binding proteins (TBP) began in 1952 with the concurrent detection by 5 groups of inter-alpha globulin ( ), now TBG ( ). From 1957 to 1958, thyroxine binding prealbumin went from a suggestive spot on the electrophoretogram to its identification ( ) and purification ( ). In 1968, TBPA, or a fraction thereof, was identified as retinol binding protein ( ). TBG was purified in 1969 ( ).

Measurement of free unbound T3 began indirectly with red blood cells as the receptor ( ). Mitchell, 3 years later, introduced the resin sponge and tested both resin T4 and T3 uptakes ( ). Dialysable fraction and absolute concentration of T4 in serum were

first estimated in 1960 ( ). In 1966, Lardy's observation that the magnesium ion chelated with and precipitated T4, though not T3 ( ), was used to quantitate dialysable fraction and absolute concentration of T4 ( ). By means of an excess of Mg ion, T3 was similarly measured ( ).

Chemical measurement of thyroid hormone concentrations in plasma became practical in 1937 with Sandell and Kolthoff's ceric sulfate arsenious acid reaction ( ). The several methods which followed ( ) have largely given way to those employing competitive protein binding displacement ( ); but comparable results have been recently claimed for measurement of the Achilles reflex V-P interval, according to a 10 year experience ( ). Radioimmunoassay to quantitate T3 ( ) has been applied to T4 testing ( ). A modification of our own T3 radioimmunoassay procedure ( ) permits both T3 and T4 concentrations to be assayed in 0.5 ml serum within 3 to 24 hours depending on the number of samples needing to be counted ( ).

In 1951, the first claim was made that labelled T4 became converted to labelled T3 (T3*) following injection into thyroidectomized mice ( ). In 1954, such monodeiodination was demonstrated in kidney slices ( ). In 1957, conversion was demonstrated in normal and thyroidectomized rat pituitaries in vivo ( ), including after transplantation to the anterior chamber of the eye ( ); and within a variety of individual cells

in 1970 ( ).

The definitive observation for man was made in totally thyroidectomized patients receiving T4 as replacement ( ). The sometimes heated controversy since over the relative importances of thyroidal secretion and peripheral deiodination ( ) may be becoming reconciled. Kinetic analysis suggests that about 50 to 60 per cent of daily T3 disposal may be derived from extrathyroidal sites ( ).

Parenthetically, intraglandular coupling of MIT and DIT to form T3 was described in 1955 ( ), as was increased MIT and T3 concentrations in the thyroid following iodine deprivation ( ). Whether DIT exists in normal serum ( ) appears from radioimmunoassay apt to be settled in favor of, though in about half the concentration ( ), claimed earlier ( ).

Kinetics. Keating and coworkers ( ) introduced the kinetic approach into the thyroid field in 1947. They calculated extrarenal and extrathyroidal disposal rates for labelled inorganic and organic iodine in eu-, hyper- and hypothyroidism. Trials of compartmental analysis in 1949 ( ) and 1951 ( ) were developed into highly complex form by 2 groups ( ); but simplification of methodologies was achieved ( ) by a third.

Hormonal synthesis has been well reviewed in relation to congenital goiter and will not be considered here (though see later). The Wolff-Chaikoff effect was described in 1949. As an extension,

administration of excesses of iodine have been used to reveal latent thyroid impairments ( ).

Thyroidal autoregulation by variation in concentrations of iodide within the thyroid was suggested in 1954 from work with hypophysectomized ( ) and antithyroid drug treated animals ( ). The view that a defect in autoregulation may be the pathogenetic mechanism of Graves' disease has recently been put forth ( ).

Thyroid Hormone Action. The nature of thyroid hormone action remains unsettled. Experiments indicating the action is on protein metabolism ( ) have required concentrations of thyroid hormone in excess of physiologic limits.

Antithyroid Agents. The antithyroid drug era opened in 1937 when Curt Richter testing taste in the rat produced goiters with phenylthiourea ( ). In 1943, Astwood and group tested 106 compounds related to thiourea and started the drug treatment of hyperthyroidism ( ).

In 1936, the first anion, SCN, was recognized as a goitrogen in patients treated for hypertension ( ). Recently, a cation, lithium, was found to cause goiter ( ), by blockade of thyroid hormone release ( ). In 1949, a plant goitrogen, goitrin, was isolated from rutabaga ( ), and in 1956, a precursor, progoitrin, identified in the rutabaga seed ( ).

By now, most of you are probably reminded of Lady Astor and

the Titanic. You will recall when the iceberg struck it ploughed into the cabin where she was dining. She looked up and exclaimed: "I ordered ice - but this is too much!" 3rd movement: Finale con brio.

CLINICAL INVESTIGATION

Most of the remainder as stated above will lean towards a point of view rather than a recital of events. A new observation and a completely overlooked therapy, both in Graves' disease, will conclude the discussion.

Pediatric Aspects. Stanbury and Hedge's pioneer study of a goitrous cretin with a defect in iodide binding ( ) opened the whole subject to physiological correlations. These are now well known and excellently reviewed ( ). Perhaps two related oddities might be mentioned: excess of circulating iodoprotein in a non-goitrous patient with amenorrhea and short stature ( ) reported at the same time the comparable goitrous defect was elucidated ( ); and two mildly hypothyroid patients with goiter whose serum and thyroid contained T3 but virtually no T4 ( ).

Complete peripheral resistance to both T4 and T3 was initially described, in 2 siblings with stippled epiphyses ( ). Last year, partial resistance was suggested in an adult ( ).

Transport of T4* and T3* across the placenta at term was demonstrated early ( ), but quantitated in 1972. The extent of

transfer was such as to make relatively little contribution to the fetus ( ). Probable failure of conversion by the fetus of T4 to T3 was evidenced by detailed studies in sheep ( ) and might explain the low serum T3 concentration in human cord blood ( ).

Nontoxic Nodular Goiter. Autonomous nodules causing suppression of the opposite lobe but not clinical hyperthyroidism were reported in 1969 to be associated with a high serum concentration of T3 ( ). Incidentally, the "T3 toxicosis" in toxic nodular goiter ( ) often is a T4 toxicosis as well ( ).

There is argument over whether the functional nodule, like the non-functioning ones seen in congenital and endemic goiter ( ) results from chronic TSH stimulation. A TSH theory poorly explains the presence of a solitary "cold" or "hot" nodule in an otherwise normal gland. The question nevertheless has importance in view of the widespread use of thyroid hormone suppressive therapy in nontoxic nodular goiter, and hence in accompanying but unrecognized thyroid cancer, as opposed to the nontoxic diffuse goiter for which it was reintroduced ( ) in 1952 ( ).

Against the TSH stimulation theory are epidemiological studies which have revealed that nontoxic nodule formation increased with age ( ), whereas cancer incidence reached its peak before age 40 according to one series ( ), or was constant at all ages in another ( ). In 1952, use of iodized salt produced a tenfold decrease in goiter incidence in Switzerland but only halved

thyroid cancer incidence ( ). Finally, the death rates per million in 1959 from thyroid cancer in Switzerland and England were identical ( ). It is unlikely then that T3 suppression to control thyroid hyperplasia due to chronic TSH stimulation can prevent cancer formation or growth.

Although radiation exposure in the adult carries little risk ( ), the occurrence of cancer in children so exposed was recognized in the 1950's ( ). In 1957, the follow-up data following thymic irradiation in infancy were presented ( ). Since then, a large collection of children developing thyroid cancer revealed a history of some sort of radiation exposure to the gland in 77 per cent ( ).

Responses to a recent though poorly worded questionnaire about treatment of nodular goiter are interesting. Leaving aside qualifying remarks and personal biases, half of surgeons remove thyroid nodules routinely, whereas 90 per cent of medical men offer surgery only when the nodules strike them as trouble makers. Since cancer has been reported in 10 to 50 per cent of nodules, much of it microscopic, a fact which obscures both the true incidence of potentially lethal thyroid cancer as well as the results of surgical treatment, the question whether microscopic cancer is a benign disease or not becomes important. The microscopic form must be considered benign by the medical men who pick and choose, or, logically, they should follow the surgeons who uniformly operate. Happily, two outstanding

surgical reports on long-term follow-up, indicate that such cancer is essentially benign ( ).

Direct measurement of uptake by the metastases of follicular thyroid cancer was first accomplished in 1942 ( ), the result of remarkably good luck, since a functioning thyroid was in situ ( ). Shortly thereafter, another clinic administered the first therapeutic dose of 131-I and accumulated a series ( ). It is still moot whether life is truly saved by radioiddine therapy ( ). Indeed, in some patients, a complication of radiation effect from such treatment may end the course rather than the thyroid cancer.

Endemic Goiter. Apart from sulfur-bearing hydrocarbons in the water bathing rocks rich in content in Cali, Colombia ( ), and a possible bacterial contaminant in Virginia ( ), most endemic goiter remains due to iodine want ( ). Rather than detail the results of many excellent physiological studies, let me mention some of the disappointment over iodized salt prophylaxis ( ); and raise the question, if an excess of iodide has caused one endemia ( ), and blocked the latently defective thyroid ( ), whether the increasing exposure to iodine, at least in this country, ought not to be scrutinized. With only a bit of urging, this year's Ad Hoc Committee on Iodine has begun to examine this other facet of intake.

Finally, Toxic Diffuse Goiter or Graves' Disease.

Pathogenesis. Interest in its pathogenesis concerned the

Association from its inception. Dr. Sloan, the founder, suggested that a virus might be responsible for the disorder, a view that our own studies suggest may not be entirely far-fetched ( ). The thymico-lymphatic constitution era ( ) gave way to the hyperpituitary theory. This lasted about 25 years before it was questioned in 1952 ( ). The storm of opposition to the challenge took 6 years to subside. By then, it was shown that hypophysectomy in Graves' disease patients neither affected the hyperthyroidism nor altered the distribution of the iodinated compounds in serum ( ), as it did in operated rats ( ) and euthyroid man ( ); a panhypopituitary patient developed Graves' disease ( ); LATS, originally "abnormal thyroid activator", was discovered ( ).

The LATS era blossomed with the suggestion that this substance might be an autoimmune antibody ( ). However, inconsistencies between its presence or absence and the clinical status of the thyrotoxic patient led to disenchantment ( ). About this same time, IgG, M, and E, and complement were found in the connective tissue stroma and basement membranes of the Graves' disease gland ( ) likening the disorder to the immune diseases such as systemic lupus. Evidence that CMI was operative in the disorder, but differently for the thyroid and the eyes, was also forthcoming ( ). Unfortunately, it is virtually impossible to distinguish whether release of antigen from exogenous sources such as from a

concurrently with 130-I ( ), and 131-I ( ). Since then, the problem of late or delayed hypothyroidism after the latter ( ) remains unresolved. A five year experience with 125-I suggests the incidence of hypothyroidism has been lessened, recurrences of hyperthyroidism, increased ( ).

As for surgery, the one advance has been preparation with propranolol in patients with allergic manifestations to anti-thyroid drugs and to iodides ( ); and its use in thyroid crisis ( ).

Completely unknown to the thyroidolotist is a therapeutic method from the past. According to my experience with one patient, our one time domestic, the method seems highly effective. She evidently had had Graves' disease and was advised by her family that the cure lay in placing the hands of a just deceased person about her throat. Obligingly, her then employer, a kindly lady, died and our patient in the small hours of the night entered her bedroom where she lay. She placed the hands about her throat and sat for an hour thus embraced. Her disease ended shortly thereafter. I pass this along to the younger among you who may wish to apply for NIH support for a Cooperative Study.

This recital has been incomplete, and long. I can only hope that, nonetheless, the journey through 50 years has had something rewarding for each and every one of you.

Thank you.