THYROTROPIN

Proceedings of a Conference on Thyrotropin
Sponsored by
The Endocrine Study Section, National Institutes of Health

Compiled and Edited by

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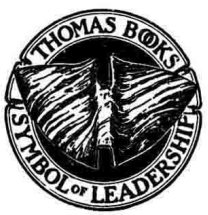

CHARLES C THOMAS • PUBLISHER
Springfield • Illinois • U.S.A.

Published and Distributed Throughout the World by
CHARLES C THOMAS • PUBLISHER
BANNERSTONE HOUSE
301–327 East Lawrence Avenue, Springfield, Illinois, U.S.A.

Library of Congress Catalog Card Number: 62-16450

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Printed in the United States of America

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PREFACE

THIS CONFERENCE is the second on tropic hormones of the pituitary gland initiated by the Endocrine Study Section during the chairmanship of Dr. Alfred E. Wilhelmi. The first conference had Dr. A. Albert as Chairman, and reviewed the subject of gonadotropins. The present one is concerned with thyrotropin.

A planning committee was formed consisting of Drs. A. E. Wilhelmi, A. Albert, R. T. Hill and the undersigned. The committee contemplated a work conference in which the status would be appraised of knowledge about current problems pertaining to thyrotropin from comparative biology through chemistry, assay methodology, and clinical relations to goiter, Graves' disease and thyroid cancer.

Since the value of such a conference lies primarily in discussion, prepared presentations were limited to ten minutes each and were designed primarily to introduce a subject for discussion. However, the formal papers in themselves contain such a wealth of material, they can be read for their own value as well as for their bearing upon the comments which follow.

It is evident that the role of the pituitary-thyroid axis in the lower forms still needs clarification although progress is being made. Advances in the chemistry of thyrotropin and of exophthalmos-producing substances (EPS) have been great and are doing much to provide this and a wealth of other information. However, despite the strides chemically, isolation of thyrotropin is still to be achieved, and little is known of the relations between thyrotropin, exophthalmos-producing substances (EPS), and the "long-acting thyroid stimulator" (LATS) found in the serum but not the pituitary of patients with Graves' disease.

The problem is compounded by the similarities and differences in response to these agents in the various assay systems currently available for thyrotropin and LATS. The suggestions that LATS may have an extra-pituitary origin but at the same time can be neutralized by an anti-bovine thyrotropin serum are but measures of the difficulties in interpretation of available data.

The current role of suppressive therapy with thyroid hormone in the treatment of non-toxic diffuse and nodular goiter and of thyroid cancer raises questions as to the role of thyrotropin in the etiology and course of these disorders as well as Graves' disease. In fact, the efficacy of suppressive treatment needs still to be defined—is it effective in true nodular goiter or only in thyroiditis; how many thyroid cancers are hormonally responsive and how many autonomous non-responsive or escape from suppression by thyroid hormone?

Although definitive answers to the questions at issue are not always to be found in the present proceedings, a survey is provided that would be difficult to obtain anywhere else and offers an excellent springboard for those wishing to familiarize themselves with, or to work in, the field.

Considerable thanks must be expressed to Columbia University for the provision of Arden House as a meeting place and for the excellent arrangements that created the necessary atmosphere for a conference of this nature. Thanks must also be expressed to Miss Edna Meininger, stenotypist, whose transcription achieved a high mark in accuracy; and Mrs. Helen C. Smith, who provided the same accuracy in handling the many secretarial details.

SIDNEY C. WERNER

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THYROTROPIN

I

THE COMPARATIVE BIOLOGY OF THYROTROPIN SECRETION

J. M. Dodd, K. M. Ferguson, M. H. I. Dodd, and R. B. Hunter

The endocrine organs of vertebrates are remarkably uniform in morphology and histology and all the main glands of the mammals except some associated with pregnancy can be recognized throughout the vertebrate series. However, the functions of similar endocrine structures in widely separated vertebrate groups are not always the same. This being so, the question arises whether the mutual interrelations which exist in mammals between endocrine organs, also exist in other groups; and, in particular, whether the pituitary exerts its familiar control over the other glands. It is the purpose of this paper to examine in the non-mammalian vertebrates the evidence that the pituitary may control thyroid function.

No doubt the few quantitative data available on comparative aspect of pituitary-thyroid interrelation are a reflection of the same difficulties in assaying thyrotropin (TSH) which have beset investigations on mammals. Indeed, until recently, most of what was known concerning thyroid-pituitary interrelations in lower vertebrates came from histological and histochemical studies of the pituitary; but these techniques are not yet sufficiently specific to yield firm conclusions.

The demonstration by Gudernatsch (1912) that thyroid extracts have a dramatic effect on tadpole metamorphosis initiated modern endocrinology. The work of Smith (1916) and Allen (1916) showed that removal of the pituitary anlage in developing speci-

mens of *Rana pipiens* blocked metamorphosis just as does thyroid removal. This was the first demonstration that thyroid activity is largely dependent on the presence of a functional adenohypophysis. From subsequent work on TSH and the thyroid gland, it appears that this finding is probably universally applicable in the vertebrate series.

There is now an extensive and diversified literature on thyroid-pituitary interrelationships in non-mammalian vertebrates and parts of this have been frequently reviewed (Olivereau, 1954, 1955; Pickford and Atz, 1957; Dent and Dodd, 1961). Hence the work cited here is restricted to a selection of papers. These deal with thyroid-pituitary interrelation in non-mammalian vertebrates as illuminated by the following techniques: pituitary removal; the injection of pituitary extracts and purified TSH; the use of goitrogenic chemicals; the identification and measurement of thyrotropic substances in pituitary gland extracts, and the identification of putative "thyrotropes" by the several histological and histochemical techniques now so widely applied though still impossible of unequivocal interpretation.

Hormone specificity and evolution are perhaps the most important aspects of comparative endocrine studies. Special attention is therefore paid to the few quantitative data which bio-assay techniques for TSH have yielded, and their relevance to the concept of "phylogenetic specificity" is examined in some detail.

REVIEW OF QUALITATIVE COMPARATIVE STUDIES

CYCLOSTOMES, like amphibia, start life as larvae and these undergo a metamorphosis to give the adult stage. The ammocoete larva of cyclostomes is noteworthy in having a structure, the endostyle, which is the undoubted progenitor of the thyroid gland of the adult. The endostyle may well have some of the functions of the thyroid even in the larva since it is known to produce the characteristic iodinated tyrosines and thyronines of the thyroid gland. It is therefore of interest not only whether pituitary-thyroid interrelationships exist in the adult, but also whether there is a pituitary-endostyle axis in the larva. The latter problem seems to have attracted more workers than the former.

Knowles (1941) concluded that the pituitary and endostyle in *Lampetra planeri* had no functional relationship since pituitary removal had no effect on the endostyle and since injection of mammalian TSH gave only slight and equivocal effects. However, more recent work indicates that mammalian TSH does in fact stimulate certain of the cells of the endostyle, increases the amount of PAS-positive secretion, slightly increases the organic binding of I-131, and induces certain changes in the endostyle reminiscent of metamorphosis (Olivereau, 1956). These metamorphic changes, as well as cellular hypertrophy, are also produced by thiourea treatment (Olivereau, 1956) and by Itrumil, thiouracil, thiocyanate and thyroxine (Klenner, 1953). These findings are of the greatest interest. They appear to demonstrate a liaison between the pituitary and a structure of great antiquity which, in the ammocoete, is still an integral part of the alimentary canal and not yet a histologically recognisable thyroid gland.

There are no reports relating to the effects of hypophysectomy or of injection of pituitary extracts or purified TSH on the cyclostome thyroid; and the action of goitrogens in adult cyclostomes does not seem to have been investigated. Our own demonstration by bio-assay methods, of a thyrotropic substance in the pituitary glands of both *Myxine glutinosa* and *L. fluviatilis* is discussed below.

van de Kamer and Schreurs (1959) believe that the mesoadenohypophysis of the brook lamprey (*L. planeri*) contains thyrotropin-secreting cells. These cells are basophilic and PAS positive and appear to be active for only a short time before, during and after metamorphosis of the ammocoete larva. It would be more difficult to resist their view that these cells are thyrotropes if it could be shown that thyroid hormones play any part in ammocoete metamorphosis. The existing evidence is against this idea.

Dent and Dodd (1961) have recently reviewed the literature on pituitary-thyroid interrelations in ELASMOBRANCHS and shown it to be discordant though largely negative so far as adults are concerned. Complete hypophysectomy of *Scyliorhinus caniculus*, even after periods of more than one year did not result in any change in thyroid cell height. However, this operation

reduced, though did not abolish, I-131 incorporation by the thyroids of the skate, *Raia naevus* (Dodd and Goddard, unpublished).

These results in adult elasmobranchs have been supplemented by those of Vivien and Rechenmann (1954) in embryo dogfish. These authors hypophysectomised embryos by partial decapitation and showed that uptake of I-131 was markedly reduced. Recently, Dent and Dodd (1961) working with newly hatched embryos of *S.caniculus* have shown that the uptake of I-131 by the thyroid is greatly enhanced by a total injection of 1.0 i.u. mammalian TSH (Thytropar, Armour), given over a three-week period and is significantly increased by a total dose of 0.1 i.u. The higher dose accelerated folliculogenesis and induced hyperplastic changes in the thyroid (Plate 1, Figs. 1–4). Dent and Dodd also obtained indications that the ventral lobe of the adult elasmobranch pituitary contains a thyrotropic principle.

Olivereau (1951) treated specimens of *Scyllium stellare* and *S.caniculus* with phenylthiourea, aminothiazole and thiourea but detected no significant histological changes in the thyroids of the treated fish. However, in a subsequent autoradiographic study (Olivereau, 1952), she found that organic binding of I-131 by the thyroids of *S.caniculus* was prevented by treatment with thiourea and thiouracil.

Thyrotropin-secreting cells have not so far been identified in the elasmobranch pituitary. Nonetheless, extensive work carried out over the last several years in our own laboratory and involving a variety of techniques leads us to believe that the ventral lobe of the dogfish pituitary may well secrete TSH. This lobe contains abundant basophilic colloid which is PAS and AF-positive and the possibility exists that this represents stores of TSH in much the same way as the colloid of the thyroid gland represents stores of thyroid hormone.

The extensive literature concerning the TELEOSTS has been fully and critically reviewed in the excellent monograph of Pickford and Atz (1957) and it is only necessary to summarize the main findings here. There is agreement that hypophysectomy in bony fish throws the thyroid into a relatively inactive state (Pickford and Atz, 1957; Table 36). Here, as in probably all vertebrates, the gland retains a basic level of activity even in the