CALCIUM, PARATHYROID HORMONE AND THE CALCITONINS

ROY V. TALMAGE PAUL L. MUNSON

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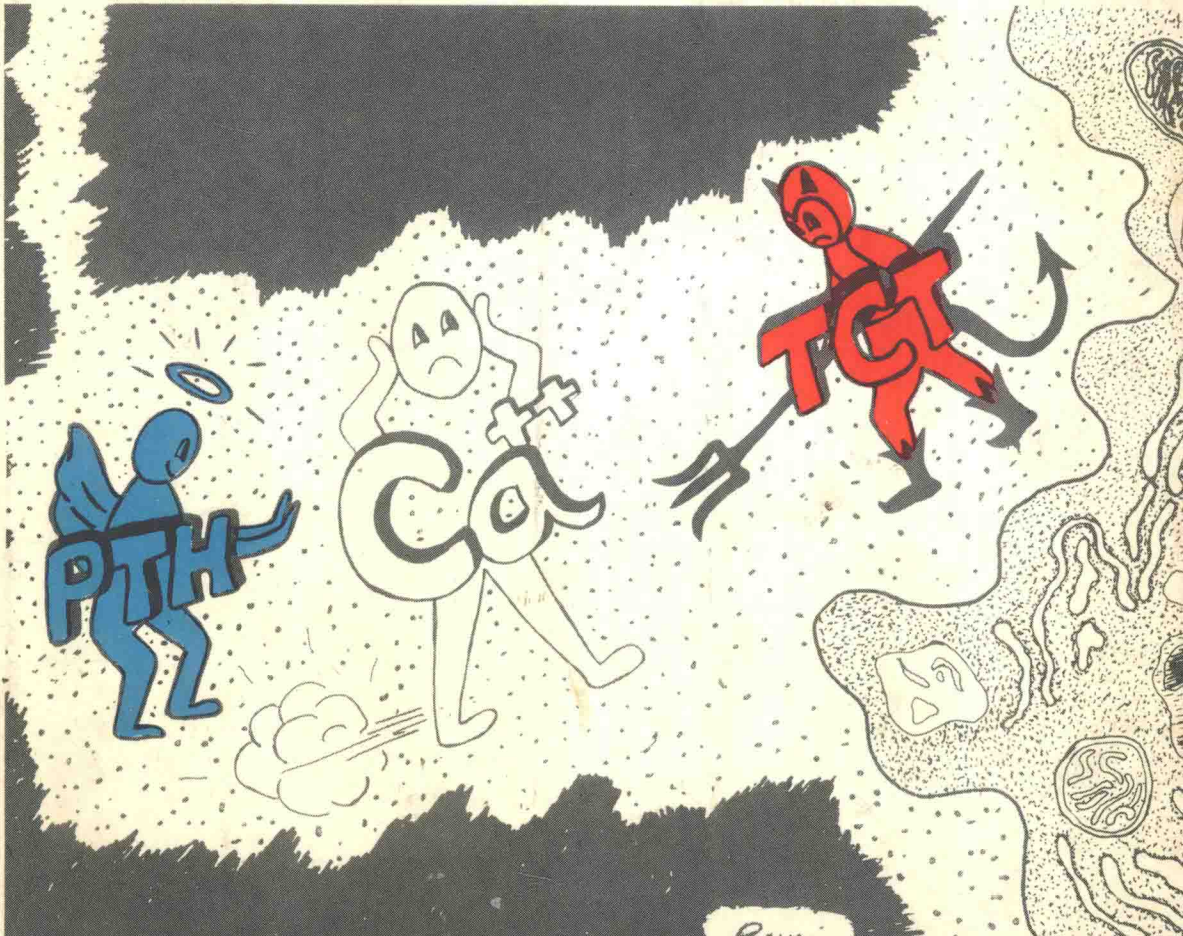

CALCIUM, PARATHYROID HORMONE AND THE CALCITONINS

PROCEEDINGS OF THE
FOURTH PARATHYROID CONFERENCE

Chapel Hill, N.C., U.S.A., March 15–19, 1971

Editors

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CALCIUM, PARATHYROID HORMONE AND THE CALCITONINS

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I. Introduction and summary

INTRODUCTORY REMARKS

ROY V. TALMAGE

The papers which make up this book are those which were presented at the Fourth Parathyroid Conference held in Chapel Hill, N.C., U.S.A., March 15–19, 1971. Previous conferences were held in Montreal, Canada (1967), Leiden, Holland (1964), and Houston, Texas (1960). Following the pattern of previous conferences, the 250 participants who attended this meeting included scientists from many parts of Europe, North and South America, Australia and Japan.

Since the authors of these reports are well recognized for their work in their particular fields related to calcium metabolism, the editors have attempted to retain as far as possible the individual styles of the authors.

The primary function of this book is to present to the reader the latest data and theories relating to the structure, function, biochemistry and metabolism of the two primary hormones controlling calcium metabolism and bone physiology, namely parathyroid hormone and the mammalian calcitonin, thyrocalcitonin. It is not suprising, therefore, that conflicting theories and ideas can be found in the various reports included in this book. It is hoped that this book will stimulate further work and aid in the solution of these differences.

In regard to format, the book has been divided into sections, only as a matter of convenience to the reader, with each section preceded by a short introduction. The placement of many papers is arbitrary since much of the material is overlapping. To make the bibliography more useful, all the references have also been combined into a single list at the end.

It is a pleasure to acknowledge support for the Conference and therefore for this book. Major thanks are expressed to two U.S. governmental agencies, the National Institutes of Health and the Atomic Energy Commission who provided grants in support of the Conference. We also wish to acknowledge the support of the School of Medicine of the University of North Carolina and that of its Department of Pharmacology and Division of Orthopaedic Surgery which hosted the Conference. Credit is also due to the many universities and granting agencies which provided travel funds for the participants.

We would also like to express our appreciation to the following organizations which made direct gifts toward the support of the Conference:

Armour Pharmaceutical Company
The Kroc Foundation
Eli Lilly and Company
N.V. Organon
Schering Corporation
Wilson Laboratories

In the final analysis, the success of the Conference and of this book depends to the greatest extent on the scientists who participated in it, and those who provided the manuscripts for this publication. The editors sincerely appreciate their contributions and their efforts, for it is upon these that the value of this publication rests.

University of North Carolina, Chapel Hill, N.C., U.S.A.

MILESTONES AND NEW HORIZONS FOR THE ENDOCRINOLOGY OF CALCIUM AND PHOSPHATE METABOLISM

PAUL L. MUNSON

Advances in knowledge about parathyroid hormone and the calcitonins since the Third Parathyroid Conference three and a half years ago, many of them reported for the first time at this meeting, have been extraordinary both in number and quality. In this brief summary of the Fourth Parathyroid Conference it would be impossible to do justice to all the excellent science that has been reported here and only a brief outline without mentioning any of the contributors by name has been attempted.

To start with the chemistry of the hormones. The amino acid sequences of 7 of the calcitonins are now known and 3 forms of the hormone have already been synthesized in the organic chemistry laboratory. The similarities in structure are readily apparent and suggest features of the molecule that are essential for biological activity. All forms of the hormone polypeptide contain 32 amino acids. The C-terminal proline amide and the disulfide ring also are common to all the calcitonins. The differences in sequence are striking; more than half of the sequences can be changed without any obvious qualitative alteration in biological effects. The much higher specific activity of salmon ultimobranchial calcitonin and its longer duration of action, apparently due in part to its biological stability, are remarkable. All these varied structures are active in every mammalian species in which they have been tested. Thus far, attempts to discover an active core of the polypeptide or to identify a fragment of the molecule that retains biological activity have been unsuccessful. This is a goal for the future. Even more recently, the entire amino acid sequence of bovine parathyroid hormone has been determined. It also is a single-chain polypeptide, but in its native form, at least as isolated from gland extracts, it is much longer, being comprised of a total of 84 amino acid residues. The amino acid sequence of porcine parathyroid hormone has also just been worked out and found to be quite similar to the bovine hormone. The structure of human parathyroid hormone is not yet known, but it appears to be chemically similar but not identical to bovine and porcine parathyroid hormones. Fortunately, as has been known for a long time, the bovine hormone is active in man. Of special interest is the fact that only a relatively small portion of the molecule at the amino terminus is essential for biological activity; the active 1–34 polypeptide has already been synthesized chemically. Unlike the thyrocalcitonins, where there is essentially no immunological cross-reactivity between human and animal hormones, there is sufficient immunochemical similarity between bovine and human parathyroid hormone to make radioimmunoassay of the hormone feasible in man. A related new development of importance is the identification of simpler compounds that, like pentagastrin, stimulate the natural secretion of endogenous thyrocalcitonin or, like imidazole, appear to mimic the effect of thyrocalcitonin on bone.

Advances in knowledge of vitamin D (a hormone as well as a vitamin) and its metabolites have been just as meteoric as for parathyroid hormone and thyrocalcitonin. The identification

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of several metabolites of vitamin D that are as active or more active than vitamin D *in vivo* and, unlike vitamin D itself, are also active *in vitro* has been an exciting new development. These discoveries and particularly the indication that the various D metabolites may serve differential functions and possess different pharmacological spectra have important implications for therapy. The mechanism of action of the vitamin D metabolites in facilitating absorption of calcium from the gastrointestinal tract has been further elucidated, although there remain areas of disagreement. End-product inhibition of vitamin D metabolism is another new discovery of significance.

The radioimmunoassay method for parathyroid hormone has undergone further clarification and improvement and analogous methods for the thyrocalcitonins have also recently been developed. It has been made clear at this meeting that these potentially very valuable methods for the basic research laboratory as well as the clinic still need further refinement and understanding before they become suitable for general use. Current investigations of the radioimmunoassay for human thyrocalcitonin have not yet taken it out of the controversial area and the resolution of remaining problems will be important for deciding a fundamental question: is thyrocalcitonin a normal human hormone? Apparently this is not certain yet.

The chemical and biological characterization of salmon ultimobranchial calcitonin represents a particularly important advance. The high relative potency and extended duration of action in man have made it the form of the hormone of choice in the treatment of Paget's disease of bone for which it has been uniformly found to be effective in a number of different clinical centers. The therapeutic usefulness of thyrocalcitonin for other human disorders is still a matter of interest and investigation. In spite of optimistic reports from at least one group of clinics the general attitude still seems to be one of skepticism concerning the use of thyrocalcitonin in the treatment of osteoporosis. Much additional preliminary investigation will be required before full-scale clinical trials would be justified. From what is known about the pharmacological properties of thyrocalcitonin the use of thyrocalcitonin in this disorder seems so logical that I take a rather optimistic view about the future of thyrocalcitonin in osteoporosis. Another promising area for clinical investigation is the relation of thyrocalcitonin to disorders of calcium metabolism that are secondary to chronic renal failure. One might think that this hormone would be useful in the treatment of this type of secondary hyperparathyroidism as well as others. It is not clear to me why thyrocalcitonin has not found more widespread use in the treatment of primary hyperparathyroidism and other forms of hypercalcemia. Use of the hormone in the prevention of nephrocalcinosis and kidney stones in susceptible patients would also seem to be logical and deserves further investigation.

Medullary thyroid carcinoma is the most thoroughly explored disease involving excess production of thyrocalcitonin. Here it is interesting that the toxic effects of this excess production of the hormone are not more serious. However, there are reports in increasing number of secondary hyperparathyroidism associated with this syndrome. Ectopic production of thyrocalcitonin paralleling production of other polypeptide hormones by nonendocrine tumors, long anticipated, is now beginning to be reported. At the Third Parathyroid Conference, evidence was presented identifying the cell of origin of thyrocalcitonin as the parafollicular or C cell in the thyroid gland and as its analogue in the ultimobranchial body. There is new evidence that this cell is of neural crest origin.

It has long been known that the kidney and the gastrointestinal tract as well as bone are target tissues for parathyroid hormone and vitamin D. The fact that thyrocalcitonin can produce hypocalcemia in the absence of the kidney and the gastrointestinal tract tended earlier to obscure these target tissues as important in its overall action. We now recognize that thyrocalcitonin can stimulate the renal excretion of sodium, calcium, and phosphate, at least under certain circumstances and in certain species, including man. Whether these particular renal effects of thyrocalcitonin are produced by endogenous physiological levels of thyrocalcitonin is still not entirely clear. The mechanism of the parathyroid hormone

effect on phosphate excretion, particularly the interaction of this effect with that on renal handling of sodium, has now been clarified and we may look forward to a similar clarification of the parathyroid hormone effect on calcium excretion. The mechanism of action of vitamin D metabolites on absorption of calcium by the gastrointestinal tract is being investigated very actively. The relative importance of the effect of vitamin D on the calcium-binding protein and on a specialized ATPase will certainly be sorted out by the time of the next Parathyroid Conference.

Factors affecting the biosynthesis of parathyroid hormone, an important subject which previously had received little attention, are now being illuminated by study of the subject in feasible *in vitro* systems. The question of a pro-parathyroid hormone different from the one that has been isolated and chemically characterized from glandular extracts has been raised and the possibility that the secreted form is chemically different from the extracted form is being considered. There is also good evidence that in addition to the secreted form of the hormone various fragments of parathyroid hormone circulate in the blood, some of them reacting in the radioimmunoassay even though they do not possess biological activity. Very likely there are others of both larger and smaller molecular weight than the extracted hormone that are biologically active whether or not they react in a specific immunoassay system. The study of the biosynthesis of thyrocalcitonin appears to be a project for the future.

The mechanisms of action of parathyroid hormone and thyrocalcitonin on bone are also receiving much attention. It is clear that cyclic AMP is an important mediator in the action of parathyroid hormone on bone as well as in kidney. The participation of cyclic AMP in the mechanism of action of thyrocalcitonin has now been more clearly demonstrated and sorting out the complexities of the participation of this mediator for both hormones on the same tissue will be a real challenge. The role of certain prostaglandins in the effect of the two hormones on bone is also now being investigated with some initial positive results. The phenomena of induction and escape relating to the effect of thyrocalcitonin on bone have been well worked out in *in vitro* systems and the correlation of these facts with the action of the hormone *in vivo* will be of great interest. New studies of the ultrastructural effects of parathyroid hormone and thyrocalcitonin are also being reported. In relation to the various cell types that are susceptible to the action of these two hormones, correlation of the ultramicroscopic observations with biochemical phenomena certainly will further our understanding of mechanisms in the future.

The control of secretion of thyrocalcitonin and the related subject of the physiological importance of this hormone are still not settled. The capacity of thyrocalcitonin to protect against hypercalcemia needs further experimentation before we can be sure that this is a true physiological function of the hormone. Under certain circumstances thyrocalcitonin protects against hypercalcemia during the intestinal absorption of calcium of dietary origin. The role of gastrin or other gastrointestinal hormones in mediating the thyrocalcitonin response is a new and interesting complication in the study of control of secretion of the hormone. What was the evolutionary rationale for the original emergence of the calcitonins? The function of calcitonin in fish and in birds, where it originated on the evolutionary scale, is still a mystery.

The Fourth Parathyroid Conference was distinguished, but it was by no means unique among its predecessors, for the number and quality of new unifying hypotheses and theories that were advanced, attacked, and defended. Along with the multitude of new facts brought to light, these generalizations and speculations were responsible for the enthusiasm shown by all participants in the Conference that now, through this publication, can be shared with a wider audience.

II. Comparative biology of the calcitonins