

calcium- regulating hormones

editors

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Calcium-regulating hormones

Proceedings of the Fifth Parathyroid Conference
Oxford, United Kingdom, July 21-26, 1974

Editors

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Preface

This book serves as the proceedings for the 5th Parathyroid Conference, held in Oxford, England, July 21-26, 1974. In this conference, the subject matter was expanded to include all three primary calcium-regulating hormones of man and other mammals: parathyroid hormone, calcitonin and the vitamin D metabolites. The coverage was designed to bring together in one book, the latest input from the many disciplines focusing on problems of calcium metabolism.

Over 300 scientists from many parts of the world attended this conference. Each speaker presented, with his research results, his individual concepts and theories. Obviously, therefore, both disagreements and controversies abound in these pages. This is done purposely, so that the reader will appreciate differences of opinion that exist, and hopefully will be stimulated toward projects which will aid in clearing up these uncertainties.

The success of this type of conference, and the published reports which result from it, depends upon the gifts and labor of many individuals and organizations. Our primary thanks go to the speakers; for it is the results of their studies put on paper that ultimately determine the value of this book.

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
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Indirect support was also provided through intangible costs borne by the University of North Carolina, Oxford University and the Medical Research Council of England who supported the conference through the labors of staff members of these organizations.

Our special thanks go to the scientists who attended this conference, for their lively discussion, agreements and disagreements. We hope the conference produced a stimulus for further progress and that this book will provide a background to the field, a starting point for future projects and a basis for research and discussion for many others who hopefully will study its pages.

Finally, we would like to express our gratitude to Dame Janet Vaughan, who was our honorary chairman. Dame Janet has long been a well known figure in the bone world. She is the author of many important books and papers which have made a valuable contribution to our understanding of bone. Her generous help and encour-

agement has been greatly appreciated by many young scientists. Her magnificent hospitality in her home and in Somerville College, Oxford (of which she was Principal for twenty-two years) has been enjoyed by many of us and so also has her colourful and stimulating personality.

During the Conference Dame Janet was presented with a miniature replica of one of the original Van Leeuwenhoek microscopes as a memento of the occasion and as a token of our respect and admiration.

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I. An overview

Calcium and phosphate homeostasis: two decades in perspective

D. HAROLD COPP

It has been traditional at these Parathyroid Conferences to invite a senior citizen in the field to open the meeting with a philosophical discussion on the state of the art. While I am very honored by the opportunity to do so at this meeting, it is a sobering thought to realize that 20 years ago I was considered one of the young 'young Turks' who helped Felix Bronner organize the first Gordon Conference on the chemistry, physiology and structure of bones and teeth, which was held in Meriden, N.H. in the summer of 1954. These conferences have had great influence on the bone field and led indirectly to the organization of the European Symposia on Calcified Tissues, and to the current series of highly successful conferences dealing with the hormones which regulate calcium and phosphate metabolism. This conference in 1974 represents an important milestone, since it is just 50 years ago that Hanson (1924) reported in an obscure journal (*The Military Surgeon*) a method for preparing a biologically active extract of beef parathyroid glands. The extraordinarily simple method consisted of boiling minced glands for 2 hours in 1% hydrochloric acid, and was similar to the much more familiar method described by Collip (1925) one year later. In spite of these discoveries, progress in the parathyroid field during the next 30 years was relatively slow. The dawn of the atomic age stimulated some interest in bone and calcium metabolism, because of the current concern regarding toxic bone-seeking radioactive isotopes, and in particular, strontium-90. Further impetus was also provided by the rather exclusive (limited to 25 participants) Macy Conferences on Metabolic Interrelations, which came to an end in 1953. However, I have chosen to confine my remarks to the last two decades, when so many exciting new developments have occurred. I would date this from the first Gordon Conference in the summer of 1954, when I rashly agreed to give the Thursday evening lecture on the subject 'Some speculations on the homeostasis of calcium and phosphorus'. The substance of this talk was published 3 years later (Copp, 1957). I can recall how little was known at that time. I stressed the commonly accepted view of McLean and Hastings (1935) that 'one of the so-called physiological constants is the concentration of calcium in the blood plasma'. While generally true, this dogma will be challenged by two papers at this conference on diurnal fluctuations in plasma calcium in the rat. The importance of the level of calcium ion on many biological processes was clearly recognized 20 years ago, but its significance at the intracellular level was not even mentioned in my review. Rapid homeostatic control of plasma calcium in dogs was attributed solely to the interaction between the parathyroid hormone and the calcium reservoir in bone. The gut and kidney were felt to be important but only in the external calcium balance. There was, of course, no mention of calcitonin and only a fleeting reference to vitamin D, which was used in the treatment for rickets. One point which I did stress was the importance of the interrelationship between calcium and phosphorus, and the dramatic effects of severe phosphate deficiency, first described by Day and McCollum (1939) and later applied by

Copp et al. (1947) in an attempt to remove radioactive strontium from bone.

There is no question that the series of Parathyroid Conferences have contributed significantly to the tremendous advances which have occurred during the ensuing years. The first symposium was organized by Roy Talmage and held in Houston, February 3-6, 1960 (Greep and Talmage, 1961). It provided a nostalgic look to the past, for tribute was paid to 4 of the great pioneers in the field, who were still living at that time, namely: J.B. Collip, Isidor Greenwald, Fuller Albright, and Franklin McLean. In opening the Conference, Franklin McLean spoke of 'unsolved problems of parathyroid physiology' (McLean, 1961). These included questions as to whether there were one or two parathyroid hormones, methods of assay, species specificity, and chemical stability. It is significant that vitamin D was mentioned rarely, and was never the subject of a paper, while calcitonin was unknown. The Second Parathyroid Conference was organized by Gaillard and Talmage in 1964 (Gaillard et al., 1965), at the charming seaside resort of Noordwijk aan Zee near Leyden in The Netherlands. The progress in 4 years was indicated by Franklin McLean's introductory talk, entitled 'The explosion in parathyroid research' (McLean, 1965), in which he gave much of the credit to the stimulating effect of the first conference. At this meeting, a new calcium regulating hormone made its appearance under the name of calcitonin, or thyrocalcitonin, depending on geographical preferences. Vitamin D was also mentioned in one of the titles, and there was considerable interest in cellular and intracellular effects of the hormones.

The next conference was held at Mont Gabriel near Montreal in October 1967 (Talmage and Bélanger, 1968) and was linked with the celebration of Canada's Centennial. At this meeting, the keynote address was presented by Roy Greep (1968) with the title 'Bulls and bears in calcium homeostasis'. In the light of his remarks, the current state of the stock market would suggest that it is suffering from an overdose of calcitonin. Important chemical advances were reported at this conference, including the amino acid sequence of porcine calcitonin, and substantial progress in elucidating the structure of bovine parathyroid hormone.

Among the exciting new developments were reports that the ultimobranchial gland was a source of calcitonin in lower vertebrates, and provided the C-cells found in mammalian thyroid and parathyroid (Copp and Parkes, 1968; Matthews et al., 1968). This discovery indicated a function for what had hitherto been a gland of mystery, and opened up a new field in comparative endocrinology. In the case of both bone and kidney, evidence was presented to indicate that parathyroid hormone acted, like many other peptide hormones, through the activation of adenyl cyclase and the increase in intracellular cyclic AMP (Chase and Aurbach, 1968). Evidence was presented for a proportional control of secretion of both parathyroid hormone (Potts et al., 1968) and calcitonin (Care et al., 1968), the former increasing as the blood calcium level fell, while release of the latter increased as the blood calcium rose. At this meeting, for the first time there was also a section on vitamin D — a portent of the exciting events which lay ahead.

The Fourth Parathyroid Conference was held at the University of North Carolina in Chapel Hill, March 15-19, 1971 (Talmage and Munson, 1972). The host, and chairman of the local committee was Dr. Paul Munson, who has contributed so much to the parathyroid and calcitonin field. He presented the keynote address on 'Milestones and new horizons for the endocrinology of calcium and phosphate metabolism' (Munson, 1972). There were important new developments reported on the chemistry of the 3 calcium regulating hormones. The full amino acid sequence of both bovine and porcine parathyroid hormone was presented along with evidence for the existence of a number of isohormones from bovine parathyroids (Potts et al., 1972a). Much work centered on the metabolism of the hormone, and included the demonstration of syn-

thesis of a parathyroid hormone in vitro (Cohn et al., 1972), and the rapid metabolism of PTH in the circulation. (The latter was brought out by the heterogeneity in the radioimmunoassay system.)

Calcitonin obtained from salmon ultimobranchials had been characterized 2 years earlier. It has the same basic structure as human and porcine calcitonin but is far more stable and potent (Niall et al., 1969). Now, 2 additional isohormones from salmon glands were described which differed by as many as 5 amino acids from the original hormone (Potts et al., 1972*b*). Embryological studies were highlighted by the demonstration of the neural crest origin of the C-cells (Pearse et al., 1972). Very striking and rapid effects of calcitonin were demonstrated by electronmicrography in both osteocytes (Matthews et al., 1972) and osteoclasts (Kallio et al., 1972). At this meeting, vitamin D at last came into its own. There were very exciting reports on the metabolism of vitamin D₃ (cholecalciferol) which is converted in the liver to 25-hydroxycholecalciferol, and subsequently oxidized in the kidney to the active form, 1,25-dihydroxycholecalciferol (DeLuca, 1972). Since the production of the latter appeared to be controlled by the calcium level in the blood, it now seems appropriate to refer to it as a steroid calcium regulating hormone. Finally, important sections dealt with control of secretion of the hormones, comparative endocrinology of calcitonin and intracellular calcium metabolism.

We now come to the Fifth Parathyroid Conference here in Oxford, where a veritable smorgasbord of food for thought is spread before us. For gourmets, there are papers on chemical structure of chicken and eel calcitonins, along with the current and somewhat controversial status of the human parathyroid hormone. Two papers present evidence that calcitonin may be a disquieting rather than a stabilizing influence on the plasma calcium levels, and there will be data to indicate its importance in phosphate metabolism. It has been suggested by Talmage that when the ultimobranchial gland first developed in marine fishes, calcitonin may have been more concerned with combating the effects of the low phosphate levels rather than the high calcium concentration present in seawater. Perhaps, as he has suggested, 'phosphatonin' might have been a more appropriate name for the hormone. Time will tell. However, it is interesting that the highest levels of calcitonin in salmon are not found in the marine environment, but occur in the female at the time of spawning. Could it be that calcitonin is an unsuspected sex hormone? The ultimate answers to these and many other questions concerning hormone action may come from an understanding of the action of the hormones at the cellular level, and particularly on intracellular calcium and phosphate metabolism. At the recent Second International Conference on Cyclic AMP held in Vancouver earlier this month, Rasmussen suggested that the role of both cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) could be mediated by their effects on intracellular cytosol Ca⁺⁺ concentrations. In a concluding slide, he showed Calcium Rex with a crown and ermine robes having his shoe shined by two lackeys — cAMP and cGMP. I would like to expand this idea and suggest that we might take as our patrons the royal couple, Calcium Rex and Phosphata Regina, served not only by the cyclic nucleotides but also by the 3 hormones, PTH, CT, and 1,25-DHCC, which play such an important role in regulating calcium and phosphate metabolism.

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