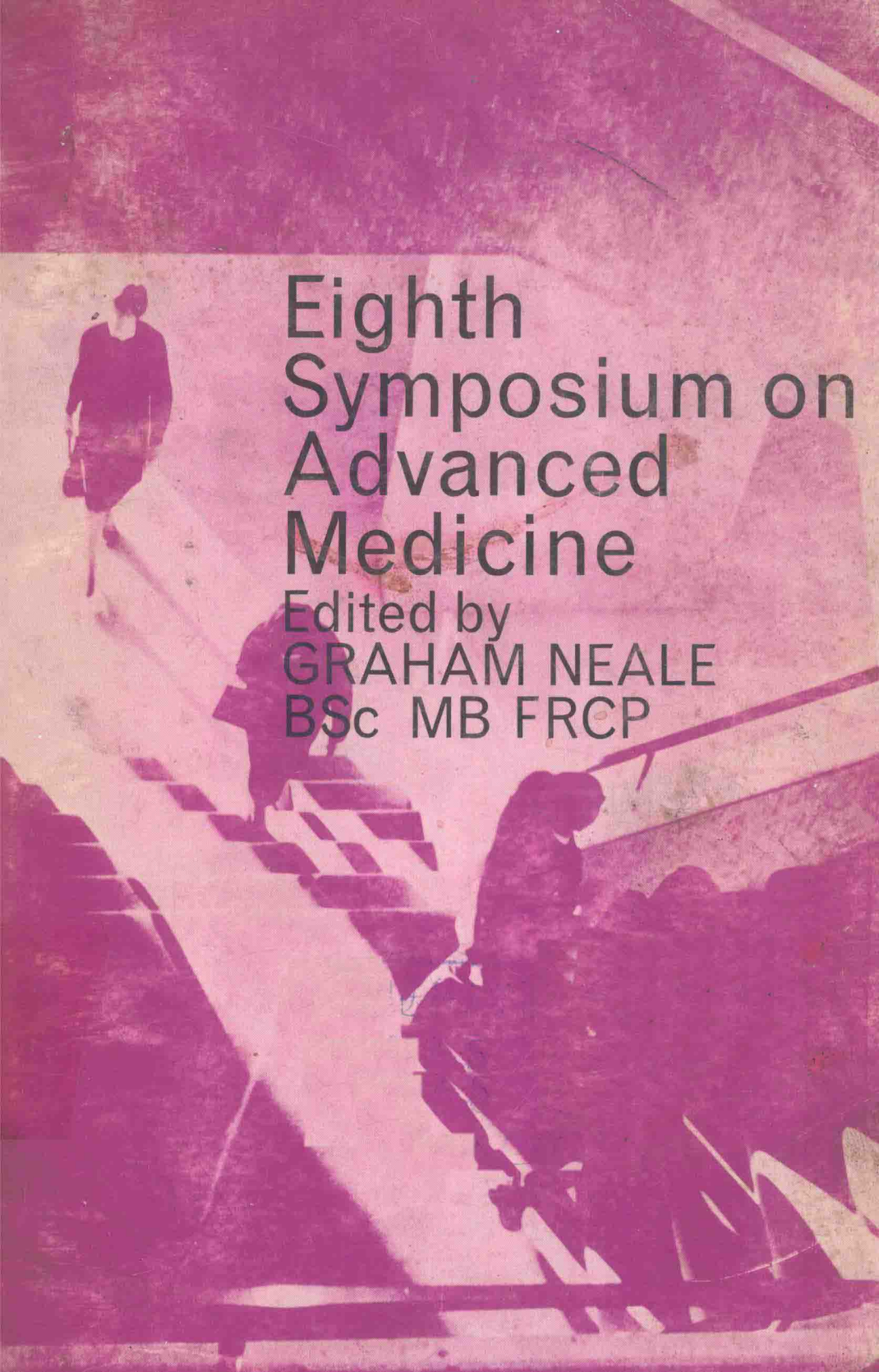

Eighth Symposium on Advanced Medicine

Edited by
GRAHAM NEALE
BSc MB FRCP

EIGHTH SYMPOSIUM ON ADVANCED MEDICINE

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EIGHTH SYMPOSIUM ON
ADVANCED MEDICINE

Editor's Foreword

The Eighth Symposium on Advanced Medicine contains papers which were to have been delivered and discussed in February, 1972, at the Conference for Physicians at the Royal College. With great regret, the conference was cancelled at short notice, because power cuts would have made it impossible to light and ventilate the lecture theatre. Most contributors to the Symposium had submitted scripts for publication and thus it was decided to produce this book which one hopes will serve as some recompense both to contributors and to those who had planned to attend the Conference.

The general format of the Symposium is similar to that of previous years. Subjects which had not been aired at previous conferences at the Royal College, or which were particularly topical, were selected for discussion. Clinical Pharmacology, Dermatology and Virology are well-represented because of the increasing impact of these subjects on the practice of general medicine. Throughout the rest of the Symposium, the reader will find that normal and abnormal internal metabolism provides a recurrent theme.

In planning the programme, I was greatly helped by Dr Peter Emerson and Dr Peter Ball, his successor as Assistant Registrar of the College, their secretary, Miss Kimber, and the physicians who would have taken the chair at individual sessions: Lord Rosenheim, Professor Waterson, Professor Sherlock, Professor Lawrence, Professor Dollery, Professor Dent, Dr Renwick Vickers and Professor Bywaters. To them I am most grateful. On behalf of the College, I would like to express special thanks to the panel of contributors. They accepted the invitation to speak with enthusiasm, and, despite the disheartening cancellation of the conference, produced detailed scripts for publication.

As in previous years, this volume has been published as quickly as possible. Without a conference, it has been difficult to check small points with individual authors and so I apologise for any errors which may have crept into this volume.

At the end of the book the reader will find an index to previous volumes. Papers have been listed under specialty headings and it is hoped that this will provide a useful service for physicians wishing to refer back to the very large number of subjects reviewed at College Conferences in the past eight years.

Pitman Medical Publishing Company are rightly proud of their record of efficient publication and my attempts to keep up with past performances would have been quite impossible without the skill and enthusiasm of Mrs Betty Dickens, and the help of my long-suffering secretary, Miss Shirley Bastin.

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Contents

PART I

CALCIUM METABOLISM

The Role of Parathormone and Calcitonin in Calcium Homeostasis

IAIN MacINTYRE

The integrated actions of parathyroid hormone, calcitonin and vitamin D are responsible for maintaining the remarkable consistency of plasma calcium concentrations. In recent years much new knowledge has been gained on the chemistry and physiology of parathyroid hormone and calcitonin (Foster et al, 1972; Parsons & Potts, 1972).

Parathyroid hormone

Despite earlier claims, it is now clear that parathyroid hormone had not been obtained completely free from contaminating peptides until just over one year ago. As soon as this was achieved by Brewer at the National Institute of Health in Washington and by Potts at the Massachusetts General Hospital in Boston, these groups independently deduced the complete sequence of parathyroid hormone. The bovine hormone consists of a single polypeptide chain of 84 amino acids. The latter group has also succeeded in synthesising the sequence 1-34. This portion of the molecule proved to be highly active. It also appears from recent work that parathyroid hormone is broken down in the circulation to several peptides, some of which are biologically inactive. However, the immunoassay for parathyroid hormone may detect inactive fragments in some cases, while in others it may be measuring the N-Terminal fragment. This explains the discrepancies found between different laboratories using the immunoassay for parathyroid hormone, and means that interpretation must be guarded until we have further information. Nevertheless, the immunoassay for parathyroid hormone remains clinically useful in two situations: (1) the diagnosis of hypercalcaemia; and (2) the localisation of parathyroid adenomas by the measurement of hormone levels in samples obtained from the neck veins by cannulation. This latter procedure may be of considerable help to the surgeon.

There have also been important advances in the physiology of parathyroid hormone. It is now quite clear that parathyroid hormone has several sites of action, the most important being the bone, the kidney, and the gut. The

action of parathyroid hormone on the bone to increase the rate of absorption is the best known effect, but parathyroid hormone also increases calcium absorption from the gut and diminishes calcium excretion by the kidney.

It has also been found that a shift of calcium into the cell is a feature of the early action of parathyroid hormone on the skeleton. This suggests that the calcium ion may itself act as a second messenger of parathyroid hormone.

These chemical and physiological advances have recently been discussed and reviewed in detail by Parsons and Potts (1972).

Calcitonin

Calcitonin is a 32 amino acid polypeptide with a 1-7 disulphide bridge and proline amide at the C-terminus. These features are constant in the various calcitonins which have been isolated, but there are considerable differences in sequence. Thus, the porcine and human hormone differ in 18 of the 32 positions. This means that the non-human materials carry the risk of causing antibody formation when calcitonin is used therapeutically. It also means that immunoassay for other calcitonins will not be suitable for estimating the hormone in human plasma.

The mode of action has been thoroughly studied. The hormone acts directly on bone to inhibit osteoclastic resorption. This action is accompanied by hypocalcaemia only when bone turnover is rapid as in young animals and children. In adult man calcitonin continues to act on the bone, but has little hypocalcaemic effect. The major function of calcitonin is to minimise the irregularities in plasma calcium level which would otherwise occur, by controlling bone resorption. This effect is only important in young animals and children. But calcitonin has another function: this is to maintain the integrity of the skeleton by opposing the action of parathyroid hormone on bone. This means that under conditions of calcium lack the effects of parathyroid hormone on the bone would be minimised, but the other calcium conserving actions would continue.

The principal practical application of calcitonin has been in the treatment of Paget's disease. It is now clear that human calcitonin can produce complete biochemical and histological remission in the features of this common bone disease without producing any undue side effects or causing antibody formation. It seems likely that it will come to have an important role in treatment.

Medullary carcinoma of the thyroid is known to be a cancer of the 'C' cells, and estimations of plasma calcitonin levels are useful diagnostically, especially in the detection of relapses before they are clinically evident. A fuller and more detailed review on recent advances in our knowledge of chemistry, physiology and therapeutic applications of calcitonin is given by Foster et al (1972).

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Foster, G. V., Byfield, P. G. H. and Gudmundsson, T. V. (1972) Clinics in Endocrinology and Metabolism, **1**, 93
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The Metabolism of Vitamin D

Vitamins are organic constituents of food. They are usually present in only minute concentrations, and yet they are essential for the life and well-being of the animal. The name 'Vitamin D' was given to the anti-rachitic factor isolated from cod liver oil by McCollum et al (1922) following the discovery by Mellanby (1921) that cod liver oil cured rickets in puppies.

Active vitamin D is found in few natural foodstuffs, whereas inactive vitamin D is present throughout the animal and vegetable kingdoms in various forms. These are termed provitamins and they are all sterols. Plant sterols (eg ergosterol) acquire vitamin D activity when exposed to ultraviolet rays (Steenbock, 1924) and it was this discovery which led to the preparation of vitamin D_2 (calciferol). Similarly, vitamin D_3 (cholecalciferol) is made in the skin of animals by the ultraviolet irradiation of 7-dehydrocholesterol. The chemical structure of this compound (Figure 1) was elucidated by Windaus et al (1936). At present most of the work on the intermediate metabolism of vitamin D concerns cholecalciferol and it is not surprising to find that its status as a vitamin has been challenged because it is clear that it is not an entirely essential part of the diet.

It has been known for many years that vitamin D has actions on the intestine, the skeleton, and the kidney, but its mode of action has remained obscure until recently. For example, physiologists soon showed that vitamin D enhances the absorption of calcium from the intestine and mediates the mobilisation of calcium from bone, but were unable to explain the time-lag of ten or more hours after an intravenous injection of active vitamin D before any response can be detected (Carlsson & Hollunger, 1954). It was shown that the administration of actinomycin D blocks the physiological response to vitamin D_3 and it was established that RNA and protein synthesis are involved both in intestinal calcium transport and in bone mineral mobilisation (Zull et al, 1966). Nevertheless, these findings do not appear to explain the time-lag satisfactorily. Clinicians, too, have many questions to ask about the action of vitamin D. They have long been intrigued by the therapeutic action of a substance of which as little as 1 μg per day is required by the healthy adult

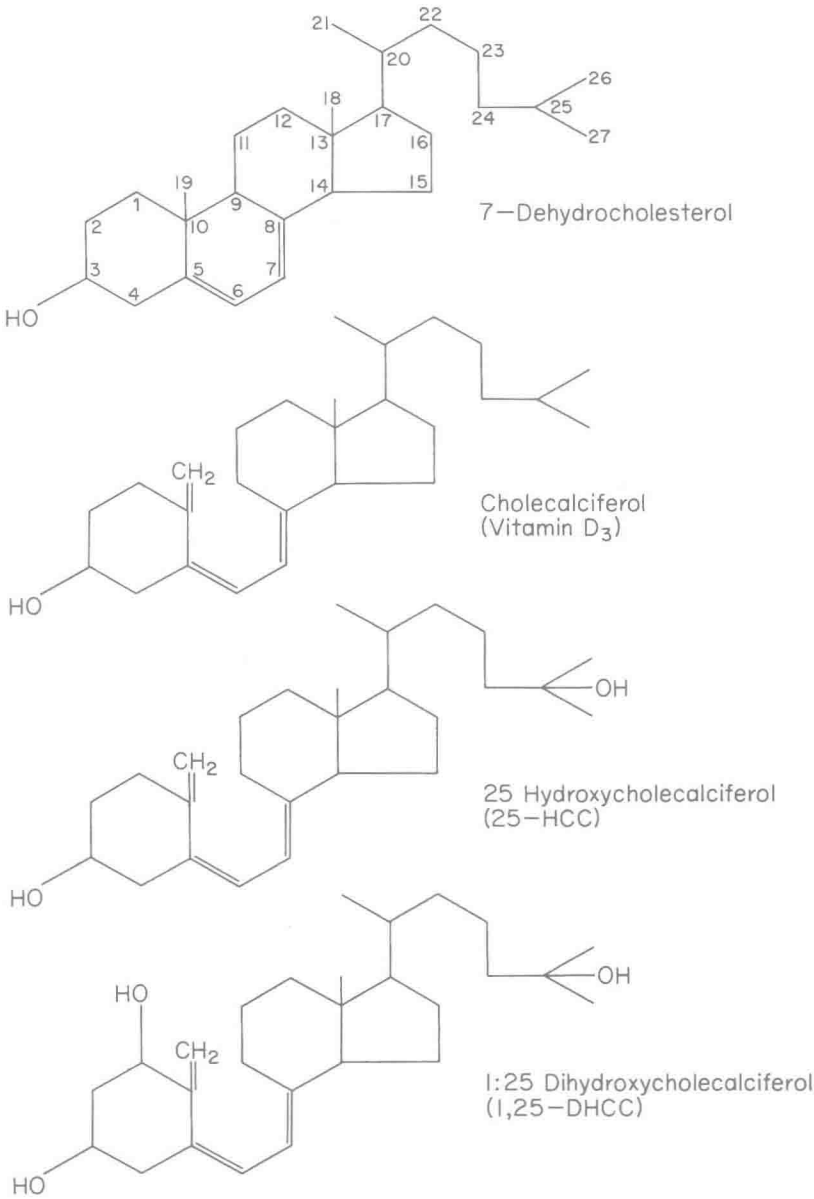

Figure 1. Chemical structure of some of the sterols concerned in the production and metabolism of vitamin D