INTERNATIONAL ENCYCLOPEDIA OF PHARMACOLOGY AND THERAPEUTICS

Section 48

PHARMACOLOGY OF THE ENDOCRINE SYSTEM AND RELATED DRUGS:

PROGESTERONE, PROGESTATIONAL DRUGS AND ANTIFERTILITY AGENTS

Section Editor

M. TAUSK

Utrecht

VOLUME I

INTERNATIONAL ENCYCLOPEDIA OF
PHARMACOLOGY AND THERAPEUTICS

Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents

VOLUME I

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PERGAMON PRESS
OXFORD · NEW YORK · TORONTO · SYDNEY
BRAUNSCHWEIG

Pergamon Press Ltd., Headington Hill Hall, Oxford
Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523
Pergamon of Canada Ltd., 207 Queen's Quay West, Toronto 1
Pergamon Press (Aust.) Pty. Ltd., 19a Boundary Street, Rushcutters Bay, N.S.W. 2011, Australia
Vieweg & Sohn GmbH, Burgplatz 1, Braunschweig

First edition 1971

Library of Congress Catalog Card No. 73-153797

PRINTED IN GREAT BRITAIN BY PAGE BROS. (NORWICH) LIMITED

08 015745 9

CONTENTS OF VOLUME II

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PREFACE

MORE than five years have gone by since I was invited to serve as a section-editor for the International Encyclopedia of Pharmacology. Seldom have I so grossly underrated the difficulties inherent in a given project and the time needed for its completion.

The progress made in research in physiology of reproduction and in the use of synthetic progestational compounds has been impressive and it was not always easy for the contributors to the present section to keep their chapters up to date. While nothing will prevent this book like any other of its kind from starting on the road to obsolescence the day it is printed, we do hope that at least some of the concepts underlying our presentation will prove to be of more than ephemeral value and should make it possible for the reader to "put in place" new facts as they emerge.

We have given preference to readability over completeness and we can only hope that in so doing we have not thwarted the purpose of this Encyclopedia.

In his "Historical Introduction" the section-editor deals with some questions of terminology and preference was expressed for the term "progestational compounds" over "gestagens" or "progestagens". This terminology met with reluctance on the part of several authors who preferred shorter names. We have to plead guilty of inconsistency but the reader may like it better this way.

Another shortcoming of which we are conscious is the lack of a chapter on the role of progesterone in the development of tumors. One colleague had at a very early time undertaken to write this contribution but found it increasingly difficult as time went on, until he finally gave it up at a time when it was too late to look for another expert. We can only refer the reader to existing reviews which will be mentioned in a short note, taking the place of the missing chapter.

The principle, adopted in planning the book, of separating animal from human studies has occasionally been violated, particularly in cases where certain basic pharmacological properties are demonstrated more clearly by "human pharmacology" than by animal experiments. In such cases some human studies are anticipated in the chapter on animals.

Chapters 4 and 5 are partly overlapping, which brings out differences of opinion, apparently resulting from different conceptual approaches and the

use of different techniques. It was felt that these presentations would help the reader to get a clearer picture of the problems as they appear today.

The reader is reminded of the fact that other sections of the encyclopedia deal with natural and synthetic estrogens and with androgens.

Except for one author, none of us can claim English as his mother tongue, but the Editorial Department of Pergamon Press has rendered us great service in matters of language. We feel confident that any difficulties encountered in reading and digesting the present volume will not primarily be due to linguistic deficiencies.

I gladly express my gratitude to the medical library of N.V. Organon, Oss, The Netherlands, for invaluable help and to the Management of that company for unlimited secretarial services.

My thanks are also due to the following companies and persons who provided me with bibliographical data and reprints:

BDH (Research) Limited, Godalming (Surrey) (Dr. D. K. Vallance).
Leo Pharmaceutical Products, Ballerup (Denmark).
The Lilly Research Laboratories, Indianapolis (Dr. D. M. Brennan).
Merck Institute, Rahway (N.J.). (Dr. S. L. Steelman).
E. Merck A.G., Darmstadt (Dr. H. G. Kraft).
Organon, Oss (Scientific Information Department).
Ormonoterapia Richter, Milano (Dr. Fugazza).
Philips-Duphar, Weesp, The Netherlands (Dr. V. Claassen).
Roussel, Paris (Dr. Leguay).
Schering A.G., Berlin (Prof. M. Kramer, Dr. F. Neumann).
Searle & Co., Chicago (Dr. V. A. Drill).
Syntex Research, Palo Alto, Calif. (Dr. W. H. Rooks).
The Upjohn Company, Kalamazoo (Mich.) (Dr. G. W. Duncan).

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M. TAUSK

CONTENTS

HISTORICAL INTRODUCTION

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IN recent years the term "progestational compounds" and many similar ones have been used and misused with remarkable frequency. A systematic treatise on these substances should be prefaced by a clarification of terminology which will take us right into the history of the subject.

Names like "progestational", "progestative", "progestogens", "gestagens" and "gestogens" are all derived from Progestin, a name which for the first time appeared in a paper by Willard M. Allen, bearing the title: "Physiology of the corpus luteum. V. The preparation and some chemical properties of progestin, a hormone of the corpus luteum which produces progestational proliferation." The paper was received for publication on September 23, 1929 and published in the *American Journal of Physiology* **92**, 174–188 (1930). The second paragraph of the paper reads as follows:

"We have as yet proposed no name for this hormone of the corpus luteum, referring to it only as a hormone which induces the above-described characteristics in the rabbit. In so far as we are acquainted with its physiological behavior, its chief action lies in its ability, by alteration of the endometrium, to aid gestation in the castrated rabbit; and for this reason we wish to propose for it the name progestin, i.e. a substance which favours gestation." In reply to my inquiry as to when the name was first used, Dr. Allen kindly called my attention to the communication just quoted and then went on to say: "This paper does not have George W. Corner as co-author. However, the name was really proposed by him." It would therefore hardly seem unfair to ascribe the introduction of the name to the two authors who first described extracts containing the hormone of the corpus luteum: Corner and Allen.

The paragraph just quoted from Allen's paper clearly shows that the extracts had two properties, (rightly) ascribed by the discoverers to a single substance: they produced characteristic changes in the rabbit's uterus and they maintained pregnancies which otherwise would definitely have been doomed because of the castration of their bearers.

Historically the assumption that the transformation of the rabbit's endometrium is caused by the corpus luteum goes back to the French biologists Bouin and Ancel (1910). On the other hand it was the German gynecologist Ludwig Fraenkel (1903) in Breslau who found that the corpus luteum is responsible for maintenance of pregnancy in the same species. In his beautiful little book: *The hormones in human reproduction,* George W. Corner says: "It fell to my own lot (in 1928) to conduct the experiments which tied together the discoveries of Fraenkel and Bouin and Ancel, by showing exactly what happens, and when, to embryos deprived of the support normally afforded them by the corpus luteum."

As early as 1930, Erich Fels and K. Slotta from Breslau, a town still pervaded by the spirit of Prof. Fraenkel, presented a paper at the Second International Congress on Sex Research in London, confirming the work of Allen and Corner and showing that corpus luteum extracts produced histological changes in the rabbit's uterus and had some pregnancy maintaining effect in the rabbit. They advanced the hypothesis that the corpus luteum hormone might be present in the placenta, although they had not been able to demonstrate this. In the following year already Fels (1931) in a paper at a German gynecological congress reported that he and Slotta had obtained the hormone "practically pure".

In the United States Willard Allen pursued the purification of the corpus luteum hormone and in 1932 described a crystalline though still impure substance as Fevold and Hisaw had done that same year. In 1933 Allen reported on the important "quantitative separation of progestin from oestrin in extracts of the corpus luteum". Allen at the time at the Department of Anatomy of the University of Rochester Medical School (Rochester, N.Y.) collaborated with Oskar Wintersteiner (biochemist at Columbia Univ.) and, to quote a personal communication, "he and I had independently, in so far as purification of the crude crystals are [*sic*] concerned isolated α-progesterone* before January 1, 1934. Also he had arrived at the correct empirical formula $C_{21}H_{30}O_2$ by October 28, 1933." Wintersteiner and Allen's paper on "Crystalline Progestin" was received for publication by the *Journal of Biological Chemistry* on July 25, 1934, which was, however, more than one month after a "preliminary communication" by Slotta *et al.* (1934) had been received by the Editor of *Berichte der Deutschen Chemischen Gesellschaft*. In it the authors describe Luteo-

* The term α-progesterone is no longer used. The empirical formula is of course that of progesterone.

steron C as having the same melting point, the same empirical formula as Wintersteiner and Allen's substance, and both groups of authors state that the oxygen atoms are in the form of carbonyl groups. (See also Allen and Wintersteiner (1934).) In the work leading to this achievement, Slotta *et al.* had been guided by a histological rabbit's uterus test based on the work of Bouin and Ancel and the corresponding tests developed by Corner, and by Clauberg (1930), whose technique was rapidly superseding the older tests because of its greater simplicity and sensitivity. In a footnote Slotta *et al.* acknowledged that Butenandt, then in Danzig, had described a crystalline substance from the corpus luteum at the congress of the German Society for Internal Medicine, held in April of that year, and Butenandt and Westphal (1934) indeed lost no time in claiming (though not proving) priority. A number of papers from both laboratories (Butenandt *et al.*, 1934; Slotta, K. H., *et al.*, 1934 b) followed, while in Switzerland Hartmann and Wettstein practically simultaneously reported on what appeared to be the same substance.

Butenandt had been helped by the pharmaceutical company of Schering A.G. in Berlin, where Hohlweg did the bio-assays and Hartmann and Wettstein were working in the laboratories of Ciba in Basle. These three groups of workers were joined by Fernholz *et al.* in Göttingen, who in 1933 had elucidated the structure of the plant steroid stigmasterol and showed how its side chain could be split off at its double bond. Butenandt *et al.* (1934) followed his lead in an attempt to synthesize the corpus luteum hormone, an operation which Fernholz (1934 a and b) had independently undertaken and successfully completed, thereby finally establishing the structure. It is a tragedy that this gifted chemist, who a short time later went to the United States, lost his life soon afterwards. The very rapid elucidation of the structure of the corpus luteum hormone was made possible by the earlier work of Butenandt (1930/1931), which in essence established the structural characteristics of pregnanediol.

In 1935 a most remarkable and very short paper by W. M. Allen, A. Butenandt, G. W. Corner and K. H. Slotta on the nomenclature of the corpus luteum hormone appeared in *Berichte der Deutschen Chemischen Gesellschaft*. These authors proposed jointly that the active substance present in "progestin" which the Breslau group had named "luteosteron" should henceforth be called "progesterone" and the hope was expressed that this name would generally be accepted in scientific literature, a hope which was indeed fulfilled.

By 1934 or 1935 then we knew what was believed to be the active substance of the corpus luteum; we knew its chemical structure, we knew

how to make it synthetically from abundantly available steroids and the world had agreed on one scientific name. A few things remained to be clarified.

In 1929 the Austrian gynaecologist Knaus had published a summary of his investigations, showing that under the influence of the corpus luteum, the uterus no longer responded to oxytocin. This seemed to provide another possibility for a bio-assay which could be used in the purification of corpus luteum extracts and in standardizing the preparations so obtained. This is in fact what Knaus (1930) did. We too at Organon became interested in this possibility and therefore tried to ascertain whether in the process of purifying glandular extracts the activity in the Clauberg-assay ran parallel with that in the Knaus-test. For a time we thought (de Fremery *et al.*, 1932) that it did not, but after crystalline progesterone had become available it was soon decided that both effects could be elicited by one and the same substance (Makepeace *et al.*, 1936).

So it looked as though progesterone, the hormone of the corpus luteum, would have a number of effects on different sites of the reproductive organs apparently all converging towards one single goal, to make possible nidation of the ovum, to keep it sheltered in a quiet uterine muscle and to preserve it during the entire period of gestation. Soon another, extra-uterine, effect was discovered which seemed to fit into the picture. Progesterone appeared to be responsible for the *inhibition of ovulation* at least in the rabbit where this ovulation occurs as the result of a reflex triggered by copulation (Makepeace *et al.*, 1937). With reference to this last fact it is interesting to quote Pincus (1965) who says:

"But the logical extension of this observation into a more intensive study of the nature of the progesterone action as well as the action of certain derivatives and putative metabolites were not reported by us until 1953."

A new era of investigations must be considered to have started in 1938 when Inhoffen and Hohlweg (Inhoffen, 1938) reported that a synthetic steroid now generally known as ethisterone produced the histological effects in the Clauberg-test which up to that time had been considered characteristic for progesterone. Particularly remarkable was the fact that this compound was active in relatively low dosage after oral administration in rabbits as well as in the human. It was described as a progesterone derivative because the authors at the time were not yet aware of the important differences in steric configuration of the two steroids.

Because of its effects on the rabbit's endometrium, which was once chosen to characterize the effect of progesterone, ethisterone was called

progestational, though proof of its ability to maintain gestation was lacking.

Here we see for the first time clearly that, as Stolte (1940) showed in his thesis, there do exist steroids, other than progesterone, which have some but not all of its biological activities. These activities can become dissociated and other activities, not present in progesterone, may show up in these synthetic compounds, e.g. a certain degree of androgenicity, as was demonstrated by Stolte in ethisterone.

For a long time ethisterone remained the only "oral substitute" for progesterone, until Hertz *et al.* (1954) discovered that a compound of the same structure except for the lack of the angular methyl group between rings A and B ("norethisterone" or "norethindrone", synthetized by Djerassi *et al.* (1954)) when given orally in the Clauberg-test had 5 times the activity of ethisterone. The clinical usefulness of this new compound was described by Tyler (1955). This was confirmed by Greenblatt (1956). At about the same time Ferin (1956) discovered to his surprise that another so-called nortestosterone derivative, known under the generic name of methylestrenolone, produced progestational changes in women, whilst Pincus *et al.* (1956) compared the activity of a number of so-called 19-norsteroids.

By that time, however, oral contraception was well under way and soon an increasing number of steroids were synthetized and studied with a view to imitating the ovulation inhibiting effect of progesterone (Saunders and Drill, 1958; Zarrow *et al.*, 1958; Pincus *et al.*, 1958; Drill and Riegel, 1958). It was almost as if the main function of progesterone was to prevent pregnancy, rather than to further it.

However, the latter aspect was not entirely forgotten. In Holland a team headed by Overbeek working at the Organon research laboratories, compared a number of synthetic steroids and found that the ability of a substance to maintain pregnancy in the castrated rat was by no means reflected by its activity in the Clauberg-test (Madjerek, 1960).

Allylestrenol was singled out for its pregnancy-maintaining property and its lack of certain other activities. It was suggested that of the "progestational" compounds those maintaining pregnancy should be called gestagens, the others pregestagens. These terms cannot of course replace one common name covering both of these patterns of activity. They are, however, considered useful by some authors.

Many other studies made it clear that of the numerous new synthetic compounds each has its own pattern of activities, corresponding in part to those of progesterone though often with quantitative differences, to which may be added other biological properties such as one might encounter in

those steroids which, because of their dominant features, are referred to as estrogens, androgens, etc.

It will be clear from this brief account of the historical background that in this field terminology is truly important and should be handled with care.

In this volume we shall of course use the term *progesterone* only for the compound originally endowed with the name (Δ4-pregnene-3,20 dione). We shall call *progestational compounds* all those that have in common with progesterone *at least* the potency of producing in the rabbit's uterus the characteristic endometrial structure as discovered by Bouin and Ancel ("la dentelle utérine") and as may be conveniently demonstrated in the Clauberg test.

Etymologically and linguistically this terminology could be criticized because it does contain the elements "pro" and "gestation" even when applied to substances that do not deserve a name suggesting a favourable effect on pregnancy. This is, however, one of the inconsistencies inherent in the development of scientific language. It is less objectionable than the term progestogenic which (as has been remarked during a symposium of the International Association for Sterility and Fertility) contains alongside the root gest(-ation) both the prefix "*pro*" and the somewhat synonymous suffix "*genic*".

It will have become clear from this introduction why we have planned this volume as it now appears. We had to separate a discussion of progesterone, as supplied by nature in the corpus luteum (and other organs), from that of the numerous only partially analogous synthetic substances known today, many of which have become useful drugs. Some of these are used in a field which has only recently been added to the wide area of the medical sciences and medical practice: the control of fertility, involving the regular administration of potent drugs to healthy human beings.

Everyone is now acquainted with the impact of oral contraception on population control and its many consequences for the development of moral codes, legislation and government controlled scrutiny of new drugs. There are thus quite a number of reasons why progestational compounds should be allotted a fair amount of space in an International Encylopedia of Pharmacology and Therapeutics, though their therapeutic use is now largely exceeded by a non-therapeutic one, a development for which medicine is in no small measure indebted to the vision, the courage and the imagination of Gregory Pincus and his colleagues.