RECENT ADVANCES IN 12 OBSTETRICS AND GYNAECOLOGY

Edited by
John Stallworthy and Gordon Bourne

Churchill Livingstone

RECENT ADVANCES IN OBSTETRICS AND GYNAECOLOGY

EDITED BY

JOHN STALLWORTHY
GORDON BOURNE

NUMBER TWELVE

SIR JOHN STALLWORTHY

MA Hon DSc (Leeds & Otago) FRCS FRCOG
Hon FRCSI Hon FCOG(SA) Hon FACS Hon FACOG

Emeritus Nuffield Professor of Obstetrics and Gynaecology, University of Oxford; Consultant Obstetric Surgeon, Royal Prince Alfred Hospital, Sydney; Honorary Associate, National Maternity Hospital, Dublin

GORDON BOURNE

FRCS FRCOG

Consultant in Charge, Department of Obstetrics and Gynaecology, St Bartholomew's Hospital, London; Consultant Gynaecologist, Royal Masonic Hospital, London

CHURCHILL LIVINGSTONE

Edinburgh London and New York
1977

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by
Longman Inc., 19 West 44th Street, New York,
N.Y. 10036, and by associated companies,
branches and representatives throughout
the world

First published 1977

ISBN 0 443 01020 X
Library of Congress Cataloging in Publication Data
Recent advances in obstetrics and gynaecology
Includes index.
1. Gynecology. 2. Obstetrics. I. Stallworthy,
John Arthur, Sir. II. Bourne, Gordon Lionel.
[DNLM: 1. Gynecology—Period. 2. Obstetrics—Period.
W1 RE105YJ]
RG101.R38 1977 618 76-28429

Printed in Great Britain

PREFACE

Ten years have passed since the eleventh edition of *Recent Advances in Obstetrics and Gynaecology* was published. These years have witnessed great progress in all branches of medicine, and in obstetrics and gynaecology there have been some dramatic discoveries and significant changes. Change does not necessarily indicate progress, but sometimes it takes years for this fact to be established. The history of medicine contains many examples of apparently exciting developments which further experience proved disappointing, while on the other hand the clinical application of discoveries of revolutionary potential have on occasions remained unexplored until fresh vision stimulated a new approach. The therapeutic miracle by which penicillin, and the antibiotic agents which followed, have saved the lives of an uncounted multitude is an example of this.

In the last decade there has been unparalleled progress in technology, from which medicine has benefited. The space programme and man's successful visits to the moon have had their influence on procedures in the operating theatre, the labour wards, as well as on scientific techniques of laboratory investigation and clinical assessment. The obstetrician and gynaecologist has been helped in his practice until his problem is how to equate the new science with the established art of his specialty. The increasing use of ultrasound in precise diagnosis; the application in endoscopy of dramatic improvements in fibreoptic illumination; greatly improved techniques of precision radiotherapy; more delicate and accurate hormonal assays; and more precise equipment for maternal and fetal monitoring are examples.

The giant jet airliner makes a perfect automatic landing under computer control at Heathrow Airport, but it is comforting for the passengers, and probably for the crew, to know that the pilot on the flight deck is still the final arbiter. His skill and experience of the new techniques on which his life, as well as theirs, depends is the final safety factor. So it is in medicine that the doctor himself is of fundamental importance, and clinical experience and skill remain his greatest assets. They enable him to interpret and use the contributions of new or improved technology for the benefit of his patients in the knowledge that because machines, electronic equipment, and automated techniques are not free from error the patient's safety depends even more on his clinical vigilance.

Since writing the last edition both authors have worked in generously equipped and well-staffed departments with heavy clinical responsibilities as well as research and teaching programmes. They have shared the benefits of close association and cooperation with scientists in the laboratory and animal house as well as with clinicians in other disciplines. They have seen at close quarters the application in clinical obstetrics and gynaecology of discoveries made in basic research. Examples are the contributions of advances in neuroendocrinology on reproductive physiology; in haematology to the elucidation of thrombo-embolic problems, coagulation defects, and fetal dysmaturity; in electronmicroscopy and ultrasound techniques to the scientific investigation of fetal wellbeing in utero; in the therapeutic role of prostaglandins; and in the contribution which multidisciplinary teams can make to the study and treatment of infertility and fertility control, perinatal mortality and morbidity, hypertension and diabetes in pregnancy, or the treatment of pelvic cancer.

Experience of this team approach has been exciting but humbling. Junior members of these teams often have greater specialised knowledge than their clinical seniors, and it is they who will be responsible for the advances of tomorrow. This is why the authors decided on a major change of policy. Instead of writing the edition themselves, they invited contributions from a carefully selected few whose research and experience equipped them to present with authority their work and its implications. We acknowledge our indebtedness to these authors and we hope and believe that readers will find the value of this edition enhanced by the change.

JOHN STALLWORTHY
GORDON BOURNE

Oxford and
London, 1976

CONTRIBUTORS

J. BONNAR MD(Hons. Glas.) FRCOG
Professor and Head of Department of Obstetrics and Gynaecology, Trinity College Medical School, Rotunda Hospital, Dublin

L. E. S. CARRIE MB ChB FFA RCS DA
Consultant Anaesthetist, The Nuffield Department of Anaesthetics, and the John Radcliffe Maternity Hospital, Oxford

T. CHARD MD MRCOG
Professor of Reproductive Physiology, St Bartholomew's Hospital Medical College, London, and London Hospital Medical College

M. COPPLESON MD(Syd.) FAGO FRCOG
Honorary Gynaecologist and Obstetrician, King George V Hospital, Royal Prince Alfred Hospital, Sydney, Australia

C. J. DEWHURST FRCS(Edin.) PRCOG
Professor of Obstetrics and Gynaecology, Queen Charlotte's Hospital for Women, London

M. P. EMBREY MA FRCS FRCOG
Clinical Reader in Obstetrics and Gynaecology, University of Oxford

G. FINK MB BS(Melb.) MA DPhil(Oxon.)
Fellow of Brasenose College and University Lecturer, Department of Human Anatomy, Oxford University

K. HILLIER BSc PhD
Senior Lecturer in Clinical Pharmacology, University of Southampton

C. W. G. REDMAN MB BChir MRCP
Consultant Obstetric Physician, United Oxford Hospitals

H. P. ROBINSON MB ChB MRCOG
Honorary Senior Registrar, Queen Mother's Hospital and Western Infirmary, Glasgow

P. C. STEPTOE FRCS(Edin.) FRCOG
Consultant Gynaecologist to the Oldham Group of Hospitals, Director of Research Unit on Human Reproduction

S. WAY FRCS FRCOG
Lecturer in Gynaecological Oncology, University of Newcastle upon Tyne

E. A. WILLIAMS FRCS FRCOG
Consultant Gynaecologist, John Radcliffe Hospital, Oxford

ALECK BOURNE

MA MB ChB(Cantab) FRCS FRCOG
Hon. Fellow Royal Society of Medicine

1886–1975

With the publication of the first edition of *Recent Advances in Obstetrics and Gynaecology* just half a century ago in 1926 Mr Bourne established his reputation in the English-speaking world of medicine as a great teacher. A fact which was already well known to his students and colleagues at St Mary's Hospital, London, was now recognised by a much enlarged band of grateful admirers which increased with the passing years.

We pay our farewell tribute to a distinguished obstetrician and gynaecologist, an outstanding and inspiring teacher, and a generous friend.

J.S.
G.B.

CONTENTS

Part I
REPRODUCTIVE PHYSIOLOGY

Part I
REPRODUCTIVE PHYSIOLOGY

1
HYPOTHALAMIC PITUITARY OVARIAN AXIS

G. Fink

'. . . *what benefits will this work and knowledge confer on human welfare?*'
G. W. Harris (Dale Lecture, 1971)

Since the publication of the eleventh edition of 'Recent Advances' our understanding of the hypothalamic–pituitary–ovarian axis and capacity to investigate it have advanced by several orders of magnitude. The advances were due mainly to the perfection of radioimmunological and competitive protein binding methods for the assay of hormones in blood, and the isolation, characterisation and synthesis of the factor (gonadotrophin releasing hormone; GnRH)[1] which mediates the neural control of pituitary gonadotrophin secretion. The various endocrine control systems relevant to gynaecology can no longer be described adequately by a simple diagram comprised of one or two arrows and a plus and minus sign. Nevertheless broad patterns have emerged, and, although these are often complex, the clinician is now much better equipped to diagnose, classify, and therefore treat the patient who seeks his aid.

The details of radioimmuno, and competitive protein binding, assays and their application to the measurement of pituitary and sex steroid hormones in biological tissues and fluids are the subject of several reviews (Diczfalusy, 1970; Odell and Daughaday, 1971; Kirkham and Hunter, 1971). These assays are more sensitive by three to six orders of magnitude than bioassay systems, and, because they depend upon many millions of molecules in a test tube rather than a few animals, are also much more precise. Many hours of work are required to estimate hormone concentrations in a few samples by bioassay; hundreds of samples can be assayed in a few hours by radioimmunological and competitive binding methods. The major disadvantage of radioimmunoassays is that the immunological activity of a biological fluid or tissue is not necessarily the same as its biological activity (e.g. Diebel, Yamamoto and Bogdanove, 1973; Peckham et al, 1973). For this reason attempts have been made to develop assay systems which retain the advantages of competitive binding methods but use various properties associated

[1] This term is used since the decapeptide releases both LH and FSH. It is synonymous with luteinising hormone releasing factor (LRF or LH-RF) or hormone (LH-RH) found in other publications.

with the biological activity of a hormone to determine its concentration. Thus, for example, Catt, Dufau and Tsuruhara (1972) have used the binding capacity of testicular homogenates for the assay of luteinising hormone (LH), and Rees et al (1973) are exploring the possibility of using histochemical methods for the assay of this hormone.

Although the view that the decapeptide GnRH is the only factor which under physiological conditions mediates the neural control of gonadotrophin secretion must be accepted with reservation, its discovery by Schally and Guillemin and their co-workers (Matsuo et al, 1971; Burgus et al, 1972) was the climax of more than a decade of intense and competitive endeavour by workers on both sides of the Atlantic. Apart from providing crucial evidence for the neurohumoral hypothesis of anterior pituitary control (Harris, 1955, 1972), the decapeptide has proven a valuable tool by means of which it has been possible to elucidate many aspects of the interactions between the various components of the hypothalamic–pituitary–ovarian axis. Of equal or greater importance to the gynaecologist is the fact that GnRH, and its potential analogues, may prove an important addition to the agents available for investigating and treating problems related to fertility.

NEURAL COMPONENTS OF THE AXIS

Connections, Nuclei and Cell Bodies

The topography of the nuclei and the extrinsic connections of the hypothalamus are reasonably well established (Haymaker, Anderson and Nauta, 1969; Raisman, 1970), but the function of the extrinsic connections has not been elucidated. Thus, for example, some studies (Velasco and Rothchild, 1973) suggest that the hippocampus inhibits while the amygdala facilitates the neural mechanism responsible for regulating LH release. Brown-Grant and Raisman (1972), however, have shown that the major connections between the hypothalamus and the hippocampus and amygdala are not essential for the occurrence of regular, ovulatory, oestrous cycles. The long-standing question of a direct connection between the retina and the hypothalamus has been answered with the aid of new techniques which show that such a link exists (Hendricksen, Wagoner and Cowan, 1972; Moore and Lenn, 1972; Lincoln and Mason, 1975). However, it must be stressed that the retina appears to project directly to only one hypothalamic nucleus, the suprachiasmatic. The role of indirect neural pathways involving the neo and allocortex (e.g. Cragg, 1965; Powell, 1972) or the pineal (Reiter, 1974) by means of which photic stimuli (especially those affecting seasonal changes in reproductive activity) could exert an influence on the axis, should not be ignored.

Even less is known about the intrinsic connections of the hypothalamus, which have defied analysis by classical methods. Electrophysiological methods

offer some hope (e.g. Dyer, 1973; Harris and Sanghera, 1974), but for reasons outlined by Cross (1973) the problems are immense.

The neurons which synthesise and presumably release GnRH into the hypophysial portal vessels are located in the medial basal hypothalamus ('hypophysiotrophic area'; Szentágothai et al, 1962; Harris, 1972). There is debate, however, whether GnRH is also produced outside this area (Fink and Jamieson, 1976). This is relevant to the question of whether GnRH acts

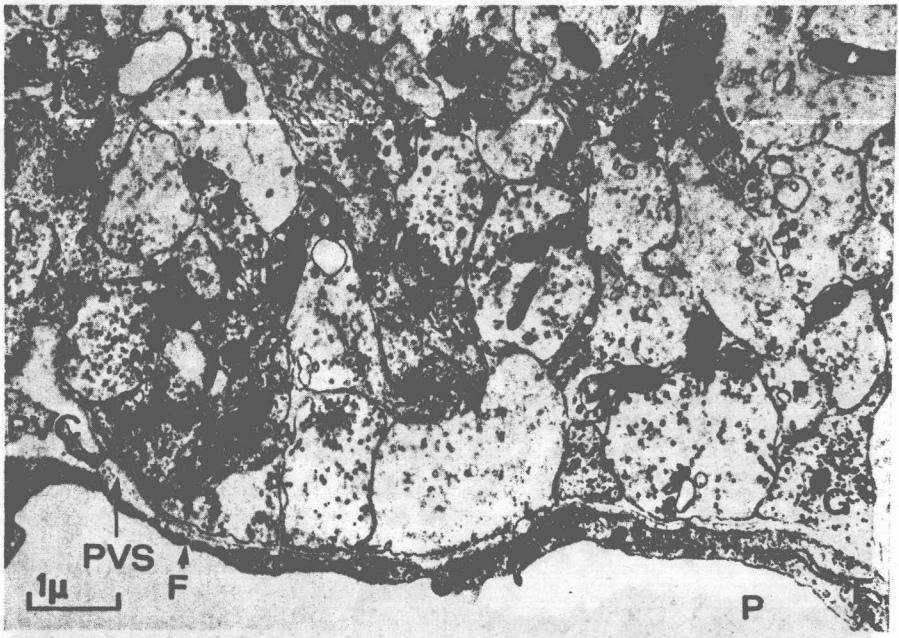

Figure 1.1 Ultrastructural appearance of the external layer of the median eminence of a rat on the first postnatal day. Note the presence of agranular and granular vesicles in the nerve terminals, the glial cell (G), and the fenestrations (F) in the endothelial cells (E) lining a primary capillary (P) of the hypophysial portal system. A perivascular space (PVS), across which releasing hormones must presumably diffuse, separates the capillary endothelium from the nerve terminals. The process of a perivascular cell (PVC) may be seen. From Fink and Smith (1971) with permission

as a neurotransmitter within the nervous system, and whether, in addition to releasing gonadotrophins, it is capable of exerting psychogenic effects (e.g. Moss et al, 1975; Mortimer et al 1974b). Unpublished studies of E. Bird, S. A. Chiappa and G. Fink showed that, at least in the human, relatively large amounts of immunoreactive GnRH are located considerably anterior (preoptic region) to the medial basal hypothalamus.

Ultrastructural studies revealed that the primary plexus of the hypophysial portal vessels are surrounded by glial and neuronal cell processes which are separated by about 100 nm from the capillary endothelium (Fig. 1.1). It has

not been possible to correlate the ultrastructural appearance of nerve fibres with a particular releasing hormone; however, GnRH activity has been demonstrated in broken off nerve terminals (synaptosomes) (e.g. Fink et al, 1972).

Fluorescence histochemical studies have revealed the presence also of a dense plexus of monoaminergic fibres which surround the primary capillaries (Fig. 1.2). Discovered by the Swedish workers (see review by Fuxe and Hökfelt, 1970), most of these fibres are thought to be dopaminergic and

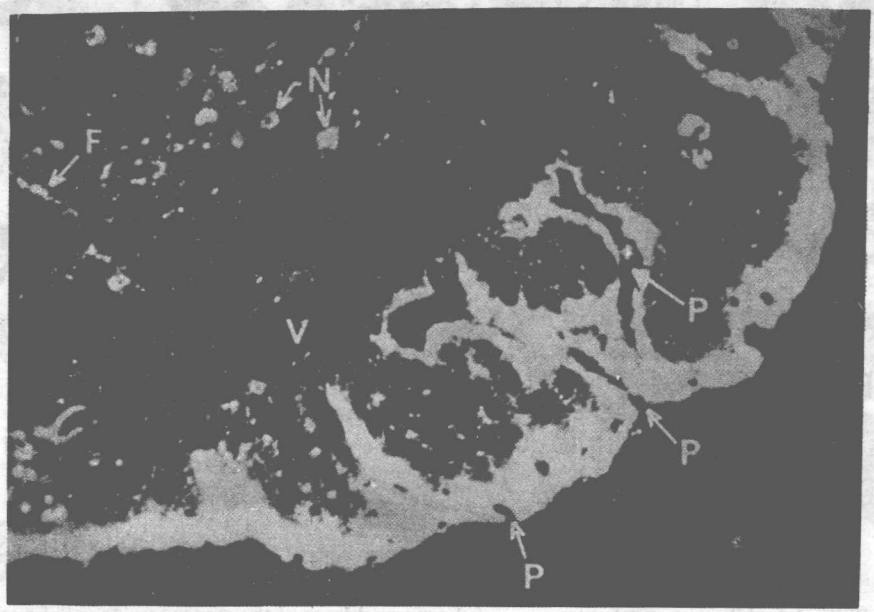

Figure 1.2 The fluorescence photomicrograph shows the dense plexus of monoaminergic nerve fibres which surround the capillary loops of the primary plexus of the hypophysial portal vessels (P). Close to the third ventricle (V) is the arcuate nucleus which contains many fluorescent neurons (N). Their terminals contribute to the monoaminergic plexus surrounding the portal capillaries. The fluorescent dots (F) in the arcuate nucleus region are extrinsic nerve fibres, probably noradrenergic. From Fink et al (1975c) with permission

derived from cell bodies in the tuberal region of the medial basal hypothalamus (so-called 'tuberoinfundibular system'). Others, probably derived from neurons extrinsic to the hypothalamus, are probably noradrenergic (Björklund et al, 1970). There is good evidence that physiological levels of monoamines cannot release pituitary gonadotrophins by a direct action on the anterior pituitary gland, but it has been suggested that the aminergic tuberoinfundibular system modulates the activity of the GnRH secreting neurons. While the evidence on this point is conflicting (Fuxe, Hökfelt and Nilsson, 1972; Smith and Fink, 1972; Fink et al, 1975c), it seems likely that

the hypothalamic aminergic systems play a role in modulating the release of prolactin (see below).

Autonomy of the Hypothalamus

In the rat, separation of the medial basal hypothalamus (i.e. the region of the ventromedial and arcuate nucleus) from the medial preoptic area results in anovulation but not atrophy of the ovaries (Halász and Pupp, 1965). These

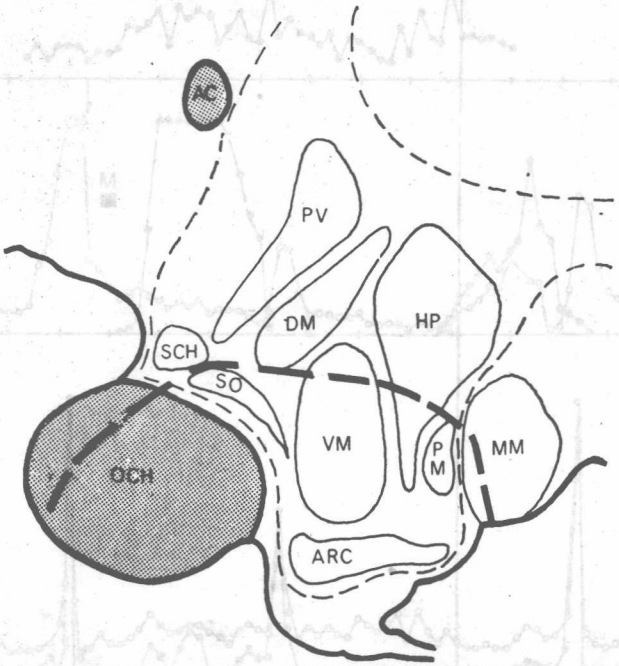

Figure 1.3 A schematic parasagittal section through the hypothalamus of the rhesus monkey showing the extent of a lesion (dashed line). Abbreviations: AC = anterior commissure; OCH = optic chiasma: hypothalamic nuclei; ARC = arcuate; DM = dorsomedial; HP = posterior hypothalamic; PV = paraventricular; SCH = suprachiasmatic; SO = supraoptic; VM = ventromedial; MM = medial mammillary body; PM = pre-mammillary area. Reproduced from Krey, Butler and Knobil (1975) with kind permission of the authors

and other data (Barraclough, 1966) have led to the view that, at least in this species, the preoptic area is essential for the occurrence of the preovulatory LH surge. However, the situation may be different in the primate, for Knobil and his co-workers (Knobil, 1974; Krey, Butler and Knobil, 1975) have shown that regular ovulatory menstrual cycles can occur in rhesus monkeys in which the medial basal hypothalamus has been separated completely from its extrinsic connections (Figs. 1.3, 1.4). Further, the gonadotrophin response to oestrogen administration in ovariectomised rhesus monkeys bearing a hypothalamic island is indistinguishable from that in animals in which the extrinsic connections of the hypothalamus are intact. An attractive though

not exclusive interpretation of these results is that primates are less dependent than subprimates on environmental (exteroreceptive) stimuli for the regulation of their reproductive cycles.

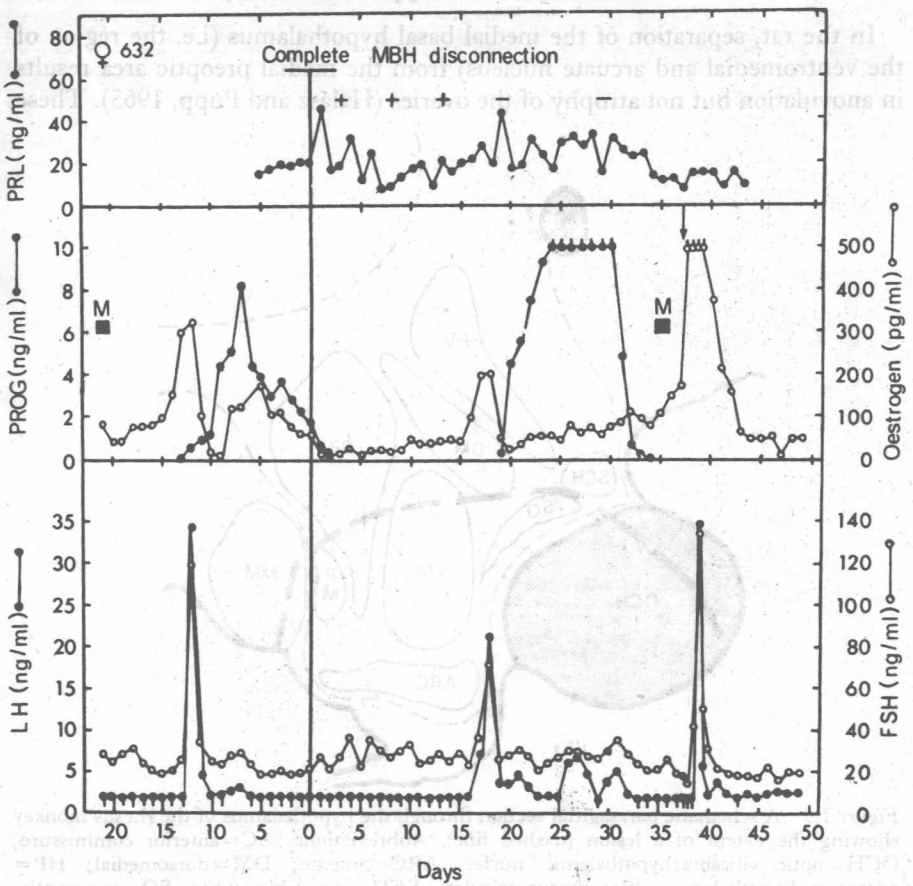

Figure 1.4 Plasma concentrations of gonadotrophins and ovarian hormones before and after complete deafferentation of the medial basal hypothalamus of a female monkey on day 0 (lesion shown in Fig. 1.3). Arrow on day 38 indicates the subcutaneous injection of oestradiol benzoate in oil. The signs in the top left panel indicate the presence (+) or absence (−) of lactation as judged by the expression of milk from the nipples. Menstrual periods are indicated by M, while PRL and PROG are abbreviations for prolactin and progesterone, respectively. From Krey et al (1975) and Butler et al (1975) with kind permission of the authors

THE GONADOTROPHIN RELEASING HORMONE

In Extracts of Hypothalamic Tissue

The decapeptide GnRH (Fig. 1.5) was first isolated from porcine hypothalamic fragments by Matsuo et al (1971) and Schally et al (1971). Shortly afterwards the structure of the GnRH was confirmed by Burgus et al (1972)

who used ovine hypothalamic fragments. The history of the isolation is reviewed in detail by Harris (1972) and Schally, Kastin and Arimura (1972). The main reason for the difficulty in isolating GnRH was probably due to the small amount of the substance present in the hypothalamus. Thus, Gregory (1971) stated, 'Contamination from non-hypothalamic sources can be quite serious; for example, a single finger print on a glass surface will provide more amino acids (but different ratios!) than can be obtained from purified LRF from over 1000 SME (stalk median eminence) fragments'. The successful isolation of the decapeptide required many hypothalamic fragments (e.g. Schally et al, 1972, obtained 11·4 mg from 240 000 porcine fragments), and careful and tedious chromatography (six to nine steps). The structure of the peptide was determined by the use on a microscale of the combined Edman-dansyl procedure combined with a selective tritiation method for C terminal analysis, and was confirmed by mass spectroscopy (Schally et al, 1972).

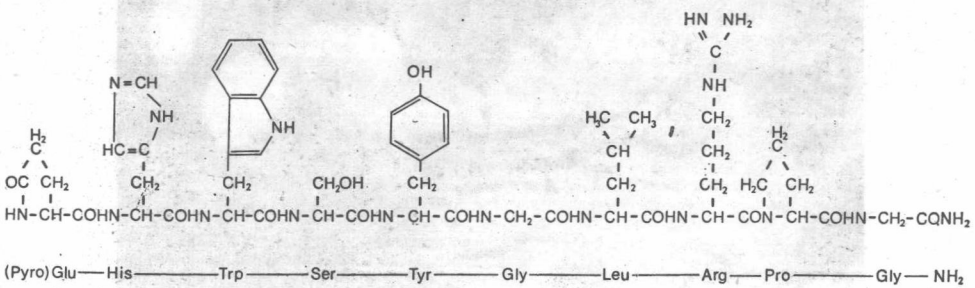

Figure 1.5 The structure of the decapeptide GnRH

Until recently it was thought that FSH (follicle stimulating hormone) secretion was regulated by a neurohumor different from that which released LH, but this FSH-releasing activity appears to have been due to the action of polyamine contaminants which are not active in the more specific assays for FSH release (Schally et al, 1972). Currie et al (1973) have reported the presence of FSH-releasing activity in partially purified extracts of median eminence tissue. But their report has not been confirmed and, so far, the structure of a hypothetical FSH-releasing hormone has not been published.

In Pituitary Stalk Blood

The first investigation of the LH-releasing activity of hypophysial portal vessel blood was carried out by Fink, Nallar and Worthington (1967) who collected blood from the cut pituitary stalk of pro-oestrous and hypophysectomised animals using a transpharyngeal approach (Fig. 1.6).

It was found that the 'LH-free' fraction of acid–ethanol extracts of rat stalk, but not systemic blood, possessed LH-releasing activity in three different bioassay systems (Fink and Harris, 1970). Further gel filtration