Advances in reproductive medicine

The aim of this conference was to highlight new developments in reproductive medicine likely to improve the understanding and practice of physicians and gynaecologists, particularly those working in endocrinology and infertility. The conference was held at the Royal College of Physicians on 22 November 1990.

The brain

Professor Denis Lincoln (MRC Reproductive Biology Unit, Edinburgh) took as his main theme the control of the secretion of gonadotrophin releasing hormone (GnRH), the unique mediator of the central control of reproduction. While catecholamine (generally stimulatory) and opioid peptide (generally inhibitory) control of gonadotrophin secretion is well established, neuropeptide Y-containing (NPY) inputs coincide with mono-aminergic input to the GnRH terminals in the median eminence of the brain. There is also substantial experimental evidence of NPY controlling the release of GnRH into the pituitary portal circulation. Another novel peptide in this system is galanin which is co-expressed and co-secreted with GnRH in GnRH neurones. Galanin directly stimulates the release of LH.

As yet, however, the physiological significance of NPY and galanin remains unclear although NPY is a known modulator of satiety/appetite. It is well recognised that weight change, especially loss, dramatically inhibits GnRH secretion leading to hypogonadotrophic amenorrhoea. Is NPY the hormone of anorexia?

Mammalian female reproduction fails totally if there is no midcycle ovulatory surge of LH. How this is generated has exercised the minds of reproductive biologists for decades. Is this massive outpouring of LH, which in women lasts for 12–24 hours, primarily driven by the brain through increased frequency or amplitude of GnRH secretion, or by the ovary through the positive feedback effect of oestradiol, or by a combination of both?

It is impossible to address this directly in humans but the sheep provides a good model because (a) most strains are uniovulators (one follicle/cycle) and the patterns of hormone changes are similar to those of the primate menstrual cycle, and (b) the anatomy of the sphenoidal sinus makes it possible to obtain samples from the portal vessels in conscious animals. Professor Lincoln described the work of a French group which concluded that there is a massive discharge of GnRH during the LH surge but that the frequency of bursts of GnRH secretion is similar to that during the follicular phase. Moreover, at the height of the LH surge there is dissociation between pulsatile GnRH and LH secretion. Furthermore, as the LH surge falls, GnRH secretion continues though LH levels fall, perhaps due to pituitary desensitisation by the massive GnRH discharge. These data argue in favour of neural control of the LH surge but other studies have shown that oestradiol is clearly able to generate a normal LH surge without changing the GnRH input signal. Hence, the ovary is as good an LH surge generator as the brain. Electrophysiological studies show altered neural activity during the surge. The electrical activity arises not from GnRH neurones but from nerve terminals, possibly from interneurones, which impinge on GnRH axon terminals in the median eminence. Early studies showed bursts of electrical activity coincident with pulses of LH secretion, but more recent results showed no change in median eminence discharge during spontaneous LH surges and they were paradoxically suppressed during oestrogen induced LH surges. This conundrum is not explained.

The ovary

Still on the subject of the LH surge, Professor Alan Templeton (Obs. and Gyn., Aberdeen) reported his group’s recent work on a putative peptide factor in ovarian follicular fluid (GnSAF) which attenuates the spontaneous LH surge. Although there was considerable initial scepticism regarding its existence, and much work still needs to be done to purify, characterise and synthesise the material, evidence for its existence is becoming increasingly strong.

The physiological role of GnSAF is unknown but its greater production by smaller rather than larger follicles suggests a role in suppressing LH during follicular development and preventing the premature release of LH by rising oestradiol concentrations. Premature LH surge/luteinisation has been documented as a cause of infertility.

When inhibin was first identified, many respected endocrinologists/reproductive biologists doubted its significance. We have only to look now at the many and varied actions of the inhibin family of peptides outside the reproductive system to realise how misplaced was the scepticism. As an example of the diversity of sites of inhibin synthesis Professor Lincoln drew attention to work from the Salk Institute which had recently demonstrated expression of both α and β subunit genes within pituitary gonadotrophs, the very cells upon which ovarian inhibin acts selectively to reduce FSH secretion. What inhibin is doing there is anybody’s guess.

Endocrinology is no longer only the study of molecules produced by one organ, transported in the blood stream, and acting on a distant target gland. The discipline has proliferated into paracrinology and autocrinology, terms used to describe cell–cell crosstalk and communication via molecules traversing very small distances and not necessarily appearing in
the systemic circulation. This was clearly exemplified by Dr Stephen Hillier (MRC Reproductive Biology Unit, Edinburgh) with a description of the two cell – two gonadotrophin control of follicular steroidogenesis. The theca interna, which surrounds the granulosa cell layer, is highly vascular and is the mesenchymally derived compartment which synthesises the androgenic precursors for granulosa cells (epithelially derived) to produce oestradiol by aromatisation under the control of FSH. During the growth of the dominant follicle granulosa cells proliferate and aromatase enzyme activity increases 100-fold. Since granulosa cells are incapable of synthesising the androgen precursors on which aromatase can act, they must somehow tell the surrounding thecal cells to make more androgens. How do they do this? Granulosa cells are a rich source of many peptide growth factors, including activin and inhibin, whose synthesis is under FSH control and increases with follicular growth. Since oestradiol itself does not stimulate thecal androgen production, one looks to follicular peptides as the signal to the theca. In a series of elegant experiments with human thecal cells in culture Dr Hillier reported that activin inhibited androgen production whilst inhibin not only stimulated androstenedione production but also reversed the inhibitory effect of activin. Others have shown that insulin-like growth factor 1 (IGF-1), which is also synthesised by granulosa cells, stimulates thecal androgen production. There are at least two peptide signals from the growing follicle which help satisfy its demands for more precursors for oestradiol synthesis. It is tempting to speculate that at least some disorders of folliculogenesis may be related to a failure of this intercompartmental communication within the ovary.

Continuing the theme of folliculogenesis, Professor S. Franks (St Mary’s Hospital) described the stages of progression over twelve weeks from primordial to pre-ovulatory follicle, the final stages of which depend upon the intercycle rise in FSH. Although it is believed that the single follicle destined to ovulate in any cycle is the one that is capable of continued growth despite falling FSH levels, it is not clear what attributes select that follicle. Of interest in this connection has been the observation by Professor Jacobs and colleagues that recombinant human growth hormone (GH) can augment FSH action on folliculogenesis in vivo. Professor Franks described in vitro experiments with human granulosa cells showing direct stimulation of oestra- diol production by GH and its amplification of FSH action. Turning to monitoring of follicular growth, Professor Franks highlighted specific ovarian morphological appearances, assessed with transabdominal and more recently transvaginal ultrasound, which characterise functional disorders of gonadotrophin secretion. In experienced hands this is the method of choice for monitoring follicular growth during induction of ovulation. The traditional method of serum oestradiol measurement does not produce an immedi-
especially assisted conception, younger patients presented themselves to hospital clinics.

There followed a brief review of the results of assisted conception. The high risk of multiple pregnancies (20–30% depending on method) is something that warrants urgent research because of the economic and emotional consequences of coping with multiple pregnancies. If embryo viability and implantability could be predicted prior to return to the mother, this would be a major step forward.

The embryo

Enormous strides have been made in embryo research and Dr Alan Handside (Royal Postgraduate Medical School, London) described the potential of embryo biopsy for pre-implantation diagnosis of inherited disease. His research has shown that one or two cells can be removed from an eight-cell blastomere, and after this procedure successful pregnancies and normal live babies can be born. Many technical improvements are still to be made before applying this technique widely. Once it becomes possible to use biopsied single cells from an embryo for karyotype analysis, in situ hybridisation histochemistry for sexing, and DNA amplification for detection of mutations in specific genes (particularly of male embryos in X-linked conditions), this will allow patients to elect not to have an abnormal embryo transferred back into the uterus.

The uterus

Of course, without a normally functioning uterus, none of these discussions about infertility and its treatment would have any practical value. This vital organ has received much less scientific attention than the brain, pituitary or ovaries. The imbalance is beginning to be addressed by Professor S. Smith and his group in Cambridge. Endometrial shedding is preceded by contraction of spiral arterioles; in addition to the prostaglandins, other vasoconstrictor agents play a role in this action. Endothelins, a family of short peptides related to the snake venom sarafotoxin, have receptors at the endomyometrial junction; they are produced by endometrial cells and are potent vasoconstrictors. Could they act on the spiral arterioles?

What of the mechanisms of implantation in the uterus? How does the blastocyst signal its presence and readiness for embedding to a local area of endometrium? The answers to these questions are crucial to our understanding of early pregnancy loss and first trimester abortion. Yet again peptide growth factors are implicated, some of which may come, at least initially, from the blastocyst. Human endometrium is a site for epidermal growth factor (EGF) gene expression and peptide production, and in cultured endometrial cells EGF synergises with oestradiol to stimulate proliferation. A third potential endometrial proliferative agent is transforming growth factor alpha (TGFα) which may derive from endometrial platelets and lymphocytes. The fact that circulating mononuclear cells may be a source of growth factors in the capillary bed has precedents in wound healing and the gastrointestinal tract. Attractive though these peptides are as growth promoters in the uterus, their relative physiological importance still needs to be determined. Nevertheless, the availability of large amounts of recombinant growth factors opens the way for therapeutic intervention if their respective roles can be precisely defined.

Growth factors may also have a role to play in dysfunctional uterine bleeding and maintenance of endometriosis. Professor R. Shaw (Royal Free Hospital) discussed the therapeutic use of the long-acting agonists of GnRH in sex-steroid dependent disease relating to women. It is now well established that these compounds desensitise pituitary gonadotrophs and produce a state of reversible hypogonadotrophic hypogonadism when administered chronically. Their efficacy for treatment of endometriosis is as good as with danazol, the traditional remedy, but without the androgenic side effects sometimes experienced with the latter. Moreover, symptoms may remain suppressed for as long as one year after stopping analogue therapy though they recur when cyclic ovarian function resumes. Leiomyomata can also be reduced in size by GnRH analogues which may be useful before surgery, in some instances making myomectomy technically feasible where hysterectomy would otherwise be required. Other gynaecological uses of agonists include ovulation induction for IVF, in circumstances when premature luteinisation (see earlier) accompanies exogenous gonadotrophin induction of ovulation, and in severe premenstrual tension. However, a serious consequence of more than six months of amenorrhoea induced by analogues (apart from the typical symptoms of oestrogen deficiency) is a reduction by about 5–6% in mineral content of trabecular rather than cortical bone. This limits the duration of analogue treatment unless ways can be found to prevent the bone loss, maybe with progestins.

The testes

In most symposia on reproductive medicine, and this one was no exception, investigation and treatment of the female occupies the lion’s share of the time and attention. This is not because male problems are not relevant, indeed they account for 30–40% of cases of infertility, but because much less is known about spermatogenesis, and its investigation in primates and humans is limited by inability to obtain germinal epithelium in vivo. Rats’ testes are not good models for the human organ, largely because seminiferous tubule organisation is different and all stages of spermatogenesis occur at all points of the tubule. Nevertheless a large amount has been learned about mammalian spermatogenesis from studies in rats and was reviewed...
Infectious diseases

A joint conference of the Royal College of Physicians and the Royal College of Pathologists. held on 13th and 14th December 1990.

First day

In the past ten years, the specialty of infectious diseases has had a new lease of life, which has been associated with a greater demand for the expertise of communicable disease physicians and microbiologists. This change is not simply due to the advent of newly identified diseases such as acquired immuno-deficiency syndrome (AIDS), legionnaire’s disease, and toxic shock syndrome, but has also arisen as a result of new problems with old diseases such as tuberculosis and malaria, the expansion of the immunosuppressed patient population, and the growing awareness of a need for rational antibiotic prescribing. The conference was a timely appraisal of new developments in this rapidly changing specialty, and paid particular attention to advances in our understanding of the molecular biology and pathophysiology of infection. The conference affirmed a multidisciplinary approach to the subject with the chairmanship of the presidents of the Royal College of Physicians of London and the Royal College of Pathologists.

In his introductory lecture, Professor Lambert (St George’s Hospital, London) suggested three areas of change that deserve particular interest. First, he pointed to the recent studies of the pathogenesis of bacterial meningitis which have emerged largely from the United States. It has become clear that, while bacterial invasion and the release of cell-wall products, such as endotoxin, remain important, much of the damage that occurs in bacterial meningitis results from the elaboration of inflammatory cells, cytokines and other inflammatory mediators. Interestingly, several groups have observed that administration of antibiotics is associated with a rise in endotoxin concentrations in the cerebrospinal fluid, resulting in a marked increase in the intensity of the destructive inflammatory process. This observation is most striking with highly bac-