PHARMACOLOGICAL REVIEWS
Vol. 29, No. 2

Printed in U.S.A.

The Role of the Adrenergic Innervation of the Oviduct in the Regulation of Mammalian Ovum Transport

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I. Introduction

The presence of a structure connecting the ovary with the uterus has been known for at least two thousand years. The interesting history of the elucidation of the anatomy and physiology of this structure, the oviduct, has been extensively reviewed by Bodemer (15). Gabriel Fallopius finally established in 1561 the existence and anatomical relationships of the mammalian oviduct or Fallopian tube. In 1797, William Cruikshank reported that the ovum is formed in the ovary, passes down the oviduct and reaches the uterus on the fourth day. By the middle of the nineteenth century, the general structure of the oviduct was known, the oviduct was recognized as the site of fertilization of the ovum and of early embryonic development and the role of the oviduct as a secretory organ was suspected (15).

The oviducts of adult mammals are specialized structures, derived embryonically from the cranial region of the Müllerian ducts. The embryology of the oviduct has been reviewed by Price *et al.* (175).

Detailed reviews of oviductal physiology and pharmacology are contained in the proceedings of meetings (74, 79, 106), and the monographs (164, 210) and other reviews by Pauerstein and his colleagues (165, 171). The role of the sympathetic nervous system in oviductal function has been previously reviewed by Brundin (25), Marshall (132), Black (8) and Hodgson and Eddy (89).

II. Pattern of Ovum Transport

The oviduct is intimately involved in ovum transport, *i.e.*, the passage of the ovum from the ovary to the uterus. The total time for ovum transport is fairly constant for each species, but varies from

species to species. Figures for the duration of ovum transport in various species have been summarized by Blandau (11) and Croxatto and Ortiz (43). Ovum transport can be as short as 24 hours in the opossum or as long as 8 to 10 days in the dog.

The details of the pattern of ovum transport have only been studied in a few species. The long duration of the process precludes lengthy direct observation of the oviduct in the living animal while the thickness of the walls of the isthmus prevent the ready localization of ova within its lumen. In man and subhuman primates additional problems are posed by the necessity to time ovulation accurately and recovery of ova is difficult as usually only one ovum is released.

In 1961, Harper (77) described a technique in which he withdrew the oviducts of rabbits through an abdominal incision and then observed directly the transport of ova in the ampulla. The walls of the ampulla are sufficiently thin to reveal the movements of supravitally stained ova in the rabbit, rat and mouse. With this basic approach, it is possible to make continued direct observation of ovum transport in the ampulla *in situ* and *in vitro*. Such techniques have been described for the rat, rabbit and monkey by Blandau and his colleagues (12, 13). Unfortunately, the technique is not applicable to transport in the isthmus because of the thickness of the walls in this portion of the oviduct.

A seond approach is to locate the position of ova at selected times after the ovulation by various histological techniques (150, 167), or by flushing of oviductal segments for the collection of ova (33, 58). This technique has been used to describe in detail the pattern of transport in the rabbit (167) and mouse (98) and to provide the first information on transport in man (33) and the subhuman primates (58).

In rabbits, ova are transported rapidly, in 10 minutes or less, to the proximal end of the ampulla (18, 77). This is followed by a period of hours during which little further net forward movement occurs. Between 24 to 36 hours after the ovulatory stimulus, ova begin to enter the isthmus and reach the proximal isthmus after 60 to 63 hours. Ova do not pass through the uterotubal junction for a futher 3 hours, but passage through this area appears to be rapid (167).

In mice, passage through the ampulla takes less than 1 hour, followed by a period of about 24 hours at the ampullary-isthmic junction (98). Passage through the isthmus takes 12 to 18 hours followed by a prolonged period of 30 to 36 hours at the uterotubal junction. Ova enter the uterus 72 to 75 hours after coitus.

In man (33), rhesus monkey (58) and baboon (58), ovum transport appears to take about 72 hours. Ova apparently remain for prolonged periods in the ampulla in these species: up to 48 hours in the human (33) and rhesus monkey (58) and up to 24 hours in the baboon (58).

Surrogate ova have also been used to study the pattern and regulation of transport in the oviduct. Pauerstein and his colleagues (42) have described a technique for producing plastic ovum surrogate microspheres labelled with ^{125}I for use in rabbits. A collimated end window Geiger-Muller tube is used to locate the position of the surrogates within the oviduct. These radioactive microspheres have been shown to be reasonably good models for the transport of normal ova and their transport was modified by progesterone and estrogen in the same manner as normal ova (87). Surrogate ova have been used to study ovum transport in the human (52).

The regulation of ovum transport is extremely important since the success of the reproductive process is dependent upon implantation of the ovum occurring at the right stages of endometrial maturation and of embryonic development (1, 31). Drugs that accelerate or retard ovum transport disturb this delicate balance and prevent uterine implantation (7, 31). Bennett (7) has discussed and tabulated the agents known to alter ovum transport.

The pattern of and time required for ovum transport is profoundly altered by the administration of estrogens and progesterone (31, 68, 171). The exact effect on transport is dependent on the species being studied, the timing of administration and the dose administered. For example, in the rabbit, guinea pig or hamster the administration of large doses of estrogen before ovulation causes a marked delay in ovum transport (often referred to as "tube-locking") with most ova being retained in the ampulla or at the ampullary-isthmic junction (68, 167), whereas the administration of smaller doses of estrogens at suitable time causes accelerated ovum transport in the mouse, rabbit, rat, guinea pig and hamster (68). The administration of progesterone before ovulation causes acceleration of ovum transport in rabbits (50).

These findings suggest that drugs that accelerate ovum transport would prevent implantation and pregnancy in woman and hence would have potential as contraceptives. Since 1972, a Task Force of the WHO Expanded Programme of Research, Development and Research Training in Human Reproduction has been concerned with the search for such a compund (78).

III. Mechanism of Ovum Transport

How ovum transport is regulated is still unknown. The transport of ova through the oviduct may involve a number of mechanisms: muscular contractions of the tubal wall; epithelial ciliary activity; and the flow of oviduct secretions. Definitive information about the relative contribution of these processes in ovum transport is still not available. However, it is generally believed that ciliary activity is of more importance in the ampulla than in the isthmus (11, 13, 14). There has been at least one proponent of the importance of isthmic secretory activity in regulating ovum transport (113). Peak secretion and flow toward the ovary occurs on the first postovulatory day. Koester (113) has related the decreased flow on the following days with a decreased resistance to ovum transport and subsequent entry into the isthmus.

However, it is generally considered that the muscular activity of the ampullary-isthmic junction and isthmus contribute directly to the transient arrest of ova at the ampullary-isthmic junction and subsequent slow movement of ova through the isthmus (23, 79, 171). Indeed, most work on ovum transport has focused on the muscular activity of the oviductal isthmus (13).

As this review will show, histological studies have revealed a fairly rich adrenergic innervation to the circular muscle of the isthmus, while pharmacological investigations have demonstrated the presence of α-excitatory and β-inhibitory adrenoceptors in oviductal smooth muscle. These findings suggested that the distal isthmus might function as a sphincter under the control of the sympathetic nervous system (23, 25). The adrenergic transmission could in turn be regulated by the prevailing hormonal dominance (171). It has been proposed (171) that estrogen enhances α-adrenoceptor activity and thus constriction of the isthmus, and that by the third postovulatory day the production of progesterone has enhanced β-adrenoceptor activity with a consequent reduction in constriction of the isthmus thus allowing ova to continue their journey to the uterus. This review is concerned with evaluating this hypothesis and the possible role of the adrenergic innervation of the oviduct in the regulation of ovum transport.

IV. Anatomy of the Oviduct

A. General Anatomy

The Fallopian tubes, or oviducts, are a pair of open-ended tubes connecting the ovaries with the uterus or uterine horns. The oviduct is usually divided into four regions: the uterotubal junction, isthmus, ampulla and infundibulum, although at least one other form of classification has been proposed (148). It is held in place by

that portion of the broad ligament known as the mesosalpinx. In many instances, although not in the human, the oviduct lies dorsal to the free border of the mesosalpinx. The part of the mesosalpinx lying free from the oviduct is known as the mesotubarium superius. It is these two ligaments that determine the position of the oviduct in relation to the rest of the internal genitalia (5).

The oviduct is specialized at its ovarian opening and this region is known as the infundibulum. The infundibulum is adapted for receiving the ova after ovulation, a process known as ovum-pickup. Here the tube is thin-walled and has an abundance of highly ciliated mucosal folds in close contact with the ovary. In the human the oviduct opens directly into the peritoneal cavity. However, in many species the ovary and infundibulum are enclosed to varying extents by folds of the mesosalpinx or both the mesosalpinx and the mesotubarium. These folds may fuse to envelope completely the ovary and infundibulum in a sac known as the ovarian bursa. In some species the bursa maintains contact with the peritoneal cavity via a small pore, while in others this pore is missing (5).

The distal portion of the oviduct connecting with the infundibulum is known as the ampulla, while the section proximal to the uterus is called the isthmus. The ampulla is thin-walled and its lumen is largely obscured by ramifying mucosal folds. This is the usual site for fertilization of the ovum. The isthmus has much thicker, muscular walls and a correspondingly reduced lumen with far fewer mucosal folds. The ampulla is generally of greater external diameter than the isthmus; their relative lengths vary between species. The transition between ampulla and isthmus is known as the ampullary-isthmic junction and is frequently quite well defined and abrupt.

The relative length of the tube varies considerably between species. In the human the oviducts are short and extend horizontally from the uterus to the ovaries. In the mouse, and most other rodents, however, the oviducts are relatively longer and form a multitude of convolutions on the surface of the ovarian bursae. Beck (5), in a detailed study of about 40 species, distinguishes eight anatomical arrangements of the oviduct.

The uterotubal junction consists of the portion of the oviduct where its lumen continues on through the uterine wall. There are great species differences at this region. The various gross anatomical types, and the extensive literature on this region have been reviewed by Hafez (71) and Hafez and Black (73) who distinguished six gross anatomical types. In an alternative classification, Beck and Boots (6) distinguish ten types of uterotubal junction. Various functions have been assigned to the uterotubal junction. It has been suggested that the specializations seen in this region may function as sphincters to prevent the movement of ova from the oviduct to the uterus or of fluid from the uterus into the oviduct (6, 73).

The blood supply to the oviduct comes jointly from the uterine and ovarian arteries. These vessels run in the mesosalpinx and anastomose when they reach the oviduct. A recent study indicates that, in the nonpregnant rabbit, the oviduct receives its blood supply predominantly from the ovarian artery (53). In the human there is disagreement as to the relative contributions of the two vessels (171). The venous drainage follows the arterial supply (210).

The lymphatic system has been described in most detail for the pig (3). In this species three separate networks drain the mucosa, muscularis and serosa, respectively. These vessels combine in the mesosalpinx and eventually drain into the para-aortic nodes. The human lymphatic system is similar (210).

For further information on the comparative anatomy and morphology of the oviduct, the reader is referred to the books edited by Hafez and Blandau (74) and by Johnson and Foley (106). The anatomy of

the human tube has been reviewed by Pauerstein and his colleagues (164, 171, 210). Wislocki (209) described the comparative anatomy of the oviducts of the great apes and some monkeys.

B. Light Microscopy

The oviductal wall can be differentiated into four concentric layers by light microscopy. Innermost is a single-celled layer of columnar epithelium. Underlying this is a region of connective tissue, the lamina propria, which separates the epithelial cells from the tunica muscularis, the muscle layer which forms the bulk of the wall's thickness. The outermost layer (the tunica serosa) is again connective tissue.

The epithelium of the oviduct is columnar and consists of two main types of cells: ciliated and secretory. It is now generally accepted that they are separate entities as no transitional forms have been seen using the electron microscope (148). Two other much rarer types of cells have been described: the rod cell (also known as peg or intercalary cell), and basal cells. Peg cells are thinner than either ciliated or secretory cells. Their function is unknown, although they may be exhausted secretory cells (6). The basal cells lie beneath the other cells; there is some dispute as to their nature and function (149, 172).

Cyclical changes in the form of the secretory cells have been described in several species. In the anestrous rabbit few secretory granules are seen, while at estrus granules are common and concentrated in the apical portion of the secretory cells which become hypertrophied. After coitus the cells produce balloon-like bulges containing many granules which are discharged into the lumen (20). Beck and Boots (6) list further references on this subject. In general, one can state that cyclic changes are most marked in species with the longer estrous cycles (72).

The distribution and cyclical changes of the ciliated cells within the oviductal epithelium was a matter of some controversy before the advent of electron microscopy. This controversy has been reviewed by Brenner (21). Knowledge of the cyclical changes in the oviduct's epithelium and their hormonal dependence has advanced rapidly with the advent of the electron microscope. The literature on the histochemistry of the Fallopian tube is extensive and has been reviewd by Fredricsson (63) and Hafez (72).

The lamina propria underlies the epithelium and forms the framework for the mucosal folds, which vary in number depending on the species and the part of the oviduct; they tend to increase in number and complexity with increasing distance from the uterus. The matrix of the lamina propria consists of collagen in which are embedded fibroblasts, mast cells, nerves and blood vessels. Muscle fibres are few or absent. Except in certain marsupials the laminal propria is gland-free (6). The presence of glands in marsupials may be related to the fact that these species deposit extensive albuminous coats on the zonae pellucidae of their ova.

In contrast to the large amount of literature on the cytology of the oviductal epithelium, very little has been published on the arrangement of the tubal musculature. In general, one can state in all species the isthmus is far more muscular than the ampulla and that there is a progressive decline in the thickness of the tunica muscularis toward the infundibulum. Both circular and longitudinal layers can be differentiated. However, the circular layer is always far more developed then the longitudinal. Depending on the species and the part of the tube, longitudinal layers are found inside, outside or on both sides of the circular.

In the human tube, textbooks generally describe two muscle layers: a thick inner circular layer and a thinner outer longitudinal layer. These are clearly defined in the isthmus, but in the less muscular ampulla they become somewhat indistinct. There is no clear arrangement of muscles in the infundibulum.

However, as long ago as 1891, Williams

(207) described a third inner longitudinal muscle layer in the human oviduct which was present in the intramural part of the tube and gradually thinned out distally, disappearing in the early portion of the isthmus. The existence of this layer was confirmed by later authors (48, 127, 166), although both before and after Williams' work the presence of this layer was neglected. Pauerstein *et al.* (166) claim that a similar muscle layer exists in the oviducts of the rabbit and rhesus monkey, while Hook and Hafez (96) have described it in other species. In the monkey, David and Czernobilsky (48) described an inner layer of hyalinized connective tissue rather than the longitudinal muscle found by Pauerstein *et al.* (166). Pauerstein *et al.* (166) believe this discrepancy may have been caused by the large numbers of collagen fibrils in this region.

Possibly the most detailed study on tubal musculature is that of Schilling (184). He found that the tubal muscle in cows and sheep was arranged in spiral bundles. In the ampulla the spirals were very flat being almost circular and in cross section no clear longitudinal muscle layer could be differentiated except near the isthmus. In the isthmus, however, from a circular base the loops of the muscle spirals moved inward and became progressively further apart finally giving rise to longitudinal muscle strands. Thus, in cross section, an inner longitudinal muscle layer appeared. In addition, in the isthmus only, there was an outer longitudinal muscle layer of uterine origin.

Thus, the sheep and cow resemble the human in having three muscle layers in the isthmus. In the dog and pig there is apparently no inner longitudinal muscle (96). In the rhesus monkey and rabbit (96), rat (108) and guinea pig (148) the outer longitudinal layer is missing. Beck and Boots (6) describe the layers of the tunical muscularis for a wide variety of nonlaboratory animals.

By far the greatest amount of work on the tubal musculature has been confined to the uterotubal junction. This is probably because of the possibility that there may be a functional sphincter at this point. Vasen (202) describes in great detail the arrangement of the intramural oviductal muscles in women. He found four systems of muscle bundles arranged in spirals. In cross section these gave the appearance of an outer and inner longitudinal layer, with a circular muscle layer in between. The arrangement of the muscles of this region in a variety of species has been thoroughly reviewed by Hafez and his coworkers (71, 73, 96).

It has also been suggested for the human that there may be a functional sphincter at the abdominal ostium. Stange (193, 194) describes how muscle fibres from the inner part of the outer longitudinal muscle layer become spirally arranged to create a thickening of the circular muscle at this point.

The tunica serosa, the outermost layer of the oviduct, is a thin sheath of connective tissue covered by a single-celled layer of squâmous epithelium. Within the tunica serosa the largest blood vessels, lymphatics and veins run, parallel to the oviduct, before branching down into the muscle layers (6).

C. Electron Microscopy

Electron microscopy has resolved many of the uncertainties as to the nature of the tubal epithelium and its cyclic changes. The idea that secretory and ciliated cells may be parts of the life cycle of the same cell (61) has been laid to rest by the inability of the electron microscope to reveal intermediate forms. The proportion of the two types of cells in the varying regions of the tube has been described for a number of species, as have their changes in form and number with the sexual cycle and its underlying hormonal changes. The early work in this field is reviewed, together with the previous light microscopic studies, by Brenner (21) and Nilsson and Reinius (148).

The secretory cells are easily recognized by their secretory granules, well developed

rough endoplasmic reticulum and Golgi bodies. The ciliated cells, though at times deciliated (21) are clearly distinguished by the lack of these features and the presence of basal bodies.

Cyclical changes have been described in the epithelium of several species (21). In all species studied the secretory cells show marked cyclical changes reaching their maximal degree of differentiation at mid-cycle. In some species the number of ciliated cells show a similar correlation with the cycle.

In the human the secretory cells undergo the same type of cyclical change as in experimental animals; however, there is little change in the degree of ciliation throughout the cycle (160). The differentiation of the human tube may depend on similar hormonal influences as for other animals. This is indicated by the findings of Brosens and Vasquez (22) that hypo-oestrogenic amenorrhea led to deciliation as also did pregnancy and steroid contraception.

The electron microscope has essentially confirmed the gross arrangement of muscle coats described by the light microscopists. In the rabbit ampulla, Kushiya (118) reported an inner circular and outer longitudinal layer, although the distinction between these is gradually lost as the fimbria is approached. Also in the rabbit, Henderson *et al.* (84) reported that the more circularly oriented fibres predominated near the lumen, while the more longitudinally oriented fibres predominated near the outer margin. However, they state that there was no clear separation into layers. In the human oviduct, Daniel *et al.* (47) described three isthmic layers: an inner longitudinal, a central circular and an outer mixed. This arrangement broke down in the ampulla where no distinct layers were found.

The form of the muscle cells resembles that of other smooth muscles. Longitudinally arranged actin filaments, caveolae, glycogen granules, large central nuclei surrounded by endoplasmic reticulum and Golgi bodies have been found in rabbit (84, 118, 166), human (47) and monkey (J. H. Widdicombe and D. M. Paton, unpublished results, 1975). In all species studied the muscles are spaced relatively far apart with many collagen fibres in between.

The most detailed study on the types of muscle cell contacts is by Henderson *et al.* (84) using estrogen-dominated rabbit oviducts. Cell contacts were frequent and consisted of simple appositions (*i.e.*, where muscle cells approached to within 20 nm of one another with no intervening basement membrane), and interdigitations (*i.e.*, where processes from one muscle projected into another with the same separation as for a simply apposition). A few intermediate contacts (*i.e.*, where the cell membranes run parallel at a distance of 40–60 nm apart with an increased density of cytoplasm and an intermediate dark line or row of particles) were also seen. No nexuses were found. The same conclusions had earlier been reached by Daniel *et al.* (47) for the human, and have recently been confirmed in this laboratory for the monkey (206). An early report by Clyman (36) of nexuses and "protoplasmic bridges" between muscle cells in the human oviduct was probably in error (84).

V. Adrenergic Innervation of the Oviduct

A. Origin of the Efferent Innervation

The oviduct is dually innervated, receiving nerves from both the sympathetic and parasympathetic divisions of the autonomic nervous system. The sympathetic supply to the genitalia of the cat and rabbit was elucidated in great detail, 80 years ago, by Langley and Anderson in anatomical (123) and physiological studies (121, 122). They concentrated on the uterus and vagina but stated that (121): "We made one or two experiments on the Fallopian tubes, they behaved exactly like the uterus."

In the cat, the nerve fibres to the genitalia pass to the sympathetic chains via

the 2nd to 5th lumbar nerves; in the rabbit, via the 3rd to 5th. There is considerable individual variation as to which nerves contribute most fibres. They then pass from between the 3rd and 6th lumbar ganglia of the chains via about four rami to the inferior mesenteric ganglia. These nerve ganglia are arranged in a circle of four around the inferior mesenteric artery. The upper pair send branches anteriorly to the superior mesenteric ganglia, while from each of the lower emerges a hypogastric nerve. These are separate in the cat, but are initially surrounded by a common sheath in the rabbit. The hypogastric nerves divide into a dorsal and a median or ventral branch. The dorsal branch merges with the sacral parasympathetic supply in the ganglia of the pelvic plexus, while the median or ventral branch continues to groups of ganglia situated at the uterovaginal border. Similar arrangements are found in the rat (132), the guinea pig (132) and the dog (138).

In the human, however, the situation is rather different (137). Firstly, the distinct hypogastric nerves of other species are replaced by diffuse plexuses. Mitchell (137) believes the supply to the human tube to originate from three sources: from the inferior hypogastric plexus, from the ovarian nerve which runs directly to the ovary from the renal plexus and also from a small group of nerve fibres that run directly to the region of the oviduct from the superior hypogastric plexus.

Older textbooks have generally stated that the hypogastric nerve contains postganglionic fibres and the sympathetic supply to the oviduct is stated to synapse in the inferior mesenteric ganglia. This view was based on morphological (120) and electrophysiological data (69) which indicated that about 90% of the hypogastric nerve fibres in the cat were unmyelinated. However, the view that many of the preganglionic sympathetic nerve fibres to the oviduct synapsed peripherally was advanced as long ago as 1895 (122). Langley and Anderson found that when the inferior mesenteric ganglion was soaked with nicotine, stimulation of the rami to the ganglia still led to contraction of the genitalia. Further, although after injection of nicotine, stimulation of the inferior mesenteric ganglia produced an unaltered effect on the descending colon, stimulation of the ganglia or hypogastric nerves had a reduced action on the internal genitalia. It was concluded that at least some of the nerves to the genitalia synapsed peripherally (122). Kuntz and Moseley (117) determined the preganglionic supply of the ganglia in the pelvic plexus by looking at nerve fibre degeneration in the ganglia after section of either the sacral or pelvic nerves or extirpation of the inferior mesenteric ganglion and the sympathetic trunks caudal to the second lumbar segment. They found that some ganglia received a predominantly sympathetic supply, some predominantly a mixed supply and others a parasympathetic supply. Their most important conclusion was that "the ganglia of the utero-vaginal plexus receive preganglionic fibers mainly via the thoraco-lumbar outflow."

Despite these studies it was generally assumed, until the 1960's, that the preganglionic nerve fibres synapsed in the inferior mesenteric ganglion. With the use of the Falck-Hillarp technique (59) for fluorescent localization of catecholamines, it was demonstrated, in several species, that the hypogastric nerve to the male genitalia contained predominantly preganglionic fibres which synapsed with adrenergic cell bodies close to or within the walls of the male sex organs (158). Physiological and biochemical evidence for this peripheral sympathetic connection was also presented (190, 191). Shortly after this, Owman, Sjöberg and their colleagues demonstrated a similar pattern of innervation to the female genitalia (188). Using the Falck-Hillarp fluorescence technique, Owman and Sjöberg (154) demonstrated noradrenaline-containing ganglion cells at the periphery of the vaginal wall in the rabbit. It was further shown (152) that

either stripping of the vaginal ganglion cells, or sectioning of the hypogastric nerve combined with removal of the inferior mesenteric ganglion, approximately halved the total noradrenaline content of and the numbers of fluorescent terminals in the oviduct. These two procedures were additive; when both were combined virtually no fluorescent terminals remained in the oviduct. Thus, in the rabbit, the postganglionic adrenergic supply to the oviduct appears to consist in about equal numbers of "long-adrenergic fibres" originating in the inferior mesenteric ganglion and "short-adrenergic neurons" from ganglia located on the vaginal wall.

Sjöberg and co-workers demonstrated similar adrenergic ganglion formations in the human (153), cat (177) and dog (155). In the cat, denervation experiments indicated that virtually all of the nerves in the oviduct were short neurones arising from the ganglia at the uterovaginal junction. Thus it seems that there may be considerable interspecies differences in the origins of the postganglionic adrenergic nerves.

In the oviducts of the rabbit and cat (123), human (117), rat (29) and dog (138), branches of the 2nd to 4th sacral roots unite or pass individually as the pelvic nerve or nerves (nervi erigentes) to the ganglia of the pelvic plexus. How many postganglionic fibres reach the oviduct from this plexus and their role is uncertain.

It seems fair to say, however, that the cholinergic innervation is slight compared to the adrenergic (8). Langley and Anderson (121), for instance, found that in the cat and rabbit stimulation of the sacral nerves was without effect on the genitalia, nor, in the rabbit, did simultaneous stimulation of sacral and hypogastric nerves affect the hypogastric response. They concluded that: "the sacral nerves send neither motor nor inhibitory fibres to any of the internal generative organs." Later, however, Schofield (185) stated that stimulation of the nervi erigentes produced some contractile response in about 25% of the rabbits she studied.

By staining for acetylcholinesterase activity, Jordan (107) and Owman and Sjöberg (154) were unable to demonstrate nerve fibres in the guinea-pig or rabbit ampulla and very few in the rabbit isthmus. However, by incubating tissues for longer periods of time, Jacobowitz and Koelle (101) were able to demonstrate many nerve fibres that stained for acetylcholinesterase in the cat oviduct, but these frequently corresponded to nerves that also stained for noradrenaline. These workers concluded that the lamina propria, but not the muscles, received a cholinergic innervation. In the studies on the fluorescence of the uterovaginal ganglia, occasional nonfluorescent nerve cells were seen. These were presumably cholinergic. Woodruff and Pauerstein (210) state that there is a dual parasympathetic innervation of the human Fallopian tube by the vagal and sacral nerves.

The oviduct may also have a well developed afferent innervation (198). During hysterectomies done under local anaesthesia, the reactions of the patients to the touching of various viscera were tested. It was found that touching the oviducts with forceps or gauze invariably led to severe pain; they were the most sensitive structures in the abdominal cavity. Some light microscopists have reported sensory receptors of the Paccinian type in the oviduct. Perhaps these are pain receptors.

3. Distribution of Nerves within the Oviduct

There was much initial controversy as to the nature of the nerve network in the oviduct walls [reviewed by Damiani and Capodacqua (45) and Martinez and Peréz (135)]. Several early authors believed that nerve cells were present in the plexus. Von Gawronsky (204) for instance, suggested that the human oviduct contained a plexus analogous to Meissner's plexus of the intestine. Most later authors, however, using similar techniques, reported

that no nerve cells are present in the oviduct (34, 45, 143). The distribution of nerves within the tube determined by traditional heavy metal staining methods is well described by Müller (143). He states that nerve fibres follow the large subserosal blood vessels and then branch down smaller blood vessels to produce a plexus within the muscle layers. The finest fibres were followed to just under the epithelium; none penetrated the epithelium.

With the development of the Falck-Hillarp method for the localization of catecholamines, a resurgence of interest in the tubal innervation took place. Brundin and Wirsén (27, 28) were the first to apply the new method to the oviducts of the rabbit and human. Few fluorescent terminals were observed in the ampulla of the rabbit and most, if not all, of these were associated with blood vessels (27). There was an increase in the number of terminals in the isthmus and these were concentrated in the thick circular muscle layer, ran parallel to the muscles and were often free of the vasculature. They suggested that the rich innervation of the isthmus was correlated with a sphincteric function. In the thick circular muscle layer at the uterotubal junction adrenergic nerves were abundant. Brundin and Wirsén (28) reported that the distribution of adrenergic terminals in the human oviduct was essentially similar to that of the rabbit.

The early work by Brundin and Wirsén was considerably expanded by Owman, Sjöberg and co-workers (188). They confirmed the essentials of the results of Brundin and Wirsén for the rabbit, but stated that the highest concentration of terminals occurred at the ampullary-isthmic junction and that the numbers of terminals decreased towards the uterus. There was no increase in innervation at the uterotubal junction comparable to that at the ampullary-isthmic junction (154).

The results of Brundin and Wirsén (28) on the human tube have been confirmed by later authors (116, 153). However, Owman *et al.* (153) state that, as with their results on the rabbit tube, the numbers of nerves in the isthmus decrease as the uterus is approached, and that there is a further decrease in the intramural part of the tube.

The general picture for these two species is that there are few adrenergic nerves in the ampulla and these are almost entirely associated with blood vessels. There is a marked increase in the numbers of nerves in the isthmus and these are concentrated in the thick circular muscle layer of this organ, are often free of the blood vessels and are parallel to the muscle fibres. There is no increase in innervation at the uterotubal junction.

Generally similar patterns of innervation have been reported for the rat (26), cat (177), dog (155), cow (26) and rhesus monkey (40, 151). Some cats showed an increased innervation at the uterotubal junction (177). The rat differed from other species in that only the outer half of the circular muscle layer received an adrenergic innervation (26). In the monkey oviduct, Cottle and Higgs (40) found a dense innervation of the tunica mucosa; these nerves appeared to be closely associated with small blood vessels. A somewhat less dense vascular innervation of the mucosa has also been reported in the oviduct of the dog (155), rat (26) and human (116).

The few electron microscopic studies of the tubal innervation have confirmed the light microscopists' results. Daniel *et al.* (47) state that in the human, the nerves generally follow the blood vessels and are largest in the tunica serosa, where several bundles are frequently surrounded by a perineurium. The nerve bundles themselves consist of several axons which are partially or completely surrounded by a Schwann cell sheath. When the nerves lay free from the blood vessels, they ran parallel with the muscle fibres. Similar results have recently been obtained for the monkey and rabbit oviducts (J. H. Widdicombe and D.M. Paton, unpublished results, 1975). An additional finding of this study was that in both species small

nerve bundles were frequently found underlying the tubal epithelium.

Hervonen and Kanerva (85) report two types of nerve profile within the same nerve bundle. In the one type, small granular vesicles (300–600 Å diameter) and large granular vesicles (800–1100 Å diameter) were present. In the other type, only small granular vesicles (300–600 Å diameter) were present. They suggest that these represent adrenergic and cholinergic neurones, respectively.

The muscles of the rat mesotubarium receive a dense adrenergic innervation and it has been suggested that this membrane may play an important role in ovum transport in this species (26). A similar dense adrenergic innervation of the intraligamentary muscle of the mesosalpinx of the rabbit has been reported (196). Also, in the monkey there is some innervation of the mesotubarium musculature (40).

One point which electron microscopy has been unable to resolve is whether or not sensory endings exist in the oviduct. Using light microscopy, Martinez and Peréz (135) and Chiara (34) describe sensory endings of the Paccinian type; Damiani and Capodacqua (45), on the other hand, state that no capsulated endings could be demonstrated. No such endings have so far been revealed by electron microscopy. Some authors, *e.g.*, Martinez and Peréz (135), also describe myelinated fibres; again electron microscopists have not yet seen these.

C. Relationship of Nerve Terminals to Smooth Muscle

There have been very few electron microscopic studies of the tubal innervation, and none of them have attempted to quantify the numbers and type of nerves within the various parts of the oviduct.

Kushiya (118) published one of the most detailed studies. He reported that in the ampulla of the preovulatory rabbit, the nerves were unmyelinated, occurred usually in small bundles surrounded by a Schwann cell sheath and were generally in the proximity of blood vessels. Small diameter nerve axon sections (0.3–0.5 μm diameter) were granule free but contained neurofilaments. Larger sections (1–2 μm diameter) contained numerous vesicles and a few mitochrondria. Longitudinal sections of nerves showed that they were varicose, the varicosities containing the vesicles. Various types of vesicle were found in any one varicosity, but the commonest type was dense core vesicles of from 55 to 100 nm in diameter. The varicosities were often partially free of the Schwann cell sheath. Although the nerve bundles and varicosities were generally far from the muscle cells and enveloped by Schwann cells, Kushiya observed a few individual axons free of a Schwann cell sheath and also some close contacts between nerve endings and muscle. Here the gap between the two cells was about 20 nm and there were no intervening basement membranes. No specializations were seen in the opposing muscle membrane.

Similar results were obtained in studies of oviducts from oestrogen-dominated rabbits (84). As reported by Kushiya (118), the nerve bundles consisted of varicose nerves which were usually at least partially enclosed by Schwann cell processes and were commonly found near blood vessels. The nerves were usually 500 to 1000 nm or more from the nearest muscle fibre, although a few were found within 200 nm of muscle fibre. In rare instances close appositions were found with a gap between nerve and muscle of about 25 nm. Small dense-cored vesicles were occasionally found in the nerve varicosities; the numbers of these were increased by treatment with 5-hydroxytryptamine or 5-hydroxydopamine indicating that the nerves were adrenergic. The types of nerve contacts were the same in the isthmus and the ampulla and were not noticeably changed by progesterone treatment.

Daniel *et al.* (47) reported that there were few nerves in the ampulla of the human oviduct. These usually consisted of a few bundles of nerve fibres enclosed

in a perineural sheath. The axons in each individual bundle were enclosed by a common Schwann cell sheath. Such nerves were generally found in the periphery of the ampullary wall. Occasionally nerve bundles free of a perineural sheath were found in the muscle layer. However, these were generally associated with blood vessels. No varicosities were seen free of Schwann cell coverage. Many more nerves were found in the isthmus of the human oviduct than in the ampulla, and these were mainly located in the circular muscle layer. Varicosities containing small dense-cored vesicles were seen and these varicosities were occasionally free of a Schwann cell sheath. A few close contacts between nerve and muscle were observed.

Kubo *et al.* (116) show an electron micrograph of a nerve bundle in the human oviduct, but give little information on neuromuscular relationships. In a later, more detailed study, Ishii (100) found varicose nerves in the human and the rat. Most varicosites contained small granular vesicles, the numbers of which were increased by $KMnO_4$ fixation and, in the rat, were reduced by reserpine treatment suggesting that these nerves were adrenergic. Ishii concentrated mainly on the types of varicosities present and gave no information as to the distribution of nerves throughout the oviduct. However, in common with other authors, he found that close contacts between nerve and muscle (20 nm gap) were very rare, and stated that usually the closest approach of nerve to muscle was 60 to 100 nm.

The observation that the monkey oviduct is far less sensitive to exogenous noradrenaline and transmural stimulation (206) than the rabbit oviduct (103, 104) led to a recent study in this laboratory (J. H. Widdicombe and D. M. Paton, unpublished results, 1975) to determine if there was any difference in the arrangement and distribution of nerves between the two species. The results were similar to those of the earlier studies described above. In both species, the nerves were varicose and normally were present in bundles of from three to ten axons, enclosed in Schwann cells. Although often associated with blood vessels, some were found in smooth muscle bundles running parallel to the muscle fibres. The varicosities were frequently free from complete Schwann cell cover and contained small granular vesicles. There were considerably fewer nerve bundles in the monkey than in the rabbit oviduct. Furthermore, only in the rabbit oviduct were axons seen free of the Schwann cell sheath. Also this was the only species in which close contacts between nerve and muscle of the type described by Kushiya (118) were seen. However, these were very infrequent, comprising less than 5% of the total axon profiles. An interesting feature of this study was the finding in both species of many small nerve bundles lying close to the epithelium. It is possible that these are cholinergic nerves corresponding to the acetylcholinesterase-staining nerves described in the lamina propria of the cat by Jacobowitz and Koelle (101).

In summary, the appearance of nerves within the tunica muscularis in all species so far studied by electron microscopy is typical of adrenergic nerves. The nerves present are varicose, and the varicosities contain small granular vesicles. Close contacts between nerve and muscle are very rare. Generally the exposed surfaces of the varicosities are separated from the smooth muscle cells by distances of greater than 100 nm.

VI. Biochemical Studies of the Adrenergic Innervation of the Oviduct

A. Changes in Noradrenaline Content

1. Introduction. The availability of biochemical methods for the quantitative estimation of noradrenaline in biological tissues has made it possible to study changes in oviductal noradrenaline content that may be of physiological importance. Chemical determinations have revealed that noradrenaline is the predominant

monoamine in the oviduct and fluorescence histochemistry has illustrated that the transmitter is stored within neurons. The noradrenaline content of any given tissue is generally considered to be proportional to the degree of sympathetic innervation; findings in the female reproductive organs of the human (153), rabbit (16), cat (177) and sheep (95) are in general agreement with this belief.

von Euler (203) has proposed that the activity of adrenergic neurons varies directly with their content of noradrenaline. If this is indeed so, a change in noradrenaline content that is associated with a particular state or function of the oviduct might indicate a functional involvement of the adrenergic nerves in the process. Numerous studies have investigated such a possibility by measuring oviductal noradrenaline content during normal ovum transport, and by attempting to correlate changes in transmitter content with changes in levels of endogenous sex hormone, with the administration of sex hormones, with pregnancy or following surgical denervation, 6-hydroxydopamine, reserpine or iproniazid (see below).

2. Measurement. A number of methods are available for the estimation of catecholamines in tissues. However, most of the studies of noradrenaline content in the oviduct are based on the trihydroxyindole method (161). While the techniques available for the measurement of noradrenaline have sufficient precision and sensitivity, there is a general inadequacy in the expression of results. This makes it difficult to compare data from different laboratories. For example, the sensitivities of the techniques employed may differ between laboratories, not all workers report the recoveries they obtained and the oviduct portions studied have frequently differed from study to study.

3. Normal levels. Biochemical analyses of the oviducts of different species have generally shown that noradrenaline levels are higher in the isthmic portion than in the ampullary part. The distribution of noradrenaline in the rabbit oviduct was first examined by Brundin (23) who reported that the uterine half contained 2.3 ± 1.2 μg/g wet tissues while the ovarian half contained 0.3 ± 0.4 μg/g. Owman *et al.* (152) performed their determinations on the whole rabbit oviduct and obtained a value of 0.9 ± 0.1 μg/g wet tissue for the noradrenaline concentration. Bodkhe and Harper (16) reported noradrenaline levels of 0.9 μg/g for ampulla, 2.2 ± 0.2 μg/g for distal isthmus and 0.5 ±0.1 μg/g for proximal isthmus of rabbit oviduct. Hence, in these rabbit studies alone, at least three different ways of sectioning the oviduct were used. Thus, one is unable to compare levels in a given portion of the oviduct, *e.g.*, in the more densely innervated distal isthmus where adrenergic nerves may be of the most physiological significance.

Brundin and Wirsén (28) reported approximately equal values (0.1–0.3 μg/g) for the levels of noradrenaline in the isthmic, ampullary and infundibular thirds of the human oviduct. However, Owman *et al.* (153) later reported a significantly higher concentration of noradrenaline in the human isthmus (0.5 ± 0.1 μg/g) than in the ampulla (0.3 ± 0.1 μg/g) or intramural portion (0.3 ± 0.03 μg/g). The noradrenaline content was not found however to differ between three equal sections of isthmus. These estimations were made on samples from menstruant, nonpregnant females. However, the hormonal status was not defined by either group of investigators. Brundin and Wirsén (28) suggested that the similarity of noradrenaline content in the different oviductal parts, compared to the histochemical findings, could possibly be due to the presence of a plexus of adrenergic innervation along the ampulla and infundibulum which was absent in the isthmic region.

While noradrenaline levels in the human oviduct were found to be substantially lower then those in the rabbit oviduct, the contents of noradrenaline in the cat (177) and sheep (95) oviduct have been shown to be comparable to those in the

rabbit. Black (8) has listed in tabular form the noradrenaline contents (in micrograms per gram wet tissue) and the assay method employed for four different species.

There is considerable debate in the literature concerning the advisibility of expressing noradrenaline levels in terms of concentration, *i.e.*, micrograms per gram wet tissue. Brundin (23) has argued rather that the content of noradrenaline, *i.e.*, micrograms per pair of oviducts, is a more valid measure. One can readily appreciate the complications when sex hormones induce water retention, muscle hypertrophy and stimulate secretion, all of which may influence tissue weight and consequently noradrenaline values when expressed as micrograms per gram of weight. The increase in tissue weight with hormone treatment probably reflects mainly an increase in non-nervous tissue and, therefore, the content of noradrenaline per oviduct may be a more meaningful method of expression (17). Indeed, many workers have calculated both noradrenaline concentration and total content in their assessment of adrenergic influences in oviduct function.

4. Changes in noradrenaline content during normal ovum transport. Studies attempting to correlate levels of noradrenaline with the course of normal ovum transport were performed by Bodkhe and Harper (16). Rabbits were killed at various times after induction of ovulation by human chorionic gonadotrophin and artificial insemination. The content of noradrenaline was not altered in the proximal isthmus. The content of noradrenaline was significantly less 72 hours after insemination in the ampulla and significantly less in the distal isthmus at 17, 50, 72 and 90 hours after insemination. The concentration of noradrenaline (micrograms per gram) varied only in the distal isthmus, being significantly less than levels in estrus at 17 hours after insemination. The most significant finding was the decreased content and concentration of noradrenaline in the distal isthmus at 17 hours since this appeared to be correlated with the passage of eggs from the ampulla into that segment of the isthmus.

However, while correlations may be fairly readily discovered, conclusions concerning the influence of noradrenaline levels on ovum transport are less readily drawn. The relation of the amount of transmitter to physiological function is modulated by many factors, including release, reuptake and other inactivation processes, receptor sensitivity and so on. Weiner (205) has warned of another fundamental problem in attempting to correlate noradrenaline content with physiological phenomena: there is more than one noradrenaline compartment or pool in adrenergic nerve endings. Of these, a small, active pool may be of most significance physiologically.

A second finding in the study of Bodkhe and Harper (16) was that the noradrenaline content in the rabbit isthmus remained low during ovum transport when circulating estrogens are reported to be low. Hormone assays were not performed, however.

5. Changes in noradrenaline content correlated with endogenous hormone levels. A recent investigation (55) has attempted to correlate the noradrenaline content of the human oviduct with plasma levels of oestradiol and progesterone. In the proliferative phase when plasma levels of oestradiol and progesterone were 171 ± 33 and 495 ± 133 pg/ml, respectively, the noradrenaline concentration in the isthmus was 2 to 3 times that in either the infundibulum or ampulla. In the secretary phase following ovulation when plasma levels of oestradiol and progesterone were 249 ± 20 and 3027 ± 162 pg/ml, respectively, there was no difference in levels of noradrenaline between the three oviduct segments since noradrenaline levels in only the infundibulum and ampulla increased with the rise in plasma progesterone. Dujovne *et al.* (55) considered this correlation between noradrenaline and

progesterone in the secretory or luteal phase to suggest that ovum passage through the human oviduct may be concomitant with an increase in adrenergic transmitter.

An earlier study (153) reported no significant variation in the total content of noradrenaline in the human oviduct between the proliferative and secretory phases. However, these workers failed to consider cyclical changes in the regional distribution of noradrenaline and did not measure plasma steroid levels. A similar, more recent investigation (151) determined that the noradrenaline concentration in the proliferative phase was about twice that in the luteal phase in human and rhesus monkey oviducts.

Thus, reports in the literature have, for the most part, indicated that the oviduct exhibits differences in noradrenaline content concomitant with changes in hormonal dominance. Dujovne *et al.* (55) have determined that this is a regional phenomenon in the human oviduct.

6. Changes in noradrenaline content and sex hormone administration. Attempts to establish whether endocrine factors are responsible for changes in transmitter content have involved the administration of exogenous sex hormones and the subsequent measurement of noradrenaline levels.

Bodkhe and Harper (17) employed doses of 17β-estradiol (25 or 250 μg/day) or progesterone (2 mg/day) known to either retard or accelerate normal ovum transport in the rabbit (167). Treatment with 17β-estradiol appeared to have little or no effect on the noradrenaline concentration in the ampulla and proximal isthmus, but did result in elevated noradrenaline contents in these regions and this was associated with an increase in tissue weight. However, in the distal isthmus adjacent to the ampulla 17β-estradiol treatment had pronounced effects: both noradrenaline concentration and content were increased without consistent increases in tissue weight. A correlation was observed between these increased noradrenaline levels in the distal isthmus and estrogen-induced retention of eggs at the ampullary-isthmic junction. However, the corollary that progesterone-induced accelerated ovum transport would be associated with decreased levels of noradrenaline in the distal isthmus was not observed. In fact, noradrenaline concentrations in the distal isthmus were elevated with progesterone treatment. The hormonal modification of ovum transport cannot, therefore, be explained simply in terms of changes in noradrenaline levels.

The literature concerning the effect of administered sex hormones on noradrenaline levels is wrought with inconsistencies in methods and in results. This is illustrated by the following examples. Brundin (23) treated one group of rabbits with 17β-estradiol (50 μg i.m./day/8 days) and another group with this estrogen treatment plus progesterone (1 mg i.m./day for the last 4 days). No significant differences were reported in the mean noradrenaline contents per oviductal pair between the hormonal groups nor between these groups and a control group. Significant variations in oviduct weights were, however, observed and, therefore, expression of noradrenaline levels in terms of concentration (micrograms per gram of tissue) would have been substantially different.

Sjöberg (189) used much lower doses of 17β-estradiol in rabbits (0.5 μg/kg s.c./day for 7 or 14 days). However, both treatment regimes produced significant increases in noradrenaline content per pair of oviducts. This was associated with significant increases in tissue weight after the 14-day treatment so that, had the noradrenaline level been expressed as a concentration (*i.e.*, in micrograms per gram of tissue), it would not have been different from controls. In a more recent paper, Owman and Sjöberg (157) have reported further data on oviductal noradrenaline levels and the effect of exogenous hormones. Treatment with 17β-estradiol (0.5 μg/kg/day for 14 days) caused a 2-fold increase in the con-

tent of noradrenaline in the rabbit oviduct. When progesterone (2 mg/kg/day for the last 7 days) was added to the treatment schedule, transmitter content did not differ from controls. In both this and the preceding study, changes in noradrenaline content corresponded to changes in the number of adrenergic nerves detected by histofluorescence microscopy. Other workers (141) have determined the amount of noradrenaline in groups of control (estrous), estrogen and estrogen + progesterone-treated rabbits. They found no significant differences in noradrenaline concentration in oviductal tissue (micrograms per unit of weight).

7. Changes in noradrenaline content during pregnancy. It has been reported that the short adrenergic neurones which supply the female genital tract (uterus, oviduct, vagina) exhibit changes in their transmitter content after administration of sex hormones and during pregnancy, while such changes were absent in organs innervated by classical long adrenergic neurones, *i.e.*, heart and ovary (156, 178). This responsiveness to hormonal status may indicate an important physiological distinction between short and long adrenergic neurones.

Rosengren and Sjöberg (178) reported a 2-fold increase in noradrenaline content in the rabbit oviduct 4 to 12 days after mating compared to nonpregnant values. An increased number of nerves paralleled increases in oviduct weight. These results are similar to those reported by Sjöberg (189) and Owman and Sjöberg (157) after 17β-estradiol treatment.

In summary, there is evidence that changes in noradrenaline content may occur with changes in hormonal status. The phenomenon appears to be specific to the reproductive tract but not to the ovary (156, 188) and hence may be related to the innervation of these tissues by short adrenergic neurones.

8. Effect of agents which affect noradrenaline levels. Surgical denervation techniques have been used to define the origin of the innervation to the female reproductive tract. These studies have usually involved sectioning of the hypogastric nerve at the level of the inferior mesenteric ganglion. Owman *et al.* (152) reported a 50% reduction in the noradrenaline content and concentration in the rabbit oviduct after denervation. Brundin (23) found that the mean content of noradrenaline in operated animals was reduced to one-third of that in oviducts of sham-operated or control rabbits. Hence, 30 to 50% of the total innervation of the rabbit oviduct probably consists of short adrenergic neurones. Such depletion after denervation was not seen in the cat (177), indicating that in this species almost all of the innervation of the female genital tract may be by "short neurones."

Surgical denervation has been considered as a potential tool for studying the relation between oviductal noradrenaline levels and physiological function. However, Marshall (132) has questioned whether complete denervation of the oviduct can ever be accomplished surgically due to the heterogeneous origin of its innervation. Owman *et al.* (152) have reported abolition of fluorescence after sectioning of the hypogastric nerve at the levels of the inferior mesenteric ganglion and the uterovaginal ganglia combined with stripping of the vaginal fascia. Lack of specificity for the adrenergic system, postoperative adhesions and erratic depletion have also been suggested as detriments to the use of surgical denervation in physiological studies (8).

An alternate procedure to produce catecholamine depletion is the use of reserpine. Brundin (23) found that reserpine (1 mg/kg for 2 days or 0.25 mg/kg 20 hours before sacrifice) depleted noradrenaline below measurable levels. Bodkhe and Harper (16) injected rabbits with reserpine (0.25 mg/day) on the day before artificial insemination and for 26, 50 and 90 hours after insemination. There was a significant reduction in noradrenaline levels (content and concentration) in the isth-

mus; the most pronounced depletion was noticed in the distal isthmus since it contained the highest noradrenaline concentrations normally. Although the ampulla was depleted of noradrenaline to levels less than 10 ng, these amounts were not significantly different from controls.

However, the use of reserpine to deplete noradrenaline in the oviduct in functional studies has serious limitations since it also may cause centrally induced hypothermia, interference with gonadotropine release and inhibition of ovulation (170).

A third method for causing depletion of noradrenaline from sympathetically innervated organs is the use of 6-hydroxydopamine. Administration of this agent causes the selective destruction of peripheral adrenergic nerve terminals in adult animals (199). Black (8) measured changes in noradrenaline content after perfusion of the rabbit oviduct with 6-hydroxydopamine. The range of 6-hydroxydopamine doses used (0–20 mg) induced decreased levels of noradrenaline, and the segments closest to the uterus were most sensitive to this effect. At high doses, however, the contralateral, control oviduct was also affected. Eddy and Black (56) have discussed the need for controlled chemical denervation of individual oviducts. They suggested that a dose of 1 to 5 mg of 6-hydroxydopamine was optimal to cause denervation but insufficient to produce significant systemic effects. However, 6-hydroxydopamine denervation is associated with denervation supersensitivity. Chemical sympathectomy of the rabbit oviduct using 6-hydroxydopamine has been studied in relation to ovum transport (57, 170, 173) and to fertility (90, 102, 128) and will be discussed in a later section.

Iproniazid, a monoamine oxidase inhibitor, has been utilized to raise oviductal noradrenaline levels (16). The influence of iproniazid on ovum transport will be discussed later. The working hypothesis was that if an increased noradrenaline content alone is associated with altered oviduct function, one can surmise that noradrenaline levels may mediate hormonal influences on the oviduct.

The preceding discussion has dealt with changes in noradrenaline content in the oviduct during normal ovum transport, correlated with endogenous sex hormone levels or following the administration of sex hormones, during pregnancy and subsequent to treatment with chemicals which alter noradrenaline levels. A fundamental problem exists when one measures content changes since it is not possible to determine whether the change is due to altered synthesis and storage of noradrenaline or to changes in the metabolism of the transmitter.

B. Biosynthesis of Noradrenaline

It is presumed that, under steady-state conditions, estimates of the turnover of noradrenaline yield information regarding the rate of synthesis, and that this rate of synthesis is related to impulse activity in the sympathetic nerves (39, 205). Several authors have suggested that estimation of the rate of catecholamine turnover provides more information about neuronal activity than measurements of amine concentration in the tissue. However, measurement of turnover rates may suffer from a similar drawback that affects measurement of content: the turnover of a larger, more stable pool of noradrenaline may be reflected in turnover estimates while the turnover of a smaller pool may be much more rapid and of more significance physiologically (205).

Takeda and Doteuchi (196) estimated rates of noradrenaline turnover in the rabbit oviduct under different hormonal conditions. The initial rate of decline of noradrenaline after blockade of its synthesis with α-methyl-*p*-tyrosine methylester was used as an estimate of noradrenaline turnover rate. The turnover rate was slightly higher in estrogen-dominant tissues (0.41 nmol/g/hr) than in progesterone-dominant tissues (0.30 nmol/g/hr). No such differences were found in atria which is innervated by "long" adrenergic neurons. Hence,

the intermediate effect of hormones on noradrenaline turnover in the oviduct could be explained by its mixed ("long" and "short') innervation.

Recently, Kennedy and Marshall (112) have performed similar estimations of noradrenaline turnover rates in rabbit oviduct. While the rate constant for the decline of tissue noradrenaline was significantly lower in castrates than hormone-treated oviducts, they found no difference in turnover rates between estrogen- and progesterone-dominant tissues. This is in disagreement with the observation by Takeda and Doteuchi (196) of a higher turnover rate in estrogen-treated rabbits. However, Takeda and Doteuchi administered 10-fold greater doses of estrogen. This work requires verification, therefore, and would also benefit from separate analysis of turnover rates in the isthmus, ampulla and infundibulum.

C. Metabolism and Uptake of Noradrenaline

The physiological disposition of monoamines is another factor which may contribute to changes in noradrenaline content or turnover. Hormones have been shown to modify the metabolism of labelled amines in rat uterus (38, 159), but similar studies have not been performed in the oviduct. It would be of considerable interest to measure the activities of monoamine oxidase and of catechol O-methyltransferase in the oviduct after treatment with estrogen or progesterone.

Neuronal uptake is considered to be the major route of inactivation of noradrenaline in the rabbit oviduct (104, 105). However, few studies have investigated directly neuronal uptake processes in this tissue. Paton and Johns (162) have characterized the accumulation of (±)-[^{3}H] metaraminol, a sympathomimetic amine, in human oviduct. The accumulation of metaraminol was decreased by inhibitors of neuronal uptake but not by extraneuronal uptake blockers. The accumulation of labelled metaraminol was greater in isthmic tissues than ampulla: this reflects the more dense innervation of the isthmic smooth muscle. Such a measurement of neuronal uptake would be a valuable tool in the investigation of possible hormonal modifications of the uptake process in the oviduct.

D. Conclusion

In summary, it may be said that while techniques are available for the measurement of noradrenaline content, turnover and metabolism, there are problems and omissions in their application to the study of oviduct function. Important difficulties remain in establishing cause-and-effect type relationships between levels and turnover of transmitter and oviduct physiology. A more complete analysis would have to include investigation of noradrenaline release and effector adrenoceptor sensitivity under the various experimental conditions.

VII. Physiological and Pharmacological Studies Related to Adrenergic Transmission in the Oviduct

A. Methods of Study

An understanding of the physiology and pharmacology of the mammalian oviduct requires reliable methods for monitoring the motility of the oviduct both *in vivo* and *in vitro*. A brief summary of the techniques that have been used is presented below. Critical reviews of the methods used for measuring the motility of the oviduct have been recently published by Blandau *et al.* (13), Daniel (46) and Marshall (133).

1. Methods for the in vivo measurement of motility. These techniques can be subdivided into six general categories.

a. Visual observation. Abdominal windows have been used in the rabbit to observe the motility of both the fimbrial and ampullary portions of the oviduct (18, 77). However, this method is not quantitative and is technically difficult because other viscera block the view of the oviduct.

The peritoneoscope has also been used but its use has been criticized since it causes distension and occlusion of the lumen of the oviduct (54). Observation of the transport of oil along the length of the oviduct has also been employed to monitor the contractile pattern of the oviduct (9, 60).

b. Perfusion and flow studies. The resistance to the flow of CO_2 at a constant pressure has been used in both rabbits (49) and man (181) to assess the contractile state of the tissue. Modifications of this technique involving perfusion of normal saline at a constant flow through the oviduct while recording changes in pressure have been widely used (23, 111, 126).

c. Intratubular pressure studies. The pressure in surgically constructed cavities within the oviduct has been used as a monitor of circular muscular activity in both the isthmus and ampulla. This technique has been used in rabbit (67) and human oviducts (35). In a modification of the method closed-end, fenestrated cannulae have been placed in different areas of the oviduct (*e.g.*, 130). Other investigators have used microballoons at the end of cannulae to record circular muscle activity in the oviduct (*e.g.*, 112, 192). However, all of these methods necessitate occlusion of the lumen and distension of the oviduct.

d. Electrical activity measurement. The electrical activity of the smooth muscle of the oviduct has been used as a measure of the myogenic activity of smooth muscle. However, the magnitude of contractions and the muscle layer from which they originate cannot be determined. This method involves the placement of electrodes along the whole length of the oviduct. The electrodes used have been of the suction type (197) or platinum electrodes implanted in the wall of the oviduct (147, 182).

e. Transducer systems. The longitudinal contractions of rabbit oviduct have been measured by the use of strain gauges attached to the end of the isthmic portion. This method was used in conjunction with a perfusion study of the circular muscle of the same oviduct (111).

Miniature mercury strain gauges have been developed for the measurement of the contractility of the oviduct (131). Their use is limited to restrained animals, since any movement of the intestine or uterus would tend to produce large movement artifacts which would mask the muscular activity of the oviduct.

Ultrasonic transducers have been used to measure the phase shift of low-level ultrasonic sound transmitted through the oviduct muscle. The degree of the phase shift, measured continuously, gives an indication of the contractile state of the muscle through which the ultrasonic sound is passing (94).

Optical densitometers, custom made to fit as a half-cuff over the oviduct, primarily designed to monitor the passage of ova (13) can also be used to monitor the contractile activity of the oviduct of rabbits (13).

Minaturization of transducers and the advent of integrated circuit techology has led to the development of more sophisticated monitoring methods. These have been claimed to be an improvement over the other methods since unrestrained animals can be used in conjunction with telemetry (10). Extraluminal monitoring devices have also been used in conjunction with electrical activity recording, in order to measure both longitudinal and circular muscle activity of the oviduct. The electrical recordings were obtained from the muscle by means of etched platinum electrodes insulated to their tips with a flexible glass. The mechanical activity of the longitudinal muscle was measured with a piezo-resistive integrated circuit force transducer and the mechanical activity of the circular muscle with a sensitive integrated circuit piezo-resistive pressure transducer. These devices, along with compatible telemetry systems, have been used for measurement of human, rabbit and monkey oviductal motility and electrical activity (64, 147).

f. Electrical impedence studies. The motility of the oviduct of unrestrained rabbits has been measured with electrical imped-

ence monitors. The multiple units are attached along the length of the oviduct and the degree of contractility of the muscle below each electrode pair is monitored by measuring the change in impedence of the high frequency current passed between the most proximal and distal electrodes (70).

2. Methods for the in vitro measurement of motility. When a tissue is mounted in an organ bath the effects of anaesthetics, circulatory changes and any influence of extrinsic nervous activity are circumvented. In addition, the composition and the temperature of the medium bathing the tissue can be easily altered. In most of the *in vitro* methods either isotonic or isometric measurement of oviductal motility have been used. These studies usually involve the removal and isolation of isthmus and/or ampullary portions of the oviduct. The tissue can then be tied to a hook at the bottom of the bath and the other end attached to a transducer or lever system enabling recording of longitudinal mechanical activity. Rings or spirals can be cut to measure predominantly circular muscle activity (80, 86).

In some studies the longitudinal and circular muscle activity of both ampulla and isthmus have been studied using a combination of these methods (103, 142, 206). Attempts have also been made to record the contractions of the longitudinal and circular muscle in the same tissue preparation. The longitudinal contractions were monitored by measurement of the isometric tension of the tissue, whereas the circular muscle activity was measured by either recording perfusion pressure (186) or by using a microballoon placed in the lumen of the oviductal segment under investigation (201).

B. Types of Adrenoceptors Present in the Oviduct

The first pharmacological studies performed on the oviduct revealed that the smooth muscle of the human and pig oviducts was sensitive to adrenergic stimulation (114, 115). Davids and Bender (49) monitored contractile responses to adrenaline by measuring the *in vitro* motility of rabbit oviduct by the Rubin tubal insufflation technique. It is interesting that these early studies reported the importance of hormonal status on the sensitivity and nature of the response of the oviduct to adrenergic drugs. Subsequent to Ahlquist's classical study (2) of the adrenotropic receptors, many investigators used specific adrenergic agonists and antagonists to define the adrenoceptors in a large number of smooth muscle preparations including the oviduct. Evidence has accumulated to indicate the presence of both α-excitatory and β-inhibitory adrenoceptors in the oviducts of all mammalian species studied.

In the rabbit oviduct, adrenaline, noradrenaline and phenylephrine always elicited contractile responses of the circular and longitudinal muscle layers of ampulla and isthmus, and these were antagonized by the α-receptor blocking agents, phentolamine or phenoxybenzamine (91, 126, 176, 201). The relative potencies of noradrenaline, adrenaline and phenylephrine in the circular muscle of the isthmus in estrus were examined in the presence of propranolol (to block β-adrenoceptors), and cocaine and hydrocortisone (to inhibit neuronal and extraneuronal uptake of amine). These studies (176) demonstrated that adrenaline was slightly more potent than noradrenaline and about 8 times more potent than phenylephrine. The relative order of potencies of these amines was thus similar to that described for α-adrenoceptors in other rabbit tissues (65).

Stimulation of rabbit oviduct *in vivo,* by hypogastric nerve stimulation (23) and, *in vitro,* by transmural stimulation (93, 103) also caused contractile responses that were eliminated by α-adrenoceptor antagonists. Contractile responses to hypogastric nerve stimulation were also abolished by pretreatment with reserpine (23) while contractile responses to transmural stimulation were prevented by tetrodotoxin, guanethidine and by pretreatment with 6-hydroxydopamine (93, 103). These results indicate that these contractile responses

were caused by the activation of α-adrenoceptors by noradrenaline released from adrenergic nerve endings.

The β-agonist, isoprenaline, inhibited tubal motility in the rabbit and this was inhibited by propranolol (91, 126, 176). In the presence of phenoxybenzamine, the excitatory response to noradrenaline was reversed and was expressed as inhibition (201). Activation of β-adrenoceptors thus mediates relaxation in the rabbit oviduct.

Recently, Kendle and Lam Shan Leen (111) have endeavored to further define the type of β-adrenoceptor present in the rabbit oviduct. They reported that, in the presence of practolol, the contractile response to adrenaline was potentiated in circular muscle but not in the longitudinal layer. Salbutamol, a β_2 agonist, was found to cause inhibition in the longitudinal muscle layer but not in the circular layer. As a result of these findings, they suggested that the inhibitory receptor in the longitudinal muscle is of the β_2 type, while that in the circular muscle is of the β_1 type. No quantitative data were presented, however. Their proposals may be criticized since routes of agonist inactivation were not considered in their study. Noradrenaline is a better substrate for uptake in adrenergic nerves than adrenaline (180). Since circular muscle is more densely innervated, the influence of neuronal uptake will be significantly greater in circular than in longitudinal muscle. In fact, the difference in sensitivity to noradrenaline between circular and longitudinal muscle layers was largely eliminated by cocaine, desipramine or 6-hydroxydopamine which prevent the neuronal uptake of amines (104, 105).

The relative potencies of noradrenaline, adrenaline, isoprenaline and salbutamol in the circular muscle of the rabbit isthmus were examined in the presence of cocaine and hydrocortisone and pre-exposure to phenoxybenzamine (to block α-adrenoceptors) (176). In this study, isoprenaline was more potent than either adrenaline or noradrenaline while salbutamol was much less potent. pA_2 values for propranolol and practolol were 8.3 and 5.3, respectively. These findings indicate that the β-adrenoceptor in the circular muscle of the rabbit isthmus resembles the β_1 subtype (65). Heilman *et al.* (82) reported that the β-adrenoceptors in the rabbit isthmus were unlike the β_2 receptors present in blood vessels.

There has been at least one biochemical study of adrenergic receptors in the rabbit oviduct (32). With a [^{3}H]noradrenaline binding assay, catecholamine bindings sites were found to be located predominantly in the microsomal fraction. Mean levels of receptor sites were estimated at 4.5 pmol/unit microsomal fraction and the density of receptor sites in the oviductal segments varied by more than 400% from the ampulla to the uterotubal junction. However, the interpretation of such receptor binding assays using labelled catecholamines is difficult because: 1) the binding is not stereospecific; 2) blocking agents have little or no effect on the degree of binding; and 3) there is a discrepancy between the time course of catecholamine binding and the more rapid stimulation of adenylate cyclase activity [see reviews by Cuatrecasas (44) and Bär (4)]. Labelled agonist binding is now generally considered to reflect a nonspecific, irreversible, catechol-directed binding component which does not represent interaction with adrenergic receptors.

A growing body of evidence indicates that the use of labelled antagonists (*e.g.*, (⁻)-[^{3}H]alprenolol, (±)-[^{125}I]hydroxybenzylpindolol) provides a more reliable identification of β-adrenoceptors (124, 125). The antagonists exhibit a higher apparent affinity for the putative receptor site than agonists and lack the catechol structure associated with nonspecific binding.

In the human oviduct, activation of α- and β-adrenoceptors by noradrenaline also causes excitation and inhibition, respectively (80, 145, 179, 187). However, there are conflicting reports as to which type of response predominates. This appears to be related to hormonal dominance and is discussed below. Studies of the responses of

the isolated human oviduct to perivascular nerve stimulation (144, 145) and to transmural stimulation (140, 142, 151) have, in similar fashion, produced conflicting results. While α-excitatory and β-inhibitory receptor activity could be demonstrated in each study, the predominant response to adrenergic nerve stimulation varied.

The effects of catecholamines during anestrus and estrus were investigated in the rat oviduct in the presence or absence of α- and β-blockers (19). The inhibition of motility elicited during anestrus was abolished by propranolol, and hence was attributed to activation of β-adrenoceptors. During estrus, phenylephrine, in the presence of propranolol, stimulated the rat oviduct to contract. Thus, α- and β-adrenoceptors were demonstrated, but were influenced by hormonal status.

Ruckebusch and Pichot (182) studied the effects of adrenergic drugs on sheep oviduct motility *in vivo*. Phenylephrine and noradrenaline induced contractile responses, while isoprenaline caused relaxation. However, selective blocking agents were not employed to further confirm the presence of both α- and β-adrenoceptors. α-Excitatory and β-inhibitory responses have also been demonstrated in the guinea-pig oviduct (66).

In summary, in the oviducts of all species studied to date, α- and β-adrenoceptors are present. Activation of α-adrenoceptors results in contractions of smooth muscle while activation of β-receptors results in inhibition of contractility of smooth muscle. The β-adrenoceptor in the circular muscle of the rabbit isthmus appears to be β_1 in type. No other β-adrenoceptors in other muscle layers or species have been sufficiently studied to determine their β subtype.

C. Factors Modifying the Responses of the Oviduct to Adrenergic Agonists and Adrenergic Nerve Stimulation

1. Hormonal dominance. Early experiments revealed that estrogen and progesterone were involved in the regulation of the spontaneous muscular activity of the female reproductive tract. The general finding has been that estrogen increases and progesterone decreases the spontaneous activity of oviductal smooth muscle (41, 183).

There have been numerous studies of the effects of hormonal status on the responses of the oviduct to adrenergic agonists and to nerve stimulation. As early as 1927, the responses of the oviduct to amines were shown to be influenced by the hormonal status of the animal when Kok (115) found that the responses of the ampullary portion of the human and pig oviduct to adrenaline were inhibitory during the folicular growth phase of the menstrual or estrous cycle, whereas during the luteal phase responses to adrenaline were excitatory. Similarly, the responses of the rabbit oviduct to adrenaline were also reported to be hormonally dependent (49). Intravenous injection of adrenaline increased the contractile state of the oviduct during anestrus, as judged by the CO_2 insufflation method. These responses were greater in estrus or after pretreatment with estrogen, whereas androgen decreased the response. Castration had no demonstrable effect on responses to adrenaline.

At least two studies have attributed the effect of progesterone on the rabbit oviduct to a decrease in α-adrenoceptor sensitivity. The responses of oviducts from progesterone-dominant rabbits to adrenaline were smaller than those of oviducts from estrogen-dominant rabbits (99). However, in this study α-adrenoceptor activity was not monitored exclusively since adrenaline has activity on both α- and β-adrenoceptors. Heilman *et al.* (83) attributed the decreased sensitivity of rabbit oviduct to noradrenaline during early gestation (*i.e.*, progesterone dominant) to decreased α-adrenoceptor sensitivity and/or a decreased number of α-adrenoceptors. This conclusion can be criticized for the same reason since a β-blocker was not used to exclude changes in β-adrenoceptor activity.

A more recent study (176) was not able to confirm any changes in α-adrenoceptor

sensitivity in the circular muscle of the isthmus of rabbit oviduct as a result of progesterone pretreatment. In this study, propranolol was used to block β-adrenoceptors and cocaine was used to inhibit neuronal uptake. Under these conditions, the potencies of adrenaline and phenylephrine were not different in tissues from animals in estrus or after pretreatment with human chorionic gonadotrophin and progesterone or estrogen.

Several workers have suggested that progesterone accomplishes its inhibitory influence through increased β-receptor activity. One of the first quantitative studies on the effects of ovarian hormones on responses of the oviduct to biogenic amines was performed *in vivo* and *in vitro* using rabbits (134). The presence of β-adrenoceptors was easily demonstrable in rabbits pretreated with progesterone, whereas estrogen-treated animals showed variable β activity. It was therefore suggested that progesterone treatment enhanced β activity in the rabbit oviduct. The circular muscle of the rabbit isthmus was less sensitive to phenylephrine, 72 hours after injection of human chorionic gonadotrophin, compared to tissues from animals in estrus (91). These authors suggested that this was due to an increase in the number of β-adrenoceptors in the tissue. This conclusion has been confirmed in studies in which the activity of β-adrenoceptors has been directly examined using the β-agonist, isoprenaline in the presence of α-adrenoceptor blockade (92, 176). After treatment with human chorionic gonadotrophin and progesterone, an increase in the maximal response to isoprenaline was observed in the circular muscle of rabbit isthmus compared to tissues from animals in estrus. However, the pD_2 value for isoprenaline was not altered suggesting the progesterone had not altered the sensitivity of the β-adrenoceptor, but rather had increased their number (91, 176). By contrast, the ability of papaverine, a nonspecific spasmolytic, to inhibit the oviduct was not influenced by progesterone (91, 176).

Progesterone pretreatment also appears to have a more general and less specific effect on the contractility of the oviduct. Maximal responses of the circular muscle of rabbit isthmus to noradrenaline, phenylephrine, acetylcholine and calcium were all smaller in tissues from animals under progesterone-dominance than those under estrogen dominance (86, 88). These investigators suggested that some of the effects of progesterone could result from changes in calcium movements and binding.

It is important to note that, in the rabbit, the action of noradrenaline on α-adrenoceptors always predominates; under all hormonal conditions, noradrenaline always contracts the rabbit oviduct. Thus, although progesterone pretreatment increases β-adrenoceptor activity, no adrenergic reversal occurs in this species (93, 176).

This contrasts markedly with the situation in other species where changes in hormonal dominance have been reported to cause adrenergic reversal. In the guinea pig, noradrenaline stimulated the oviduct only during the follicular (or estrogen dominant) phase, but not during the luteal (or progesterone dominant) phase (66). In the rat, noradrenaline inhibited the spontaneous contractility of the oviduct during proestrus and metestrus, but had no effect during estrus (19). It was concluded that during proestrus and metestrus β-adrenoceptors predominated.

The responses of the human oviduct to adrenergic nerve stimulation and to adrenergic agonists during different phases of the menstrual cycle have been studied by several investigators. In one study (142), the predominant response of circular and longitudinal muscle of ampulla and isthmus to transmural stimulation and to noradrenaline was a decrease in the amplitude of spontaneous contractility. However, during the early part of the menstrual cycle, responses were more variable

and on some occasions excitatory responses were obtained (142). Moawad *et al.* (140) correlated the plasma levels of estrone, estradiol and progesterone in 83 women with the *in vitro* responses of the circular muscle of the isthmus to adrenaline and to transmural nerve stimulation. When the plasma level of estrogens was low (*i.e.*, during the early part of the follicular phase) responses were mainly inhibitory and it was concluded that β-adrenoceptors predominated. In the latter part of the follicular phase, as plasma estrogen levels rose, responses could become excitatory and this continued into the early part of the luteal phase. However, as the plasma progesterone levels rose after ovulation, the responses again became inhibitory (140). In a preliminary study (151), noradrenaline was reported to generally inhibit the activity of the circular muscle of the human isthmus except at ovulation when responses were excitatory.

2. Density of the adrenergic innervation. In the ampulla and isthmus of rabbit oviduct, longitudinal muscle was significantly more sensitive to noradrenaline than circular muscle (104, 105). Cocaine and desipramine significantly potentiated responses of both muscle layers to noradrenaline and considerably reduced the differential sensitivity. Pretreatment of animals with 6-hydroxydopamine had a similar effect on responses to noradrenaline. Cocaine and desipramine are potent inhibitors of the uptake of noradrenaline in adrenergic neurones (180) while pretreatment with 6-hydroxydopamine causes reversible destruction of adrenergic nerve terminals (199). Cocaine had no additional effect on the sensitivity to noradrenaline in tissues from animals pretreated with 6-hydroxydopamine. (104, 105).

These findings suggest that the main route of inactivation of noradrenaline in rabbit oviduct is uptake into adrenergic nerve terminals and that the differential sensitivity of longitudinal and circular muscle may be related to a differential degree of adrenergic innervation. Thus, circular muscle would be less sensitive to noradrenaline if it was more densely innervated since the amine would be more rapidly taken up by nerve terminals with a consequent reduction in concentration of amine at the adrenergic receptors. A similar proposal has been made to account for the differential sensitivity of the muscles of the cat nictitating membrane to noradrenaline (200).

However, the findings of other workers are not altogether consistent with this concept. The circular muscle of the rabbit oviductal isthmus was reported to be more sensitive to noradrenaline than the longitudinal muscle layer (201). However, this claim was not supported by quantitative data. A subsequent quantitative study showed that the longitudinal muscle of the rabbit oviductal isthmus was more sensitive to phenylephrine than circular muscle (91). It is difficult to account for this differential sensitivity in terms of a different degree of adrenergic innervation to the two muscle layers since phenylephrine has a relatively low affinity for uptake in adrenergic neurones (180).

Cocaine did not potentiate the contractile responses of the circular muscle of the rabbit oviductal isthmus to transmural stimulation and at 3×10^{-5} M caused some inhibition (103). However, the rate of relaxation after transmural stimulation was prolonged by cocaine. The failure of cocaine to potentiate responses may possibly be due to the local anaesthetic action of cocaine and increased α-receptor-mediated presynaptic feedback inhibition (119). In another study (112), cocaine was reported to potentiate responses of the isthmus of the rabbit to adrenergic nerve stimulation. However, the method of measurement apparently included not only the period of stimulation but also the first 30 seconds of relaxation after cessation of stimulation.

No sufficiently quantitative studies are

available to allow one to draw any conclusions about the presence or absence of differential sensitivity to noradrenaline in the longitudinal and circular muscle in the ampulla and isthmus of the human oviduct. The ampulla (142) and the isthmus (145) of the human oviduct have variously been reported to be more sensitive to noradrenaline and to adrenergic nerve stimulation.

Responses of the rabbit oviduct to noradrenaline were not altered by hydrocortisone, an inhibitor of the extraneuronal uptake of noradrenaline and/or by U-0521, an inhibitor of catechol O-methyltransferase (104, 105). Hydrocortisone and U-0521 also did not significantly alter the potentiation of responses to noradrenaline produced by cocaine (176). These findings were obtained in tissues from animals in estrus, after pretreatment with human chorionic gonadotrophin and a large dose of estrogen, and after pretreatment with human chorionic gonadotrophin and progesterone (176) and suggest that the sensitivity of the rabbit oviduct to noradrenaline is not significantly influenced by extraneuronal uptake of the amine.

3. Effect of prostaglandins. The circular muscule of the isthmus of rabbit oviduct responded to both noradrenaline and to prostaglandins of the F series with a contraction (192). It has therefore been suggested that the responses to noradrenaline and to adrenergic nerve stimulation could be mediated by release of prostaglandins of the F series (192). This suggestion, however, is unlikely since indomethacin, an inhibitor of prostaglandin biosynthesis, did not alter the responses of the circular muscle of the rabbit isthmus to noradrenaline or transmural stimulation at 27°C (163).

The contractile responses of the rabbit oviduct to adrenergic nerve stimulation were reduced *in vivo* and *in vitro* by prostaglandins E_1 (24) and E_2 (139, 163). Prostaglandin E_2 inhibited responses to transmural stimulation more than those resulting from addition of (−)-noradrenaline (163) suggesting that it was inhibiting release of transmitter at a presynaptic site. Prostaglandin E_2 also inhibited the release of (−)-[^{3}H]noradrenaline from rabbit and human oviductal isthmus induced by transmural stimulation (139).

In the isthmus of the human oviduct, prostaglandin E_2 always reduced the release of (−)-[^{3}H]noradrenaline induced by transmural stimulation, but had variable effects on the responses to transmural stimulation, these being either slightly depressed, not affected or even markedly potentiated (139). It was suggested that these variable responses might have resulted from variable hormonal states in the subjects from whom the tissues were obtained. No studies have been reported on the effects of estrogen and progesterone levels on the presynaptic inhibitory action of prostaglandins on adrenergic transmission in the oviduct.

Responses of the circular muscle of rabbit isthmus to transmural stimulation and to noradrenaline were reproducible at 27°C, *i.e.*, no evidence of desensitization was obtained (163). However, at 37°C, responses to both transmural stimulation and noradrenaline were markedly inhibited, *i.e.*, desensitization occurred. This effect was abolished by indomethacin. To account for these findings, it was proposed that prostaglandins of the E series are spontaneously synthesised by and liberated from the oviduct at 37°C and cause the observed desensitization. A similar degree of desensitization and reversal by indomethacin was observed in tissues from rabbits pretreated with estrogen or progesterone (163).

4. Presynaptic regulation of release of transmitter. In recent years it has become clear that there are specific receptors located on peripheral adrenergic nerves and that these presynpatic receptors are involved in the regulation of release of transmitter during nerve stimulation (119, 195). Presynaptic α-adrenoceptors mediate a negative feedback mechanism which results in inhibition of transmitter release,

while presynaptic β-adrenoceptors mediate a positive feedback mechanism which results in an increase in transmitter release. In addition there are other inhibitory presynaptic receptors: these are for dopamine, opiates, muscarinic agonists, adenosine and prostaglandins.

There has been very little study of these presynaptic receptors in the oviduct. As indicated earlier, there is evidence for the presence of presynaptic receptors for prostaglandins, activation of which inhibits transmitter release (139, 163). Presynaptic α-adrenoceptors and β-adrenoceptors have also been described in the isthmus of the human oviduct (81). Activation of these receptors caused, respectively, inhibition or potentiation of transmitter release. The effect of hormonal status on these receptors has not been studied.

D. Cellular Mechanism of Action of Noradrenaline and Other Sympathomimetic Amines

There have been very few studies that have examined the mechanism of action of noradrenaline and related amines on the oviduct. Isoprenaline only increased the level of cyclic adenosine 3':5'-monophosphate in the isthmus of the oviduct in rabbits that were under progesterone dominance and had no effect on levels in rabbits in estrus or after estrogen pretreatment (89). The concentration of isoprenaline used (4.7×10^{-6} M) caused maximal inhibition of contractility.

Phenylephrine appeared to utilize two calcium pools or compartments in the isthmus of the rabbit oviduct (88). Contractile responses to phenylephrine persisted for at least 20 to 30 minutes in the absence of calcium, whereas responses to elevated potassium were lost within a few minutes. The tonic response to phenylephrine was lost more rapidly than the superimposed phasic contractions possibly indicating that they were dependent on different calcium pools. Calcium was also required for adrenergic transmission in the human oviduct, while increased magnesium was inhibitory (146).

VIII. Effect of Drugs and Procedures that Modify the Function of the Sympathetic Nervous System on Ovum Transport and Fertility

A. 6-Hydroxydopamine

Local administration of 6-hydroxydopamine caused the degeneration of the adrenergic innervation to the rabbit oviduct (56, 170), but had very little effect on ovum transport (57, 170). In one study, transport was significantly retarded at 60 hours after mating (57). However, pretreatment with 6-hydroxydopamine significantly antagonized both the acceleration of ovum transport produced by progesterone and the delay in ovum transport induced by estrogen (170).

Systemic administration of 6-hydroxydopamine to mice (30) and rats (128) did not reduce fertility. However, the schedule of treatment with 6-hydroxydopamine used in these studies caused only a partial denervation of the heart and other tissues (30, 128). In a later study (102), the systemic administration of 6-hydroxydopamine to mice produced at least 80% denervation of the oviduct as judged by fluorescence microscopy and uptake studies. However, again fertility was not impaired. The local oviductal administration of 6-hydroxydopamine in rabbits produced 70 to 90% denervation and reduced the incidence of pregnancy and the mean number of implantations (90). However, the local administration of ascorbic acid alone as a control also reduced these parameters. Ascorbic acid was added to the 6-hydroxydopamine to reduce its oxidation.

B. Surgical Denervation

Denervation of the short adrenergic neurons by vaginal transection and stripping of the fascia reduced the catecholamine fluorescence in the rabbit oviduct by only 10 to 50% and did not alter ovum transport at 48 hours (170). Combined de-

nervation by vaginal transection and hypogastric nerve resection caused a 70 to 90% reduction in catecholamine fluorescence in rabbit oviduct and did not alter ovum transport at either 48 or 72 hours (170). However, combined denervation did antagonize both the acceleration of transport induced by progesterone and the retention or "tube-locking" of ova produced by estrogen (170).

After autograft transplantation of the oviduct, pregnancies have occurred in rabbits (208) and sheep (37). Under these conditions it is likely that the adrenergic innervation to the transplanted oviducts had undergone extensive degeneration.

C. Agents Impairing Adrenergic Transmission

In mice, ovum transport was delayed by reserpine at a dose of 2 mg/kg i.p. and was arrested by 4 mg/kg i.p. or more (109). These doses of reserpine caused hypothermia and, when this was prevented, ovum transport proceeded apparently normally (110). In rabbits, reserpine (0.25 mg/kg/day s.c.) caused marked depletion of noradrenaline in the oviduct, but produced only marginal slowing of ovum transport at 50 and 90 hours after human chorionic gonadotrophin (16).

Ovum transport and the fertility of rabbits was not altered by reserpine in a dose (90, 170) which caused the complete loss of catecholamine fluorescence in the oviduct (170). This dose of reserpine caused significant hypothermia and antagonized the retardation of ovum transport produced by estrogen, but did not antagonize the acceleration of transport produced by progesterone (170).

Administration of guanethidine (20 mg/kg/day i.m.) at the time of ovum transport did not significantly reduce the percentage of pregnant animals or the number of implantations in rabbits (90). Guanethidine was also reported not to alter ovum transport in mice (110).

D. Monoamine Oxidase Inhibitors

Administration of iproniazid (25 mg/kg/day s.c.) significantly increased the noradrenaline content of the rabbit oviduct, but had very little effect on ovum transport causing marginal acceleration at 50 hours after human chorionic gonadotrophin (16).

E. Adrenoceptor Agonists

In rabbits, adrenaline (500 μg/kg/6 hr s.c.) accelerated ovum transport at 60 and 72 hours after coitus, when administered for the 12 hours preceding death (174) but, in an earlier study, had little effect at 36 hours (174). Administration of phenylephrine (4 mg/kg/6 hr s.c.) or noradrenaline (2 mg/kg/6 hr s.c.) for 12 hours before death accelerated ovum transport in rabbits at 60 and 72 hours after mating (173). However, these doses were also associated with a mortality of 29%.

Administration of phenylephrine (1 mg/kg hourly i.m.) from 16 to 48 hours after artificial insemination did not impair the fertility of rabbits (90). In mice, fertility was reduced by oxymetazoline but not by methoxamine (102).

In rabbits, ovum transport was not altered by isoprenaline at doses that caused a mortality rate of about 50% (173). The effect of isoprenaline on ovum transport in the rabbit ampulla has been studied by direct observation *in situ* (76). During the infusion of isoprenaline, cumulus egg masses progressed through the ampulla at the same net velocity as did controls despite the complete absence of muscular activity in the oviduct wall. The fertility of rabbits was not reduced by ritodrine administered systemically (90) while salbutamol and isoprenaline did not reduce fertility in mice (102).

F. Adrenoceptor Antagonists

Phentolamine has been reported not to alter ovum transport in mice (110). Phenoxybenzamine has little or no effect on normal ovum transport in the rabbit (168, 169). However, the administration of phenoxybenzamine to rabbits antagonized the arrest of ovum transport produced by estrogen (168, 169), but did not modify the

acceleration of ovum transport at 72 hours produced by progesterone (169). The administration of phenoxybenzamine (6 mg/kg i.m. every 12 hours) for the first 3 days after artificial insemination did not reduce the number of pregnancies or implantations in rabbits (90).

Pronethalol and dichloroisoprenaline were reported not to alter ovum transport in mice (110) while propranolol had no effect on ovum transport in rabbits (169). The administration in rabbits of propranolol (10 mg/kg i.m. every 4 hours) or practolol for the first 3 days after artificial insemination did not significantly alter the percentage of pregnancies or of implantations (90).

IX. Role of the Mesenteries in Oviductal Function

Blandau (11) has pointed out that there is vigorous contractile activity of the various mesenteries and ligaments in the immediate vicinity of the oviduct (*i.e.*, the mesovarium, the various ovarian ligaments, the mesosalpinx and the mesotubarium superius) and that these result in continual changes in the position of the ovaries relative to the fimbria as well as the relations of one part of the oviduct to another. The role of such contractions in ovum transport is, however, still unknown and there has been very little study of the physiology and pharmacology of these contractile tissues (11).

The anatomy of the mesotubarium superius in the rabbit has been described by Halbert and Conrad (75) and Meiss (136). This is a muscle-containing mesentry which runs along the oviduct from the uterus to the fimbriated end of the oviduct. The outer margin is a strip of smooth muscle cells arranged in parallel longitudinal bundles with little intervening connective tissue. The tissue appears to receive many nerves.

The anatomy of the human ovarian ligament has been described by Mahran *et al.* (129). This ligament extends from the ovary to the cornu of the uterus and consists mainly of longitudinal smooth muscle fibres. The ligament is very vascular and is richly supplied with nerves.

There have been a number of recent, initial studies of the pharmacology of the mesosalpinx of the rat (19) and guinea pig (66) and of the ovarian ligament of the rabbit (62). The rat mesosalpinx receives many adrenergic nerves (26), but could not be studied separately from the oviduct (19). The isolated mesosalpinx of the guinea pig did not respond to noradrenaline (66). The rabbit ovarian ligament was shown to possess both α-excitatory and β-inhibitory adrenoceptors with α-adrenoceptors predominating (62).

Talo and Brundin (197) used suction electrodes *in vitro* to record electrical activity in the rabbit oviduct and its surrounding membranes. The duration of the train discharges in the mesosalpinx, mesotubarium superius and other membranes were larger than the discharges in the circular muscle of the oviduct. Contractions of the longitudinal peritoneal muscle in the rabbit were reflected in intraluminal pressure changes in the oviduct (51).

X. Conclusions

As indicated in section III, the principal aim of the present review was to evaluate the role of the adrenergic innervation of the oviduct in the regulation of ovum transport. In this concluding section, the evidence for and against such a role will be summarized.

Many studies have shown that the pattern of adrenergic innervation to the oviduct in all species is basically similar. The intrinsic adrenergic innervation is derived from both "long" and "short" adrenergic neurones. The muscularis of the ampulla is generally poorly innervated. The isthmus, by contrast, is more densely innervated with the greatest density of innervation usually at the ampullary-isthmic junction. The nature of the adrenergic neuromuscular relations has received much less study. The studies to date have demonstrated that individual smooth muscle cells are usually embedded in connective tissue and are generally not

in close apposition of adrenergic nerve terminals. Simple appositions are the usual type of cell-to-cell contact in oviductal smooth muscle.

The oviducts of all species studied to date contain both α-excitatory and β-inhibitory adrenoceptors. Whether the α- or β-adrenoceptors will predominate appears to be determined chiefly by the species and the hormonal status of the animal. In general, progesterone dominance increases the influence of the β-adrenoceptors. In the oviduct of the rabbit α-adrenoceptors always predominate, whereas β-adrenoceptors usually predominate in the human oviduct.

As Daniel (46) has indicated, the slow passage of ova through the ampullary-isthmic munction and the isthmus could theoretically result from: mechanical blocking; blocking of myogenic origin; blocking from neurogenic changes which control one of the above myogenic mechanisms; or, blocking from hormonal changes which act on a myogenic or a neurogenic mechanism. Daniel has also pointed out that at the appropriate time in ovum transport there should be a mechanism for reversing the above changes thus allowing onward progression of ova (46).

The variability in the responsiveness of different species to noradrenaline and to adrenergic nerve stimulation indicates that a single hypothesis based on a hormonally dependent adrenergic sphincter at the ampullary-isthmic junction cannot adequately account for the pattern of ovum transport in all species. In addition such a hypothesis requires a mechanism to produce relaxation of tension. There does not, however, appear to be a neuronal basis for such a mechanism since an intraneural neuronal system has not been described in the oviduct while the parasympathetic innervation to the oviduct is generally very sparse (8). Cholinomimetics have usually been found to have variable and weak effects on the oviduct (8, 97). Relaxation of tension in the isthmus could also be achieved if there was a hormonally determined change in either the relative predominance of α- and β-adrenoceptors or the quantity of noradrenaline released per unit time. As indicated earlier, there is evidence that after ovulation with progesterone dominance there is an increase in β-adrenoceptor activity. There is little or no information, however, on the effects of hormonal dominance on transmitter release.

More direct information on the role of the adrenergic innervation has been obtained in studies of ovum transport and fertility, principally in mice and rabbits. In summary, it can be concluded that these have demonstrated that ovum transport and fertility are not altered to any major extent by α- or β-adrenoceptor antagonists, by depletion of transmitter stores or by destruction of adrenergic nerve terminals in the oviduct. Thus there does not appear to be any information presently available to indicate that the adrenergic innervation in the oviduct is essential for normal ovum transport (89, 170). Others have, however, cautioned (151) against concluding that the adrenergic innervation has no role in normal ovum transport and have suggested that there may be significant species differences in the control mechanisms and that the denervation procedures used may have been incomplete and their effects partially compensated for by the development of denervation supersensitivity.

The administration of large doses of estrogen or progesterone causes, respectively, retardation or acceleration of ovum transport in rabbits. The evidence available suggests that adrenergic mechanisms may be involved in these effects, since they are partially reversed by α-adrenoceptor antagonists, by depletion of transmitter stores and by adrenergic denervation. The mechanisms involved are, however, unknown.

Ovum transport and fertility in rabbits and mice have also not been altered to any great extent by large doses of α- and

β-adrenoceptor agonists. These findings suggest that such agents will have very limited efficacy as contraceptives in women particularly in view of their marked systemic effects.

Much further research is required to determine: what factors regulate the type and number of adrenoceptors present in the oviduct; how transmitter release is regulated; how noradrenaline modifies myogenic electrical and mechanical activity of the oviduct; what effect the adrenergic innervation has on ciliary action and oviductal secretions; what is the role of the smooth muscle in the surrounding mesenteries, etc. Answers to these questions are required before the role of the adrenergic innervation to the oviduct can be completely understood.

Acknowledgments. Original research in the authors' laboratory was supported by grants to Dr. Paton from the World Health Organization and the Medical Research Council of Canada. Dr. Johns was the recipient of a Canadian Heart Foundation Research Fellowship while Ms. Rheaume held a Medical Research Council Studentship. We wish to acknowledge the competent secretarial assistance we have received from Miss Sharon Engelhardt and Mrs. Laurel McLachlin.

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