REVIEW ARTICLE

INDIAN CONTRIBUTION TO REPRODUCTIVE PHYSIOLOGY:
THE LAST 2 DECADES

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Abstract: The end of twentieth century is witnessing far-reaching changes in the reproductive behaviour of modern man. Population is doubling now in a record time of 30 years in some parts of the world like India. On the other hand, living-together without marriage and widespread use of contraceptives is making child-bearing highly optional in the West. Technological advances in the realm of in-vitro fertilization and genetic manipulation have opened up enormous possibilities, bringing us almost on the verge of Aldous Huxley's Brave New World.

It is natural, therefore, that reproduction has become an attractive area of research for physiologists. We review here some of the significant contributions made by Indians to reproduction physiology during the last 20 years (1970-1990). Considerable pruning of available material has been necessary. The emphasis sometimes was on Physiologists although their contribution may not be exactly basic physiology, and sometimes on Physiology although the contributors were not exactly physiologists.

ANDROLOGY

Andrology, or what may be called the male counterpart of gynaecology, has gradually emerged as a speciality in its own right. It is one of the important areas in which laboratory work and clinical service can be usefully integrated within the framework of a physiology department (1). Several basic questions in Andrology have been under study in India.

INHIBIN

The pituitary and testis are connected by two feedback loops, one each for the spermatogenic and endocrine functions. It is a good example of cybernetic control. But one arm of this feedback system has remained elusive for long. What is the signal from the seminiferous tubules to the pituitary or hypothalamus which limits FSH release? Since 1932, the suspicion has centered on a non-steroidal factor, inhibin. McCullagh had coined this name for his postulated second testicular hormone. Extensive work on the isolation, estimation and physiological actions of inhibin has been done in India by the late Dr Mrs SS Rao, AR Sheth and their colleagues at IRR, Bombay, and by NR Moudgal's group at IIS, Bangalore. Sheth et al developed one of the earliest bioassay techniques for inhibin based on suppression of HCG-induced increase in the weight of reproductive organs of mice, (2) and later a sensitive RIA system for human inhibin (3).

Has inhibin any other function besides inhibiting FSH release? Interestingly, the amount of inhibin riding on the sperms as a surface coating has shown positive correlation with the sperm motility on flow cytometric studies (4). Sperms with less inhibin on their surface have low motility for some unknown reason. Human infertility is often associated with poor sperm motility as the prime defect and the role of inhibin in such patients needs to be explored further. Estimation of inhibin in the blood and seminal fluid may soon become an important test in the investigation of infertile males. Shashidhara Murthy et al. (5) have shown that purified sheep inhibin suppresses FSH in castrated monkeys also. If pure-inhibin is not species specific and it selectively blocks FSH alone, it has the potential to be an effective male contraceptive.

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Since inhibin has to regulate FSH release and ultimately control spermatogenesis, it should be produced primarily by the seminiferous tubules (Sertoli cells). Surprisingly, inhibin was also detected in the ovarian follicular fluid in 1976. Sheth et al reported a sharp rise in inhibin level 2-4 days before the LH peak in normally menstruating women (6). This shows that inhibin has a role in the feedback suppression of FSH in the female as well.

LEYDIG CELLS

A method for computing the size of the endocrine testis, or the Total Leydig Cell Volume (TLCV), has been developed for quantitative studies in human subjects under various conditions by Kothari et al over the last 15 years. The reliability of the method was first established in dogs and models of the testis (7). In dogs, the Leydig cells constitute about 15% of testicular volume or 1.56 ± 0.45 ml/testis in absolute terms. Later, the method was used to estimate TLCV in some common mammals (8), and under various conditions in man. No specific change could, however, be detected in association with human infertility (9).

More interesting from a physiological standpoint was the significant increase in TLCV observed in ageing males. The mean TLCV rose from 2.2 ± 0.5 to 2.9 ± 0.9 ml/testis, constituting almost 20% of the testis in those aged 55 to 65 years (10). This ran contrary to the previous belief that there is an age-related involution of the Leydig cells and this is associated with the falling androgentic and anabolic drive in the elderly. It appears now that a functional exhaustion of the ageing Leydig cells triggers the feedback loop through the pituitary. A rise in LH leads to Leydig cell hyperplasia. Physiologically, it could be compared to an iodine deficiency goitre. This also has a bearing on the question of ‘male climacteric’. Whether anything like a male climacteric really exists as a definite clinical entity, however, remains highly debatable.

EPIDIDYMAL FUNCTION

The epididymis, a nearly 5-6 metre long highly coiled tube in man, can no longer be ignored as merely the first part of the testicular outflow tract. Its function has been extensively studied under MRN Prasad in laboratory animals. An interesting fact which has emerged is that the epididymis requires higher amounts of androgens for its structural and functional integrity than other accessory reproductive organs. Even within the epididymis, the lower or caudal portion has the highest androgen requirement (11). This has been confirmed by administering micro-quantities of testosterone to castrated monkeys (12). Similarly, DHT implants could maintain the weight of all accessory sex glands of castrated monkeys except the epididymis. Regional differences have also been observed in the metabolism of testosterone in different segments of the epididymis. The method involved measuring the in vitro conversion of radioactive testosterone to 5-a DHT and other metabolites (13). Some interesting experiments in collaboration with Moudgal using antiserum to LH have also highlighted the higher androgen requirement of the cauda epididymis (14). One can, therefore, think of a minimal androgen deprivation which would only suppress cauda epididymis function and leave everything else unaffected. This has led to the trial of anti-androgens like cyproterone acetate as a male contraceptive. Small amounts of cyproterone acetate interfere with the capacitation of sperms which normally occurs within the epididymis. But, physiologically, any anti-androgen on prolonged use carries the risk of suppressing libido and secondary sex characters as well. It may also be difficult to individualise the dose for every male so that the epididymis alone is affected. An anti-androgen based ‘male pill’, therefore, seems unlikely to find general acceptance.

Patni and Kothari (15) have highlighted structural differentiation within the epididymis and correlated it with function. The head or caput is primarily adapted for storage and reabsorption of fluid. The cauda has a rich musculature for acting as the ejaculatory pump. It has also been postulated that the thin interconnecting segment possibly acts as a valve, protecting the caput from any back-pressure. The size of the epididymis in relation to the testis (the ratio between the
testicular secretion and epididymal absorptive capacity) is also functionally important. It may determine the extent of testicular changes in a particular species when the outflow is obstructed, as in vasectomy.

Sperms have been analysed for their biochemical composition as they pass through the epididymis. Sialic acid, protein and various lipid fractions progressively decrease during transit through the epididymis; no change occurs in the vas or beyond (16). This is one reflection of the sperm capacitation process. The epididymis is also the source of glyceryl-phosphoryl-choline (GPC) and estimating this in the seminal plasma is a good index of epididymal function. Its concentration is markedly reduced after vasectomy and is restored after reanastomosis. Arabinda Mandal et al have recently observed that GPC influences coagulation of the ejaculate (17). One can surmise that coagulation disorders of the semen in human subjects may have altered epididymal function as one of the causes.

PROLACTIN IN THE MALE

The role of prolactin in maintaining lactation and as a luteotropic hormone is well known. But what is prolactin doing in the male? This question, naturally, is of considerable interest. Sheth et al estimated prolactin in the human seminal plasma using specific RIA homologous for human prolactin (18). Surprisingly, the levels in the semen were 4-7 fold higher than in the blood. The seminal vesicles and prostate seem to concentrate prolactin in their secretion. The role of prolactin in stimulating testosterone secretion and sperm motility is also now gradually emerging. Sheth et al., however, could not find any difference between prolactin levels in the semen of fertile and infertile men (19).

Addition of prolactin to semen in vitro increases the level of cyclic AMP in the sperms (20). Prolactin also seems to have a direct stimulatory effect on the epididymis and other accessory sex glands, apart from its indirect action through testosterone release. Convincing evidence for this comes from two sources. Bromocriptine, which markedly lowers blood prolactin level, leads to depression of metabolic activity in the epididymis even though testosterone is unaffected (21). On the other hand, pituitary homografts placed under the renal capsule of castrated rats can maintain the accessory sex gland function, although there is no question of testosterone secretion in these animals. Thus, prolactin may be an additional physiological regulator of accessory sex glands, acting synergistically with androgens (22).

BIOCHEMICAL CONSTITUENTS OF SEMINAL PLASMA

The chemical composition of the seminal plasma is already well known; only some details continue to be added. Skandhan et al have estimated several elements like zinc, copper, iron, calcium and even gold in human semen (23, 24). The reported presence of gold (personal communication) is astonishing and could be an artifact since gold has little role in biological systems. But it may gladden the hearts of those who consider this fluid supernaturally precious!

The main source of seminal zinc is the prostate, but some may be liberated by the spermatozoa during their capacitation. Whether administration of zinc orally, in the absence of any deficiency, can significantly improve sperm motility remains uncertain. In a limited trial, Manorma et al (25) did observe some improvement in sperm count and motility in infertile males. Although a large number of formulations are in the market containing zinc and other micronutrients, would physiologists approve of their use in one and all?

Das et al estimated sialic acid in human seminal plasma but found little relationship with sperm count or fertility status (26). Similarly, attempts to correlate seminal biochemistry with testicular biopsy picture have yielded no useful conclusion in infertile males. It must be appreciated that most of the commonly estimated biochemical constituents of the seminal plasma have a wide range of normality and this limits their use in clinical medicine.
Extensive work on a recently discovered antimicrobial protein present in the seminal plasma - seminal plasma - is being carried out under PM Bhargava at the Centre for Cellular and Molecular Biology, Hyderabad (27). It can lyse sperms also, besides bacteria and yeasts. Its action appears to be held under check by antiplasmins. Can a rise in seminalplasmin explain some types of male infertility or a fall predispose to infection? Many intriguing questions in this area are under study. Seminalplasmin can also be a starting point for a new type of contraceptive - the most natural spermicidal.

PHYSIOLOGICAL EFFECTS OF VAS-OCCLUSION

In 1951, India became first country in the world to adopt a national policy on population control and, initially, vasectomy was the sheet-anchor of this programme. However, few physiologists would be aware that vasectomy was first popularised in the 1920s by the biologist, E Steinach, not for contraception but as a 'biological method against the process of ageing'! Since then the long-term physiological consequences of obstructing the testicular outflow tract continue to evoke considerable interest and concern. How does vasectomy influence the pituitary-gonadal axis? What happens to spermatogenesis?

Post-vasectomy testicular changes have been extensively studied in dogs (28, 29) and even in a non-scrotal mammal like the musk shrew (30). Reviewing all such reports, one finds that post-vasectomy changes may vary from marked testicular atrophy to no change at all. Some of the possible factors involved are: a) species difference; b) age of animal; c) inadvertant vascular injury during surgery; d) infection; e) duration of follow up; and f) type of control used. In order to resolve some of this confusion, studies were undertaken directly in human subjects by Kothari and his colleagues (31). A significant depression of spermatogenesis was observed 4 weeks after vasectomy. However, repeat biopsies 2 to 3 1/2 years later showed that the testis had almost recovered and readjusted to the vasal block. Spermatogenesis was within normal limits and the testicular volume showed no significant change as compared to the pre-vasectomy volume.

The main interest, however, lies in the endocrine function of the testis after vasectomy. Steinach had reported marked hyperplasia of the testosterone producing Leydig cells in rats. Perhaps his contention was that as the seminiferous tubules degenerate after vasectomy, all the blood supply is diverted to the interstitial cells. Estimating the Total Leydig Cell Volume (TLCV) in human subjects Kothari, Gupta and their team found a modest but significant increase from 2.2 ± 0.4 ml/testis to 2.5 ± 0.5 one month after vasectomy and 2.6 ± 0.5 ml/testis 2 - 3 1/2 years later (31). This was essentially similar to their earlier observations in dogs. The TLCV had risen from 1.58 ± 0.43 ml/testis to 1.87 ± 0.70 ml/testis in dogs 8 weeks after vasectomy (32, 33). But, ultimately it is the blood testosterone level which matters. Naik et al (34) found no significant alteration in the blood hormone levels after vasectomy in human subjects. Devi, Sheth and their co-workers at the IRR, Bombay, have also monitored the hormone profile of 180 vasectomised men and compared it with a well matched control (35). No significant difference in plasma LH, FSH and estrogen was found. However, testosterone levels showed an interesting difference in the age group of 41-45 years in whom it tended to be a little higher in the vasectomised group as compared to the control. Does this bring us back to Steinach's original idea? Perhaps there are too many variables involved. Many of these physiological questions related to male sterilisation have been reviewed earlier by Kothari in this journal (36).

Biochemical studies on seminal plasma before and after vasectomy have also yielded conflicting results: increase in fructose and acid phosphatase; no change in fructose with decrease in maltase; fall in magnesium; decrease in maltase and citric acid etc. Joshi has reviewed some of these observations and has also added his own finding that the changes in seminal biochemistry return to normal after vaso-vasostomy (37). During the last few years, attention has been drawn to other long-term consequences of vasectomy, particularly the
possibility of autoimmune disorders and atherosclerosis. Lohiya and Tiwari have found no significant change in blood lipids, glucose, urea, electrolytes and proteins, at least in monkeys followed for 2 1/2 years after bilateral vasectomy (38).

Many of the post-vasectomy problems have been due to bad surgery or indiscriminate selection of cases. Several improvements have been suggested. Kothari and Gupta have evaluated the use of tantalum clips in human subjects from the point of view of reliability, reversibility and safety (39, 40). They also investigated the possibility of placing the occlusion at the testiculo-epididymal junction to see if the testicular changes are more pronounced when the epididymis is no longer there to absorb the dammed-up fluid. In a limited study in human subjects, this so-called Steinach II procedure was no different from classical vasectomy (41).

One question of paramount importance today is that of reversibility and recanalisation failure. Bad surgery alone is not to be blamed. Two physiological factors could be relevant: a) high titre of antisperm antibodies, and b) paralysis of the epididymal ejaculatory pump after the autonomic nerve plexus gets widely transected along with the vas segment. Thus, infertility may often persist although anatomical continuity has been restored.

FEMALE REPRODUCTIVE SYSTEM

FALLOPIAN TUBE

Like the epididymis, the fallopian tube had also been generally neglected by physiologists as a simple conduit connecting the ovaries to the uterus. But there is no doubt that it is a complex organ in itself and its orderly function is necessary for reproduction. Naturally, it is receiving considerable attention now.

Manchanda and his colleagues have undertaken some significant studies on the motility of the oviduct in conscious rabbits after permanently implanting plethysmographic devices around the tube (42). Continuous recording could be made through detachable lead wires and the effect of different physiological events or drugs monitored. Ovulation induced by human chorionic gonadotropin (HCG) injection led to a 3-phase change:

a. receptive relaxation for 8-12 hours
b. increased isthmic motility reaching a peak at 48 hours
c. restitution

This has brought much greater clarity to the role of the oviduct in timing the two critical events of fertilisation and implantation. Obviously, too rapid or too slow transit through the tube can both result in reproductive failure - a hint for contraceptive innovators.

The ovum moves forward along the oviduct by the synchronised effect of three forces: ciliary movement, secretory flow and peristaltic contractions. That the regulatory signals to the fallopian tube are largely hormonal can be deduced from the fact that autonomic drugs have little effect on ovum transport. Adrenergic a- and b-blockers as well as moderate renal hypertension did not prevent normal fertility and delivery in rats (43).

HORMONAL AND OTHER REGULATORY FACTORS

Manchanda has investigated the role of estrogens in implantation (44). Estrogen treatment induces embryonic activation and prevents delay in implantation. Estradiol-17B and not estradiol-17α was found to be the effective estrogen in countering the actions of anti-estrogens on the embryo. Thus, estradiol-17B seems to be essential for early embryonic differentiation and metabolic functions. Ravindranath and Moudgal have also confirmed the role of estrogen in early pregnancy in monkeys; anti-estrogens resulted in termination of pregnancy (45). Thus, progesterone alone is not the pregnancy hormone and estrogen also has a supportive role. More interesting is the observation that testosterone and dihydrotestosterone can mimic this action of estrogen in promot-
ing implantation in ovariectomised progesterone treated animals (46).

Why only one Graafian follicle finally matures every month out of the several that are under the same gonadotropic influence remains a mystery. Further, how do the two ovaries alternate at the job? In recent years, several factors, other than gonadotropins and sex hormones, have been identified that modulate gonadal function. Nandedkar et al have isolated an inhibitor of follicular growth and ovulation from the follicular fluid of sheep ovaries (47). There could be some auto-regulatory mechanism within the follicle that normally prevents excessive growth and cyst formation in the absence of ovulation - a phenomenon sometimes seen in infertile women.

The presence of a gonadotropin-inhibiting-material (GIM) in the urine of young children of both sexes has been suspected since 1960. GIM seems to decline after the age of 6 years. Work at the Cancer Research Institute, Bombay, has shown that GIM possibly originates in the hypothalamus and acts by blocking gonadotropin binding at the target cell level (48). Its exact physiological role is not clear but it could represent one mechanism that shields the gonads from stimulation before the onset of puberty.

IMMUNOLOGY AND METABOLISM

Work on the immunological aspects of reproduction is now being actively pursued at several centres in India. Prominent among these are IRR Bombay, IIS Bangalore, AIIMS New Delhi and the recently established Institute of Immunology at New Delhi. This is directed mainly towards the development of newer contraceptive methods. HCG produced by the placenta, non-hormonal trophoblastic antigens, zona pellucida proteins of the ovum, pituitary gonadotropins and sperm antigens are all being attacked by specific antibodies in the hope of evolving a safe and reliable contraceptive for long-term use. Biochemists and immunologists are at the forefront in this area. Some important contributions which have physiological implications are briefly summarised in the section on contraception.

A fundamental question in reproduction is how the mother’s body immunologically tolerates the foetus which is essentially a ‘non-self’ transplant. Local mechanisms in the uterus would shield the growing embryo from the mother’s immunological surveillance. But Dalal et al have reported that red cell antigenicity is also progressively lost during pregnancy and returns to normal within 3-6 months after delivery (49). Oral contraceptives also exert a somewhat similar action. One could conclude that excess of sex hormones inhibit the synthesis of ABO blood group antigens.

The veteran physiologist, P Brahmayyasastry, has been studying acetylcholine (ACh) production by the placenta under different conditions, using in vitro incubation and perfusion techniques (50, 51). The full term placenta contains large quantities of ACh and active synthesis from choline stores continues if the placenta is kept alive by perfusion. No change in ACh metabolism was evident in placenta from Rh incompatibility cases. But, the significance of ACh present in the placental syncytiotrophoblast is not clear. All the same, placental extracts with their rich cocktail of steroids and myriad other biologically active compounds, including ACh, continue to be used in medicine on rather empirical grounds.

It is a common belief in many parts of our country that removal of the uterus would make the woman obese and reduce her physical strength. In a series of papers in Indian Journal of Physiology and Pharmacology, Govindaraju and his colleagues have described the effects of castration, sex hormone administration etc. on the lipid content of the reproductive organs of experimental animals (52, 53). Although limited in their scope, these reports do indicate the need for examining any metabolic or hormonal changes in women who are hysterectomised at the slightest indication today.

BRAIN AND REPRODUCTIVE BEHAVIOUR

Because reproduction in all higher animals requires close cooperation between the two would-be parents, and later between the mother and infant, the whole process is under complex cerebral control. By a happy coincidence, the first study
being reviewed here is also from a husband-and-wife team of physiologists.

S. Dua - Sharma and KN Sharma created stereotaxic lesions in several forebrain structures of female rats and found that this disturbs the gonadotropin secretion and consequently the ovarian cycle (54). Both facilitatory and inhibitory neural substrates were present. This would indicate a dual control of the oestrous cycle: hormonal and neural. Emotional stress or even a sudden change of place or occupation often upset the menstrual cycle in women also.

It is well known that the hypothalamic releasing hormones flowing down to the anterior pituitary through the portal vessels regulate gonadotropin release. But, Tandon and Manchanda have made an interesting observation that LH-RH leaking into the CSF from the adjacent arcuate nucleus may act as a modulator of this response (55). Infusion of LH-RH directly into the 3rd ventricle of rats markedly increased the arcuate nucleus multiunit activity. Thus, LH-RH in the CSF may provide a short-loop positive feedback to these very neurones for building up the LH surge.

In male rats also, testicular atrophy and extensive degeneration of seminiferous tubules has been observed after lesions in the mesencephalic reticular formation in rats by Abid Ali (56). He also computed the TLCV (following the method described by Kothari et al -1972) and found a significant reduction. Obviously, the mesencephalic reticular formation influences gonadotropin release through its extensive connections with the hypothalamus.

If the brain influences reproductive performance, the converse is also true in equal measure. Borkar and Gogate studied the influence of sex hormones on the hoarding behaviour of female rats (57). Several species are known to hoard food when faced with shortage (women’s keenness to keep the family kitchen well stocked may not, after all, be a purely social phenomenon!). This hoarding is most marked in proestrous rats. Estrogen, micro-injected into the preoptic area, increased hoarding while progesterone decreased it.

Kanaka et al (58) brought out an interesting relationship between the taste preference of female rats and the phase of their estrous cycle. On the day of estrus, they seemed to like nothing but sweet (glucose solution). If sex hormones affect the central gustatory mechanisms, we know now why pregnant women often show peculiar changes in their food preferences. In India, this has often been linked to the sex of the unborn child.

Equally interesting is the relationship between pain and sex hormones. Rao and Saifi (59) found that testosterone injection reduces the pain threshold of male rats and castration raises it. Rao et al (60) further reported that estrogen and progesterone desensitise the pain apparatus while a relative fall in their level (removal of ovaries or during menstruation) gives rise to heightened pain sensitivity. Do the female sex hormones make women more tolerant to the pain associated with their reproductive responsibilities? On the other hand, in the case of the male, Jain and Barar found little relationship between aggressive behaviour and sex hormones (61). The study was on clonidine and foot shock induced aggression in mice. Aggressive behaviour was associated with marked reduction in brain ACh content but neither testosterone nor estrogen had any conclusive influence on this.

CLINICAL AND ENVIRONMENTAL

Every now and then, the colourful panorama of reproductive physiology is enriched by interesting clinical observations. For example, Chandra Kiran has described severe systemic and local allergic manifestations in a woman following normal intercourse with her husband (62). But, surprisingly, this had not in any way restricted her fertility. The allergy persisted even after her husband was vasectomised. Apparently, some protein in the seminal plasma rather than the sperms was involved in this embarrassing type of allergy.

The study of abnormalities in sexual differentiation has also yielded valuable information. One of the routine investigations in these patients is the examination of sex chromatin. But the interpretation of this simple test is not as simple as one would imagine from the theoretical maxim that

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CONTRACEPTION

What role are physiologists playing as medical specialists in solving our colossal population problem? Unfortunately, little is being done. Even the teaching of reproduction physiology often remains a mere dictation from some routine text book, unexciting and purely didactic. But other bio-medical scientists have contributed significantly to contraceptive innovation and evaluation. Some important studies carried out in India in this field are summarized in the table below. However, no basically new contraceptive developed in India is yet in the market.

IN CONCLUSION, reproductive physiology can offer many avenues for purposeful and rewarding work:

a) Improving the teaching of Reproduction Physiology to provide a strong foundation for what the students have to do later in gynecology, community medicine, mother-and-child care, pediatrics, family welfare programmes etc.

b) Initiating some basic research in man or laboratory animals. This is a high priority area for support.

c) Innovation of new and better contraceptives and evaluation of their long-term physiological effects.

d) Moving out into the community to study the innumerable biological and social factors which have been influencing our population dynamics for ages.

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